CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

NDA 20-757/S-021

Correspondence

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-757/S-021

Bristol-Myers Squibb Company
Attention: Ms. Grace D. Heckman
P.O. Box 4000
Princeton, NJ 08543-4000

Dear Ms. Heckman:

We acknowledge receipt of your resubmitted supplemental new drug application (NDA) for the following:

Name of Drug Product:	Avapro (irbesartan)Tablets
Review Priority Classification:	Priority (P)
Date of Resubmitted NDA:	March 22, 2002
Date of Receipt:	March 25, 2002

Unless we notify you within 60 days of our receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on May 24, 2002 in accordance with 21 CFR 314.101(a). If the application is filed, the user fee goal date will be September 25, 2002.

All communications concerning this NDA 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
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
1451 Rockville Pike
Rockville, Maryland 20852-1420

If you have any questions, please call:

Mr. Edward Fromm
Regulatory Project Manager
(301) 594-5313

Sincerely,

/S/

{See appended electronic signature page}

Natalia A. Morgenstern
Chief, Project Management Staff
Division of Cardio-Renal Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Zelda McDonald
4/4/02 11:04:55 AM
For Natalia Morgenstern.

Bristol-Myers Squibb
Pharmaceutical Research Institute

P.O. Box 4000 Princeton, NJ 08543-4000
609 252-6126 Fax: 609 252-6000

Grace D. Heckman
Director
Cardiovascular Products
FDA Liaison and Global Strategy Unit
Regulatory Science

NDA 20-757/S-021
Avapro® (irbesartan) Tablets

January 31, 2002

Raymond J. Lipicky, M.D.
Director, Division of Cardio-Renal Drug Products
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

Dear Dr. Lipicky:

Please refer to our approved New Drug Application for Avapro® (irbesartan) Tablets, NDA 20-757 and our supplement, S-021, providing for the use of irbesartan in hypertensive patients with type 2 diabetic renal disease.

Pursuant to 21CFR§314.65, we are now requesting withdrawal of supplement, S-021. We understand that the withdrawal of this application is without prejudice to refiling.

If you have any questions regarding this submission, I can be reached at (609) 252-6126.

Sincerely,

Mary Ellen for
Grace D. Heckman

Grace D. Heckman
Director, Cardiovascular Products
FDA Liaison and Global Strategy Unit
Regulatory Science

GDH/
Desk Copies: Edward Fromm, WOC2, HFD-110, Room 5026
Douglas Throckmorton, M.D., WOC2, HFD-110, Room 5040

Bristol-Myers Squibb
Pharmaceutical Research Institute

P.O. Box 4000 Princeton, NJ 08543-4000
609 252-6126 Fax: 609 252-6000

Grace D. Heckman
Director
Cardiovascular Products
FDA Liaison and Global Strategy Unit
Regulatory Science

NDA 20-757/S-021
Avapro® (irbesartan) Tablets

January 29, 2002

Raymond J. Lipicky, M.D.
Director, Division of Cardio-Renal Drug Products
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

Dear Dr. Lipicky:

Please refer to our approved New Drug Application for Avapro® (irbesartan) Tablets, NDA 20-757 and our supplement, S-021, providing for the use of irbesartan in hypertensive patients with type 2 diabetic renal disease. Reference is also made to the Cardio-Renal Advisory Committee meeting on January 17, 2002 when data from this supplement was presented.

At the Advisory Committee meeting, there was a request for additional data in support of the application. We are proposing to provide additional evidence of efficacy for your review. We are evaluating the regulatory, legal and commercial feasibility of providing information from two sources:

1. Data from Merck, Sharpe, and Dohme Research Laboratories' (MSDRL's) RENAAL study, in which they treated subjects with type 2 diabetes with losartan. We understand that we will have to obtain authorization from MSDRL to allow FDA to refer to their data on behalf of our supplement and to provide authorization to MSDRL to refer to IDNT in support of their supplement. Senior Management at Bristol-Myers Squibb and Sanofi-Synthelabo have endorsed this approach. We are currently discussing this option with MSDRL management, and we hope to provide documentation in the near future in support of this.

2. In parallel we propose to collect follow-up clinical event data, i.e., dialysis or transplant, for those subjects in IDNT who had a doubling of serum creatinine, but who had not reached ESRD or death by the conclusion of the study on December 31,

2000. A brief protocol outline follows this letter describing the subjects and data we intend to collect.

In the near future, we will submit detailed information on the timelines for providing the above information.

Pursuant to 21CFR §314.60, we providing this as an amendment to the file.

If you have any questions regarding this submission, I can be reached at (609) 252-6126.

Sincerely,

Grace D. Heckman

Grace D. Heckman
Director, Cardiovascular Products
FDA Liaison and Global Strategy Unit
Regulatory Science

GDH/
Attachment
Desk Copies: Edward Fromm, WOC2, HFD-110, Room 5026
Raymond Lipicky, M.D., WOC2, HFD-110, Room 5039
Juan Carlos Pelayo, M.D., WOC2, HFD-110, Room 5073
Norman Stockbridge, M.D., WOC2, HFD-110, Room 5033
Robert Temple, M.D., WOC2, HFD-40, Room 6014
Douglas Throckmorton, M.D., WOC2, HFD-110, Room 5040

PROPOSAL FOR DATA COLLECTION

PURPOSE: The purpose of this document is to outline plans for additional data collection and analysis to be performed for the Irbesartan Diabetic Nephropathy Trial (IDNT). The focus of the new data collection and analysis will be on subjects who had a doubling of serum creatinine during the double-blind study period, but did not reach end stage renal disease (ESRD) as defined as renal transplantation or dialysis prior to study closure.

OBJECTIVE: To determine the incidence and time to ESRD, as defined as transplantation or dialysis, for subjects who doubled their serum creatinine but did not progress to transplantation or dialysis by IDNT study closure on December 31, 2000.

DATA COLLECTION METHOD: A listing of subjects who fulfill the above criteria will be produced from the database. Study sites will be contacted to assess the renal outcome for these subjects from the closure of IDNT until present. The following information will be collected.

- Patient Identification Number
- End Stage Renal Disease Status
- Type of End Stage Renal Disease - Dialysis or Transplantation
- Date of Onset of End Stage Renal Disease
- Use of ACE Inhibitors/Angiotension II Receptor Antagonist post double-blind study drug.
- Vital Status
- Date of last known follow-up

ANALYSIS: Analyses will be based on all randomized subjects using the intent-to-treat principle (ITT). Summary statistics on the total incidence of ESRD as defined by renal transplantation or dialysis occurring in the post-study period will be performed. The post-study period is defined as the period from study closure until present time. In addition, an estimated time to onset of ESRD based on the date serum creatinine doubling will be calculated in the official database. In a secondary analysis, ESRD event in the post-study period will be combined with the End Stage Renal Disease event that occurred during the double-blind period to determine overall incidences and time to onset for End Stage Renal Disease as defined as dialysis or transplantation. An analysis by treatment group on the post-study data only and on the combined post-study and double-blind ESRD events will be performed.

TIME OF DATA COLLECTION: Data collection will occur between February 4, 2002 and March 18, 2002. It is expected that information will not be available on all of the subjects. Missing information will be treated in two ways. First, subjects with missing post-study information will be removed from the analysis of the post-study data at the time of the last known follow-up. Second, those subjects with missing post-study

information will be treated as subjects without events for the analysis of total incidences and being censored as of the end of double-blind phase of the study for the time to event analysis.

Bristol-Myers Squibb
Pharmaceutical Research Institute

P.O. Box 4000 Princeton, NJ 08543-4000
Tel: 609 252-6126 Fax: 609 252-6000
grace.heckman@bms.com

Grace D. Heckman
Director
Cardiovascular Products
FDA Liaison and Global Regulatory Strategy

NDA 20-757/S-021
Avapro® (irbesartan) Tablets

July 22, 2002

Douglas C. Throckmorton, M.D.
Director, Division of Cardio-Renal Drug Products
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

Dear Dr. Throckmorton:

Please refer to our approved New Drug Application for Avapro® (irbesartan) Tablets, NDA 20-757 and also to our pending supplement, S-021, providing for the use of irbesartan in hypertensive patients with type 2 diabetic renal disease.

We are now providing a revised request for a waiver of performing pediatric studies in the type 2 diabetic population with nephropathy. We have done further research into the prevalence of the disease and the feasibility of conducting the study in children and confirm that it would be difficult to recruit an adequate number of subjects and to study them within the time course of the disease.

If you have any questions regarding this submission, I can be reached at (609) 252-6126.

Sincerely,

Grace D. Heckman
Director, Cardiovascular Products
FDA Liaison and Global Strategy Unit
Regulatory Science

GDH/jo
Attachment

Desk Copies: Edward Fromm, WOC2, HFD-110, Room 5026
Juan Carlos Pelayo, M.D., HFD-110, Room 5073
Norman Stockbridge, M.D., HFD-110, Room 5033
Robert Temple, M.D., WOC2, HFD-101, Room 6014
Douglas Throckmorton, M.D., HFD-110,Room 5040

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-757/S-021

Sanofi-Synthelabo
c/o Bristol-Myers Squibb
Attention: Ms. Grace D. Heckman
P.O. Box 4000
Princeton, New Jersey 08543-4000

Dear Ms. Heckman:

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) 75mg, 150mg, 300 mg Tablets

NDA Number: 20-757

Review Priority Classification: Priority (P)

Supplement number: S-021

Date of supplement: August 3, 2001

Date of receipt: August 3, 2001

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on October 2, 2001 in accordance with 21 CFR 314.101(a). If the application is filed, the user fee goal date will be February 3, 2002.

All communications concerning this supplement should be addressed as follows:

U.S. Postal Service:
Center for Drug Evaluation and Research
Division of Cardio-Renal Drug Products, HFD-110
Attention: Division Document Room
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
1451 Rockville Pike

Rockville, Maryland 20852
If you have any questions, please call:

Mr. Edward Fromm
Regulatory Project Manager
(301) 594-5313

Sincerely yours,

/S/

Natalia A. Morgenstern
Chief, Project Management Staff
Division of Cardio-Renal Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Zelda McDonald
8/9/01 02:05:55 PM
For NMorgenstern

❖ Exclusivity (approvals only)	
• Exclusivity summary	X
• Is there an existing orphan drug exclusivity protection for the active moiety for the proposed indication(s)? *Refer to 21 CFR 316.3(b)(13) for the definition of sameness for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification!*	( ) Yes, Application #_____ (X) No
❖ Administrative Reviews (Project Manager, ADRA) *(indicate date of each review)*	PM-May 30 & September 12, 2002
General Information	
❖ Actions	
• Proposed action	(X) AP ( ) TA ( ) AE ( ) NA
• Previous actions (specify type and date for each action taken)	AE-June 6, 2002
• Status of advertising (approvals only)	(X) Materials requested in AP letter ( ) Reviewed for Subpart H
❖ Public communications	
• Press Office notified of action (approval only)	(X) Yes ( ) Not applicable
• Indicate what types (if any) of information dissemination are anticipated	( ) None ( ) Press Release ( ) Talk Paper ( ) Dear Health Care Professional Letter
❖ Labeling (package insert, patient package insert (if applicable), MedGuide (if applicable)	
• Division's proposed labeling (only if generated after latest applicant submission of labeling)	NA
• Most recent applicant-proposed labeling	X
• Original applicant-proposed labeling	X
• Labeling reviews (including DDMAC, Office of Drug Safety trade name review, nomenclature reviews) and minutes of labeling meetings *(indicate dates of reviews and meetings)*	DDMAC-January 29, 2002 Labeling T-Con's- June 12, July 24 and August 2, 2002
• Other relevant labeling (e.g., most recent 3 in class, class labeling)	NA
❖ Labels (immediate container & carton labels)	
• Division proposed (only if generated after latest applicant submission)	NA
• Applicant proposed	X
• Reviews	NA
❖ Post-marketing commitments	
• Agency request for post-marketing commitments	NA
• Documentation of discussions and/or agreements relating to post-marketing commitments	NA
❖ Outgoing correspondence (i.e., letters, E-mails, faxes)	X
❖ Memoranda and Telecons	X
❖ Minutes of Meetings	
• EOP2 meeting (indicate date)	July 26, 1995
• Pre-NDA meeting (indicate date)	NA
• Pre-Approval Safety Conference (indicate date; approvals only)	NA
• Pre-Advisory Committee	November 29, 2001

❖ Advisory Committee Meeting	
• Date of Meeting	January 27, 2002
• 48-hour alert	Not Available
❖ Federal Register Notices, DESI documents, NAS, NRC (if any are applicable)	NA
Summary Application Review	
❖ Summary Reviews (e.g., Office Director, Division Director, Medical Team Leader) *(indicate date for each review)*	Medical Team Leader-January 24, 2002
Clinical Information	
❖ Clinical review(s) *(indicate date for each review)*	August 3, 2001 and May 1, 2002
❖ Microbiology (efficacy) review(s) *(indicate date for each review)*	NA
❖ Safety Update review(s) *(indicate date or location if incorporated in another review)*	None
❖ Pediatric Page(separate page for each indication addressing status of all age groups)	X
❖ Statistical review(s) *(indicate date for each review)*	November 13, 2001
❖ Biopharmaceutical review(s) *(indicate date for each review)*	NA
❖ Controlled Substance Staff review(s) and recommendation for scheduling *(indicate date for each review)*	NA
❖ Clinical Inspection Review Summary (DSI)	
• Clinical studies	X
• Bioequivalence studies	NA
CMC Information	
❖ CMC review(s) *(indicate date for each review)*	NA
❖ Environmental Assessment	
• Categorical Exclusion *(indicate review date)*	X May 29, 2002
• Review & FONSI *(indicate date of review)*	
• Review & Environmental Impact Statement *(indicate date of each review)*	
❖ Micro (validation of sterilization & product sterility) review(s) *(indicate date for each review)*	NA
❖ Facilities inspection (provide EER report)	Date completed: NA ( ) Acceptable ( ) Withhold recommendation
❖ Methods validation	( ) Completed NA ( ) Requested ( ) Not yet requested
Nonclinical Pharm/Tox Information	
❖ Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	NA
❖ Nonclinical inspection review summary	
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	
❖ CAC/ECAC report	

DIVISION OF CARDIO-RENAL DRUG PRODUCTS
FOOD AND DRUG ADMINISTRATION

US Mail address:
FDA/CDER/HFD-110
5600 Fishers Lane
Rockville, MD 20857

Woodmont II
1451 Rockville Pike
Rockville, MD 20852

Transmitted to FAX Number:	(609) 252-6000
Attention:	Ms. Grace Heckman
Company Name:	Bristol-Myers Squibb
Phone:	(609) 252-6126
Subject:	**Approval Letter w/Labeling for NDA 20-757/S-021 Avapro (ibesartan) for Type 2 Diabetic Nephropathy**
Date:	September 17, 2002
Pages including this sheet:	27
From:	**Edward Fromm**
Phone:	**301-594-5332**
Fax:	**301-594-5494**

Please let me know that you received this!!! Thanks

RHPM NDA Efficacy Supplement Approval/Labeling Review
September 12, 2002

Avapro (irbesartan) 75, 150 & 300 mg Tablets

NDA 20-757/S-021

Sponsor: Sanofi-Synthelabo

Regulatory Agent: Bristol-Myers Squibb

Classification: SE1 (new indication)

Review Classification: Priority (6 month review)

Indication: Treatment of Type 2 Diabetic Nephropathy

Date of Application: August 3, 2001

Date of Withdrawal: January 31, 2002

Date of Resubmission: March 22, 2002

Date FPL Submitted: September 5, 2002

Date FPL Received: September 6, 2002

User Fee Goal Date: November 6, 2002

Background

An approvable letter was issued on June 6, 2002 for irbesartan for the treatment of Type 2 Diabetic Nephropathy. After labeling discussions with the firm on June 12, July 24 and August 2, 2002, the firm was informed that they could submit Final Printed Labeling (FPL).

Review

The firm submitted final printed labeling on September 5, 2002, received September 6, 2002. When compared with the last approved labeling supplement (S-022, October 3, 2001) the following changes were noted:

1. Under **DESCRIPTION**, 2nd sentence, the chemical name has been changed to "2-Butyl-3-[*p*-(*o*-1*H*-tetrazol-5-ylphenyl)benzyl]-1,3-diazaspiro[4.4]non-1-en-4-one." This change was requested by Dr. Johns Simmons to update the proper USAN name for irbesartan.

2. Under **CLINICAL PHARMACOLOGY, Clinical Studies**, this subsection has been subdivided into **Hypertension** and **Nephropathy in Type 2 Diabetic Patients** subheadings. The information under **Hypertension** remains unchanged from the previously approved labeling while the results from the Irbesartan in Type 2 Diabetic Nephropathy Trial (IDNT) have been inserted under **Nephropathy in Type 2 Diabetic Patients**.

3. Under **INDICATIONS AND USAGE**, this section has been subdivided into **Hypertension** and **Nephropathy in Type 2 Diabetic Patients** subheadings. The indication for **Hypertension** remains unchanged from the previously approved labeling while a new indication has been added under **Nephropathy in Type 2 Diabetic Patients**. The new indication reads as follows:

   AVAPRO is indicated for the treatment of diabetic nephropathy with an elevated serum creatinine and proteinuria (>300 mg/day) in patients with type 2 diabetes and hypertension. In this population, AVAPRO reduces the rate of progression of nephropathy as measured by the occurrence of doubling of serum creatinine or end-stage renal disease (need for dialysis or renal transplantation) (see **CLINICAL PHARMACOLOGY: Clinical Studies**).

4. Under **PRECAUTIONS, Geriatric Use** subsection, updated demographic information has been included as the result of the IDNT trial. This subsection now reads as follows:

   Of 4925 subjects receiving AVAPRO (irbesartan) in controlled clinical studies of hypertension, 911 (18.5%) were 65 years and over, while 150 (3.0%) were 75 years and over. No overall differences in effectiveness or safety were observed between these subjects and younger subjects, but greater sensitivity of some older individuals cannot be ruled out. (See **Pharmacokinetics, Special Populations**, and **Clinical Studies**.)

5. Under **ADVERSE REACTIONS**, new subheadings of **Hypertension** and **Nephropathy in Type 2 Diabetic Patients** have been added. In addition, the following changes were noted:

   (a). The 3rd paragraph has been changed to:

   In placebo-controlled clinical trials, the following adverse event experiences reported in at least 1% of patients treated with AVAPRO (n=1965) and at higher incidence versus placebo (n=641) excluding those too general to be informative and those not reasonably associated with the use of drug because they were associated with the condition being treated or are very common in the treated population include: diarrhea (3% vs. 2%), dyspepsia/heartburn (2% vs. 1%).

   Note: The adverse events of musculoskeletal trauma, fatigue, and upper respiratory infection were deleted following the insertion of the new language included in the above paragraph "excluding those too general to be informative...or very common in the treated population."

   (b). Under the new subheading, **Nephropathy in Type 2 Diabetic Patients,** adverse event information from the IDNT trial has been added.

6. Under **ADVERSE REACTIONS, Laboratory Test Findings**, new subheadings of **Hypertension** and **Nephropathy in Type 2 Diabetic Patients** have been added. The new Nephropathy in Type 2 Diabetic Patients subsection reads as follows:

   Hyperkalemia: Draft

7. Under **DOSAGE AND ADMINSTRATION**, the statements "AVAPRO may be administered with other anti-hypertensive agents" and "AVAPRO may be administered with or without food" have been combined and relocated to the first sentence of this section.

New subheadings of **Hypertension** and **Nephropathy in Type 2 Diabetic Patients** have been added.

New dosing information for patients with Type 2 Diabetic Nephropathy has been added that reads as follows:

Nephropathy in Type 2 Diabetic Patients

The recommended target maintenance dose is 300 mg once daily. There are no data on the clinical effects of lower doses on AVAPRO on diabetic nephropathy (see **CLINICAL PHARMACOLOGY: Clinical Studies**).

Comments/Recommendations:

I will draft an approval letter with labeling for this supplement for Dr. Temple's signature. Per Dr. Throckmorton's instructions, the Pediatric Rule Requirements for this indication will be waived in full for all age groups for this indication.

/S/

Edward J. Fromm
Regulatory Health Project Manager

dr-ef-9-12-02

RHPM NDA Efficacy Supplement Overview
May 30, 2002

Avapro (irbesartan) Tablets for the Treatment of Hypertensive Patients with Type 2 Diabetic Renal Disease

NDA 20-757/SE1-021

Applicant: Sanofi-Synethelabo
Marketing Agent: Bristol-Myers Squibb

Classification: SE1 (new indication)

Review Classification: Priority (6 month review)

Indication: Treatment of hypertensive patients with type 2 diabetic renal disease

Date of Application: August 3, 2001 (original)
March 22, 2002 (resubmission)

Receipt Date: August 3, 2001 (original)
March 25, 2002 (resubmission)

User Fee Goal Date: September 25, 2002

Background

Sanofi-Synthelabo has submitted this efficacy supplement for irbesartan for the treatment of hypertensive patients with type 2 diabetic renal disease. Irbesartan, an angiotensin II receptor blocker, is currently indicated for the treatment of hypertension. Studies for irbesartan for type 2 diabetic renal disease were conducted under IND [redacted].

The application for efficacy and safety is supported by 5 clinical trials, with study CV 131-048 (IDNT, Irbesartan Diabetic Nephropaty Trial) and study EFC 2481 (IRMA 2, Irbesartan in the study of Microalbuminaria in Hypertensive Patients with Type 2 Diabetes Mellitus) being the main supporting trials.

Study CV 131-048 (IDNT), is a study examining irbesartan's effect on morbidity and mortality in hypertensive subjects with type 2 diabetes and diabetic nephropathy. The primary endpoint was the time to the first occurrence of doubling of serum creatinine, end-stage renal disease (ESRD), or all cause mortality. The long-term effects of 300 mg irbesartan were compared to placebo or the calcium channel blocker, amlodipine.

Study EFC 2481 (IRMA 2) looked at the effects of 150 and 300 mg irbesartan versus placebo on the progression to overt proteinuria in type 2 diabetics and microalbuminuria. The primary endpoint was the time to occurrence of clinical proteinuria (defined as albuminuria excretion rate greater than 200 mcg/min and an increase of 30% from baseline at two consecutive evaluations).

The applicant believes that the pivotal trials show that irbesartan provides benefits at both early and late stage diabetic renal disease by delaying the onset of overt proteinuria and delaying the progressive loss of renal function leading to the development of ESRD (end stage renal disease). They claim this renal protective effect is independent of blood pressure lowering.

Irbesartan for the treatment of patients with type 2 diabetic nephropathy was presented before the Cardiovascular and Renal Drugs Advisory Committee Meeting on January 17, 2002. The Committee voted 6 against and 5 for the approval of irbesartan for the treatment of type 2 diabetic nephropathy. Before the final vote, the Committee had voted 10:1 against approval based on the results of the irbesartan development program alone, yet when the fact that captopril (an ACE inhibitor approved for type I diabetic renal disease) and the recently released published results from the RENAAL study (losartan in patients with type 2 diabetic renal disease) were taken into consideration, the vote narrowed to the 6 to 5 margin.

After several discussions between Dr. Temple and the Division, it was agreed that absent the right of reference from Merck for the RENAAL study data and the additional evidence of clinical benefit from surveying the IDNT population for clinical events (need for dialysis, transplant, death, cardiovascular events) beyond the period of follow-up in that study, the Agency would issue a not approvable letter. BMS and Merck were unable to reach agreement on exchange of their study data prior to the February 3, 2002 goal date and therefore BMS decided to withdrawn their application on January 31, 2002.

Subsequent to the withdrawal of the application, an agreement was reached between BMS and Merck to give the Agency right of reference to each other's pivotal studies. Consequently, BMS resubmitted their application on March 22, 2002 (our receipt date March 25, 2002) and was re-granted a priority review.

Merck's Cozaar (losartan potassium) application for type 2 diabetic nephropathy was presented before the Cardiovascular and Renal Drugs Advisory Committee on April 12, 2002. The Committee recommended by a vote of 8 for and 3 against, that Cozaar be approved for the treatment of type 2 diabetic nephropathy.

The Agency decided, that with a favorable Advisory Committee vote for Cozaar and having two positive, well-controlled studies for drugs of the same pharmacologic class, an approvable action should be granted to both applications. An approvable action was issued for Cozaar for the indication of type 2 diabetic nephropathy on May 10, 2002 and the approvable letter and labeling for irbesartan are being crafted to be as similar as possible to the Cozaar letter and labeling.

Meetings

End-of Phase 2: July 26, 1995

Review

Medical

Division Director:	Douglas C. Throckmorton
Conclusion:	Approvable (memo to be written later)
Secondary Medical:	Norman Stockbridge, M.D., Ph.D.
Conclusion:	At the time the application was withdrawn, Dr. Stockbridge recommended a not approvable action, however, in light of the favorable Advisory Committee vote for Cozaar and the Agency being allowed to consider the RENAAL data in support of the irbesartan application, he now supports an approvable action for this application.

Medical:	Juan Carlos Pelayo, M.D.
Conclusion:	Approvable; Dr. Pelayo states in his review, that the "evidence of effectiveness provided in this efficacy supplement is not overwhelming but is sufficient to support approval." He notes that the IDNT trial tested two hypotheses, irbesartan versus placebo and irbesartan versus amlodipine. Irbesartan achieved a significantly significant result in both arms of the study, although IRMA 2 which was supposed to be the "second" supportive study has several deficiencies in study design and was not interpretable.
Statistical:	John Lawrence, Ph.D.
Labeling:	None
Conclusion:	Dr. Lawrence states in his review that "study CV131-048 showed a statistically significant increase in the time to a composite endpoint (doubling of serum creatinine, ESRD, all-cause mortality) with a p-value of 0.023 and also appeared to show superior efficacy to the active control amlodipine 10 mg. However, he notes that composite effect seems to be driven by delaying increases in serum creatinine. Moreover, the "effect of irbesartan on the primary endpoint appeared to be smaller in North America than in other regions." EFC2481 at doses of 300 mg appeared to achieve a "statistically significant increase in the time to occurrence of clinical proteinuria with a p-value of 0.0013, but failed to show a statistically significant difference between a lower dose of 150 mg relative to placebo (p=0.096).
Biopharmaceutics	
Reviewer:	Angelica Dorantes, Ph.D
Labeling:	None
Conclusion:	Dr. Dorantes states that there are no biopharm review issues for this application.
Chemistry	No full review (see Environmental Assessment)
Pharmacology	Not applicable
Safety Update:	Not needed, see Dr. Stockbridge's Secondary Medical Review
Patent info:	Included in package
Pediatric info:	Waiver granted, see Dr. Stockbridge's Secondary Clinical Review
DSI:	Acceptable, "No major deficiencies were noted in the three sites inspected that could compromise the integrity of the data."

Debarment Certification: Included in package

Exclusivity Summary: Included in package

Environmental Assessment: Sponsor granted Categorical Exclusion

Financial Disclosure: acceptable, see page 1 of Dr. Stockbridge's Secondary Medical review

OPDRA Tradename Review: Not needed, the firm did not change the trade or generic name for this new indication.

DDMAC: Please see Dr. Andy Haffer's January 29, 2002 comments.

Comments: I will draft an approvable letter with marked-up draft labeling for Dr. Temple's signature.

Edward J. Fromm
Regulatory Health Project Manager

dr-ef-5-30-02

26 pages redacted from this section of the approval package consisted of draft labeling

********** -COMM. JOURNAL- ********** DATE SEP-17-2002 ***** TIME 15:13 ********

MODE = MEMORY TRANSMISSION START=SEP-17 15:09 END=SEP-17 15:13

FILE NO.=900

STN NO.	COMM.	ONE-TOUCH/ ABBR NO.	STATION NAME/TEL NO.	PAGES	DURATION
001	OK	#	916092526000	027/027	00:03:41

-FDA,CDER,OND,ODEI,DCRDP -

********** -CARDIO RENAL - ***** - 301 594 5494- **********

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Transmitted to FAX Number:	(609) 252-6000
Attention:	Ms. Grace Heckman
Company Name:	Bristol-Myers Squibb
Phone:	(609) 252-6126
Subject:	**Approval Letter w/Labeling for NDA 20-757/S-021 Avapro (ibesartan) for Type 2 Diabetic Nephropathy**
Date:	September 17, 2002
Pages including this sheet:	27
From:	**Edward Fromm**
Phone:	**301-594-5332**
Fax:	**301-594-5494**

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Rockville, MD 20852

Transmitted to FAX Number:	(609) 252-6000
Attention:	Ms. Grace Heckman
Company Name:	Bristol-Myers Squibb
Phone:	(609) 252-6126
Subject:	**Approvable Letter & Marked-Up Draft Labeling for Avapro (irbesartan) for Type 2 Diabetic Nephropathy NDA 20-757/S-021**
Date:	June 7, 2002
Pages including this sheet:	**27**
From:	**Edward Fromm**
Phone:	**301-594-5313**
Fax:	**301-594-5494**

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Redacted 4

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Rockville, MD 20852

Transmitted to FAX Number:	(609) 252-6000
Attention:	Ms. Grace Heckman
Company Name:	Bristol-Myers Squibb
Phone:	(609) 252-6126
Subject:	**Minutes of Telecon w/FDA, July 24, 2002** **Avapro (irbesartan) for Diabetic Nephropathy** **NDA 20-757/S-021**
Date:	August 26, 2002
Pages including this sheet:	**4**
From:	**Edward Fromm**
Phone:	**301-594-5313**
Fax:	**301-594-5494**

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Minutes of a Telecon between Bristol-Myers Squibb, Sanofi-Synthelabo and the FDA

Date: July 24, 2002

Application: NDA 20-757/SE1-021
Avapro (irbesartan) Tablets

Indication: Treatment of Patients with Type 2 Diabetic Nephropathy

Applicant: Sanofi-Synthelabo c/o Bristol-Myers Squibb

Subject: Labeling Discussions following Approvable Letter

FDA participants

Robert Temple, M.D., HFD-101, Director, Office of Drug Evaluation and Research
Douglas C. Throckmorton, M.D., HFD-110, Director, Division of Cardio-Renal Drug Products
Norman Stockbridge, M.D., Ph.D., HFD-110, Medical Team Leader
Juan Carlos Pelayo, M.D., HFD-110, Medical Officer
James Hung, Ph.D., HFD-110, Statistician/Team Leader
John Lawrence, Ph.D., HFD-110, Statistician
George Chi, Ph.D., HFD-710
Charles Anello, Sc.D., HFD-700, Office of Biostatistics
Edward Fromm, HFD-110, Regulatory Health Project Manager

Bristol-Myers Squibb (BMS)

Deborah Anzalone, M.D., Director, Cardiovascular Global Development
Steven Bass, Ph.D., Director, Global Labeling Strategy
Todd Baumgartner, M.D., Vice President Global Regulatory Strategy – Life Cycle Management
Melisa Cooper, M.D., M.S., Vice President, Project Planning and Management
Juergen Froehlich, M.D., Vice President, Full Development Team
Daniel Gans, Senior Research Biostatistician
Grace Heckman, Director, Global Regulatory Strategy
Paul Kramer, Director, Regulatory Strategy
Kannan Natarajan, Ph.D., Director Clinical Biostatistics
James Rusnak, M.D., Ph.D., Director, Cardiovascular Global Development
Laurie Smaldone, M.D., Senior Vice President, Global Regulatory Strategy and Outcomes Research
George Williams, Ph.D., Vice President, Clinical Biostatistics

Sanofi-Synthelabo

Richard Gural, Ph.D., Vice President of Regulatory Affairs
Jon Villaume, Ph.D., Senior Director of Regulatory Affairs

Background

Irbesartan for patients with type 2 diabetic nephropathy was issued an approvable letter on June 6, 2002. Today's telecon was to discuss revisions the sponsor submitted on June 17, 2002 in response to the Agency's markup of the draft labeling that accompanied the approvable letter.

Telecon

Dr. Throckmorton opened the telecon by noting that the sponsor's revisions were acceptable to the Agency with the following exceptions:

- Lines 180-183-"The mean blood pressure...for a mean duration of 2.6 years" should be relocated to the end of line 189.

- Lines 198-200 should be deleted. Dr. Throckmorton noted said this paragraph implies a correlation between the blood pressure lowering effect of irbesartan with renal function that we believe has not been demonstrated. Dr. Temple added that amlodipine's effects on blood pressure are clearly described in Figure 3.

- Lines 211-216-Dr. Temple said we were unsure of how many composites were referred to by this paragraph. The sponsor said there were in fact 2 secondary composites and they suggested rewording the first sentence as follows:

  "The secondary endpoint of the study was a composite of cardiovascular mortality and morbidity (myocardial infarction, hospitalization for heart failure, stroke with permanent neurological deficit, and amputation)." Dr. Temple said rewording was acceptable.

- Table 1. IDNT: Components of Primary Composite Endpoint. The sponsor noted that they had included a heading of "Percentage (%) of Subjects" for Table 1 and asked if this was appropriate. Dr. Temple said the sponsor may want to put percentages next to the numbers that are appropriate (i.e., not listing them next to hazard ratios and Confidence Intervals.

- Lines 224-226-Dr. Throckmorton said these lines that refer to the IRMA2 (Irbesartan in the study of Microalbuminaria in Hypertensive Patients with Type 2 Diabetes Mellitus) results should be deleted. They imply a claim that has not been demonstrated. The sponsor argued that the word "progression" is in the current Capoten labeling and therefore should be allowed in irbesartan's labeling. Dr. Temple said in retrospect, it was probably a mistake to include language in the labeling referring to Capoten's "decreasing the rate of progression of renal insufficiency..." but noted that we have allowed no other sponsor to include a prevention claim in ESRD (end stage renal disease). He added that irbesartan's effects on proteinuria are included in the IDNT (The Effects of Irbesartan on Morbidity and Mortality in Hypertensive Patients with Type II Diabetes and Diabetic Nephropathy) results.

- Lines 228-238-Figure 4: IDNT: Primary Efficacy Outcome Within Subgroups-Dr. Temple asked if the firm could do regional analyses for the endpoints of death and ESRD and ESRD alone to see if there any differences. If there were no differences we would be inclined to leave them out altogether. The sponsor said they would submit the analyses requested by the Agency.

- Lines 403-405 (Geriatric Use)-Dr. Throckmorton asked where the information that refers to "421 subjects..." were obtained. The sponsor replied that this information was obtained in hypertension studies done post-approval. Dr. Temple said we are not sure what "controlled clinical trials" are and therefore the sentence "These observations.....75 years and older" should be deleted.

- Lines 418-426-Dr. Throckmorton said that the adverse events of "musculoskeletal trauma" and "upper respiratory infections" are very unlikely related to the drug and should be removed from the labeling. Dr. Temple added that others throughout the **ADVERSE REACTIONS** should be removed if possible.

Bristol-Myers Squibb asked when final printed labeling could be sent in for this supplement.

He said the sponsor should submit the death and ESRD analyses to the Division for review; Dr. Throckmorton will then contact you about the timing for submitting final printed labeling.

Minutes Preparation: /S/
Edward Fromm

Concurrence, Chair: /S/
Robert Temple, M.D.

drafted/ef: 7-30-02/8-12-02/8-14-02

Rd: JLawrence-7/31/02
JHung-8/01/02
CAnello-7/31/02
GChi-7/31/02
JPelayo-8/1/02
NStockbridge-8/1/02
DThrockmorton-8/2/02

********** -COMM. JOURNAL- ********** DATE AUG-26-2002 ***** TIME 13:32 **********

MODE = MEMORY TRANSMISSION START=AUG-26 13:31 END=AUG-26 13:32

FILE NO.=660

STN NO.	COMM.	ONE-TOUCH/ ABBR NO.	STATION NAME/TEL NO.	PAGES	DURATION
001	OK	a	916092526000	004/004	00:00:43

-FDA,CDER,OND,ODEI,DCRDP -

********** -CARDIO RENAL - ***** - 301 594 5494- **********

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Transmitted to FAX Number:	(609) 252-6000
Attention:	Ms. Grace Heckman
Company Name:	Bristol-Myers Squibb
Phone:	(609) 252-6126
Subject:	**Minutes of Telecon w/FDA, July 24, 2002** **Avapro (irbesartan) for Diabetic Nephropathy** **NDA 20-757/S-021**
Date:	August 26, 2002
Pages including this sheet:	**4**
From:	**Edward Fromm**
Phone:	**301-594-5313**
Fax:	**301-594-5494**

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21 pages redacted from this section of the approval package consisted of draft labeling

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Transmitted to FAX Number:	(609) 252-6000
Attention:	Ms. Grace Heckman
Company Name:	Bristol-Myers Squibb
Phone:	(609) 252-6126
Subject:	**Minutes of Telecon w/FDA, June 12, 2002** **Avapro (irbesartan) for Diabetic Nephropathy** **NDA 20-757/S-021**
Date:	June 28, 2002
Pages including this sheet:	21
From:	**Edward Fromm**
Phone:	**301-594-5313**
Fax:	**301-594-5494**

PLEASE LET ME KNOW YOU RECEIVED THIS. THANKS!

Minutes of a Telecon between Bristol-Myers Squibb, Sanofi-Synthelabo and the FDA

Date: June 12, 2002

Application: NDA 20-757/SE1-021
Avapro (irbesartan) Tablets

Indication: Treatment of Patients with Type 2 Diabetic Nephropathy

Applicant: Sanofi-Synthelabo c/o Bristol-Myers Squibb

Subject: Labeling Discussions following Approvable Letter

FDA participants

Robert Temple, M.D., HFD-101, Director, Office of Drug Evaluation and Research
Douglas C. Throckmorton, M.D., HFD-110, Director, Division of Cardio-Renal Drug Products
Juan Carlos Pelayo, M.D., HFD-110, Medical Officer
John Lawrence, Ph.D., HFD-110, Statistician
Angelica Dorantes, Ph.D., HFD-860, Clinical Pharmacologist and Biopharmaceuticist
Edward Fromm, HFD-110, Regulatory Health Project Manager

Bristol-Myers Squibb (BMS)

Deborah Anzalone, M.D., Director, Cardiovascular Global Development
Steven Bass, Ph.D., Director, Global Labeling Strategy
Todd Baumgartner, M.D., Vice President Global Regulatory Strategy – Life Cycle Management
Melisa Cooper, M.D., M.S., Vice President, Project Planning and Management
Grace Heckman, Director, Global Regulatory Strategy
Kannan Natarajan, Ph.D., Director Clinical Biostatistics

Sanofi-Synthelabo

Richard Gural, Ph.D., Vice President of Regulatory Affairs
Jon Villaume, Ph.D., Senior Director of Regulatory Affairs

Background

Irbesartan for patients with type 2 diabetic nephropathy was issued an approvable letter on June 6, 2002. Today's telecon was to discuss revisions the sponsor has proposed in response to the Agency's markup of the draft labeling that accompanied the approvable letter.

Telecon

Dr. Temple opened the telecon by noting that the sponsor's revisions were acceptable to the Agency with the following exceptions:

- Line 184-"The study population was diverse with regard to race"..., the word "diverse" should be removed and the line reworded to just state the demographic information.

- Line 194 & 195-The words "and a 23% risk reduction versus amlodipine (p=0.0064) in this endpoint" should be deleted. We feel the above words sound too much like a comparative claim but still we would show the comparison between irbesartan and amlodipine in Figure 3 and Table 1.

- Line 199 to 201-This paragraph, which we believe somewhat overstates the effect of irbesartan, should be replaced with language from the Capoten label which reads (with your drug) as follows:

Draft

- Line 218 to 227-Dr. Temple said this section should be reworded in with more general language and suggested the following:

DRAFT

- Line 243 to 253-This section presents results from the IRMA 2 (Irbesartan in the study of Microalbuminaria in Hypertensive Patients with Type 2 Diabetes Mellitus) trial that we feel implies an additional claim that cannot be considered valid based on the proteinuria surrogate. Dr. Throckmorton noted that the last sentence of that section that reads

DRAFT

is a potential qualifier; the Agency tries not to include claims that are not meaningful, even with a qualifier. Dr. Temple believes that this whole section should be deleted; perhaps a sentence or two about IRMA 2 could be included after the IDNT data.

- Line 422 to 426-Dr. Temple said the sponsor should consider removing the adverse events of musculoskeletal pain and upper respiratory infection, as these events are not much different from placebo and unlikely to be caused by the drug.

- Line 507 to 511-Dr. Throckmorton suggested that the sponsor have two subheadings for this section, one for Hypertension and another for Type 2 Diabetic Nephropathy. The sponsor should send in proposed language for the Diabetic Nephropathy section and include a reference to the IDNT (Irbesartan Diabetic Nephropathy Trial) data for their dosing recommendation.

Dr. Temple said that there are some minor editorial changes in the labeling that Mr. Fromm will convey to the sponsor. He also reminded the sponsor that discussions are ongoing with another firm seeking the same indication and therefore submission of final printed labeling may not be possible until a later date.

Minutes Preparation: _____
Edward Fromm

Concurrence, Chair:
Robert Temple, M.D.

drafted/ef: 6-18-02/6-19-02/6-27-02
Rd: ADorantes-6-18-02
JLawrence-6-18-02
JPelayo-6-18-02
DThrockmorton-6-19-02

18 pages redacted from this section of the approval package consisted of draft labeling

********** -COMM. JOURNAL- ********** DATE JUN-28-2002 ***** TIME 15:31 *********

MODE = MEMORY TRANSMISSION START=JUN-28 15:22 END=JUN-28 15:31

FILE NO.=040

STN NO.	COMM.	ONE-TOUCH/ ABBR NO.	STATION NAME/TEL NO.	PAGES	DURATION
001	OK	#	916092526000	021/021	00:04:30

-FDA,CDER,OND,ODEI,DCRDP -

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Transmitted to FAX Number:	(609) 252-6000
Attention:	Ms. Grace Heckman
Company Name:	Bristol-Myers Squibb
Phone:	(609) 252-6126
Subject:	**Minutes of Telecon w/FDA, June 12, 2002** **Avapro (irbesartan) for Diabetic Nephropathy** **NDA 20-757/S-021**
Date:	June 28, 2002
Pages including this sheet:	21
From:	**Edward Fromm**
Phone:	**301-594-5313**
Fax:	**301-594-5494**

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Attention:	Ms. Grace Heckman
Company Name:	Bristol-Myers Squibb
Phone:	(609) 252-6126
Subject:	**Minutes of Telecon w/FDA, April 2, 2002** **Avapro (irbesartan) for Diabetic Nephropathy** **NDA 20-757/S-021**
Date:	April 11, 2002
Pages including this sheet:	**4**
From:	**Edward Fromm**
Phone:	**301-594-5313**
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Minutes of a Telecon between Bristol-Myers Squibb and the FDA

Date: April 2, 2002

Application: NDA 20-757/SE1-021
Avapro (irbesartan) Tablets

Indication: Treatment of Hypertensive Patients with Type 2 Diabetic Nephropathy

Applicant: Sanofi-Synthelabo c/o Bristol-Myers Squibb

Subject: April Cardiovascular and Renal Drugs Advisory Committee Meeting

FDA participants

Robert Temple, M.D., HFD-101, Director, Office of Drug Evaluation and Research
Douglas C. Throckmorton, M.D., HFD-110, Acting Division Director
Norman Stockbridge, M.D., Ph.D., Medical Team Leader
Juan Carlos Pelayo, M.D., HFD-110, Medical Officer
John Lawrence, Ph.D., HFD-110, Statistician
Mr. Edward Fromm, HFD-110, Regulatory Health Project Manager

Bristol-Myers Squibb (BMS)

Todd Baumgartner, M.D., Vice President Global Regulatory Strategy – Life Cycle Management
Renzo Canetta, M.D., Vice President Global Development – Life Cycle Management
Melisa Cooper, M.D., Clinical Development
Brian Daniels, M.D., Vice President, Global Development, Full Development
Ms. Grace Heckman, Director, Global Regulatory Strategy
Kannan Natarajan, Ph.D., Director Clinical Biostatistics
Laurie Smaldone, M.D., Senior Vice President, Global Regulatory Sciences

Sanofi-Synthelabo

Richard Gural, Ph.D., Vice President of Regulatory Affairs
Jon Villaume, Ph.D., Senior Director of Regulatory Affairs

Background

The Cardiovascular and Renal Drugs Advisory Committee, on January 17, 2002, voted 6 to 5 against recommending approval of irbesartan for the treatment of patients with Type 2 diabetic renal disease.

The Division, in several conversations with the sponsor, and reflecting discussions at the Cardiovascular and Renal Drugs Advisory Committee meeting, indicated that if we were able to consider both BMS' data on irbesartan and Merck's RENAAL (Effects of Losartan on Renal and Cardiovascular Outcomes in Patients with Type 2 Diabetes and Nephropathy) study of losartan, the case for approval would be strengthened. With just BMS' study, although no final conclusion had been reached, approval was less likely. We could not consider Merck's data on BMS' behalf, however, without a right of reference from Merck (or BMS' data on Merck's behalf without right of reference from BMS). Negotiations with Merck for these data, however, were unsuccessful as of the meeting and therefore the sponsor withdrew their application on January 31, 2002.

Recently, however, BMS and Merck agreed to exchange right of reference to each other's pivotal studies and consequently, BMS resubmitted their application on March 22, 2002 (our receipt date March 25, 2002). The application was re-granted a priority (6 month) review.

The telecon today is to discuss how irbesartan will be included in the April Cardiovascular and Renal Drugs Advisory Committee Meeting, which will focus mainly on Merck's Cozaar application for type 2 diabetic renal disease.

Telecon

IDNT (Irbesartan Diabetic Nephropathy Trial Follow-up) Data

BMS opened the telecon by noting that they have resubmitted their supplemental NDA and are in the process of submitting additional follow-up event data regarding the events of dialysis, renal transplant and death in patients in the IDNT study. They believe that the data confirm that the doubling of serum creatinine leads to more dialysis, renal transplants and death. Dr. Temple said that the Committee will probably want to discuss these data so the sponsor should be prepared for this possibility. Dr. Throckmorton noted however, that the Committee members will likely be told that the Division has recently received these data and may have not had enough time to adequately review and comment about the data.

Irbesartan's Role at the Advisory Committee Meeting

BMS asked how will the Advisory Committee be "orchestrated" relative to irbesartan. Dr. Throckmorton replied that the format and questions of the meeting would likely be very similar to the January 2002 meeting in which irbesartan was discussed. The plan is for an initial presentation by Merck, followed by discussion of the RENAAL data. The questions (similar to the ones in January) would then be discussed and voted on. Toward the end of the questions a specific question will be asked about "other data" that could be relied on to support the approval of Cozaar for the treatment of patients with type 2 diabetic renal disease. At this point, the irbesartan application will likely be discussed. Dr. Throckmorton noted that we will ask Dr. Joanne Lindenfeld (the April Committee primary reviewer) to have the briefing materials available from the January 2002 Advisory Committee Meeting. The Committee members, however, should remember most of the discussion from the January meeting.

BMS asked if there would be a formal vote at the Advisory Committee Meeting on the irbesartan application. Dr. Temple replied that since the irbesartan data would not be represented in its entirety to the Committee, a formal vote would not be taken. He said, however, that any advice the Agency receives from the Committee will be considered for both the losartan and irbesartan applications and are prepared to convey this to the Committee if necessary.

BMS asked if the Committee would be notified that the irbesartan application has been re-filed with the Division. Dr. Temple said that this information was not pertinent to the discussion and was unlikely to be brought up by Committee members.

BMS asked if the Agency has slides that they might present at the meeting, could they be sent to the sponsor in advance. Dr. Throckmorton said that he would have slides showing the primary endpoint analyses from IDNT, in case the Advisory Committee needed to be reminded of the general outcomes of the trial. The sponsor asked if the Division wanted their slides from the January Advisory Committee Meeting. Dr. Throckmorton said they could send them but that overheads would even be better.

Minutes Preparation: /S/
Edward Fromm

Concurrence, Chair: /S/
Robert Temple, M.D.

drafted/ef: 4-04-02/4-09-02

Rd: JLawrence-4-04-02
JPelayo-4-04-02
JLawrence-4-04-02
DThrockmorton-4-04-02

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Edward Fromm
4/11/02 03:22:18 PM
CSO
Dr. Temple signed the minutes on April 11, 2002.

Edward Fromm
4/11/02 03:25:31 PM
CSO
Dr. Temple signed the minutes on April 11, 2002.

DIVISION OF CARDIO-RENAL DRUG PRODUCTS
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Transmitted to FAX Number:	(609) 252-6000
Attention:	Ms. Grace Heckman
Company Name:	Bristol-Myers Squibb
Phone:	(609) 252-6126
Subject:	**Minutes of Telecon w/FDA, March 6, 2002** **Avapro (irbesartan) for Diabetic Nephropathy** **IND** [redacted] **NDA 20-757/S-021 (WD)**
Date:	March 15, 2002
Pages including this sheet:	**4**
From:	**Edward Fromm**
Phone:	**301-594-5313**
Fax:	**301-594-5494**

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Minutes of a Telecon between Bristol-Myers Squibb and the FDA

Date: March 6, 2002

Application: NDA 20-757/SE1-021 (WD)
IND [redacted]
Avapro (irbesartan) Tablets

Indication: Treatment of hypertensive patients with type 2 diabetic nephropathy

Applicant: Sanofi-Synthelabo c/o Bristol-Myers Squibb

Subject: Right of Reference to RENAAL Data and April 2002 Cardio-Renal Advisory Committee Meeting

FDA participants

Robert Temple, M.D., HFD-101, Director, Office of Drug Evaluation and Research
Douglas C. Throckmorton, M.D., HFD-110, Acting Division Director
Norman Stockbridge, M.D., Ph.D., Medical Team Leader
Juan Carlos Pelayo, M.D., HFD-110, Medical Officer
James Hung, Ph.D., HFD-110, Statistician/Team Leader
John Lawrence, Ph.D., HFD-110, Statistician
Yuki Anod, Ph.D., HFD-710, Statistician
Natalia Morgenstern, HFD-110, Chief, Project Management Staff
Sandy Birdsong, HFD-110, Project Manager
Edward Fromm, HFD-110, Project Manager

Bristol-Myers Squibb (BMS)

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Renzo Canetta, M.D., Vice President Global Development – Life Cycle Management
Brian Daniels, M.D., Vice President, Global Development, Full Development
Grace Heckman, Director, Global Regulatory Strategy
Kannan Natarajan, Ph.D., Director Clinical Biostatistics
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Sanofi-Synthelabo

Jean Bouthier, M.D., Vice President, Clinical Research
Richard Gural, Ph.D., Vice President of Regulatory Affairs
Jon Villaume, Ph.D., Senior Director of Regulatory Affairs

Background

The Cardiovascular and Renal Drugs Advisory Committee, on January 17, 2002, voted 6 to 5 against recommending approval of irbesartan for the treatment of patients with Type 2 diabetic renal disease. The Division, in several conversations with the sponsor, and reflecting discussions at the Cardiovascular and Renal Drugs Advisory Committee meeting, indicated that if we were able to consider both BMS' data on irbesartan and Merck's RENAAL (Effects of Losartan on Renal and Cardiovascular Outcomes in Patients with Type 2 Diabetes and Nephropathy) study of losartan, the

case for approval would be strengthened. With just BMS' study, although no final conclusion had been reached, approval was not likely. We could not consider Merck's data on BMS' behalf, however, without a right of reference from Merck (or BMS' data on Merck's behalf without right of reference from BMS). Negotiations with Merck for these data, however, were unsuccessful as of the meeting and therefore the sponsor withdrew their application on January 31, 2002.

The sponsor requested a telecon with the Division to ascertain what information would be needed to reopen their application and whether irbesartan (assuming the ability to cross reference data from Merck) could be co-presented with Cozaar (losartan potassium) at the April 2002 Cardio-Renal Advisory Committee Meeting.

Telecon

BMS opened the telecon by noting that they would like to resubmit their supplemental NDA and wanted to address the following two issues that they believe are needed to reopen their application:

1. Collection of additional event data (dialysis, transplant or death) from the Irbesartan Diabetic Nephropathy Trial (IDNT). The sponsor said they hope to finish collection of the data in April 2002, but said it might take longer and asked if it would be possible to submit this data post-approval. Dr. Temple said this information could be critical to the approval of both applications (irbesartan and losartan) and therefore should be submitted as soon as possible. He added that the protocol to collect the IDNT follow-up data was acceptable.
2. Submitting a letter from Merck authorizing right of reference to the RENAAL data in exchange for BMS granting a right of reference to Merck for the IDNT data.

BMS asked if both items above had to be submitted to reopen their application or would the right of reference letter be enough by itself. Dr. Temple said it is preferable to submit both the additional event data and the letter of authorization at the time of resubmission. He said, however, that at a minimum, the letter from Merck granting right of reference would be needed at the time of resubmission.

The sponsor asked (assuming cross-referencing to the respective applications) whether an action could take place on the same date for both applications. Dr. Temple replied that because of potential differences between the two applications he could not promise a concurrent action date.

BMS asked how irbesartan would be included in April 2002 Cardio-Renal Advisory Committee Meeting. Dr. Temple said that if the follow-up data from the IDNT study were available then the sponsor could be asked to present these data at the meeting. If these data were not available, then the sponsor should be available for any questions the Committee might pose. We planned to review the IDNT data and the Committee's comments in the questions or possibly in a statement to the Committee.

The sponsor asked if the labeling (if approved) would reflect the data from both applications or would they be specific to each application. Dr. Temple said the labeling would probably be drug-specific; for example, only the IDNT and perhaps the IRMA 2 data would appear in the labeling for irbesartan.

BMS asked, when reviewing the irbesartan and losartan applications, would the Agency perform a combined analysis by pooling the data from both applications. Dr. Temple stated that the Agency would look at results of both studies but would not pool the data.

Minutes Preparation: /S/

Edward Fromm

Concurrence, Chair: /S/

Robert Temple, M.D.

drafted/ef: 3-8-02/3-14-02/3-15-02

SBirdsong: 3-8-02
JLawrence: 3-8-02
JHung: 3-8-02
JPelayo: 3-8-02
NStockbridge: 3-12-02
DThrockmorton: 3-12-02
NMorgenstern: 3-12-02

MESSAGE CONFIRMATION

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DIVISION OF CARDIO-RENAL DRUG PRODUCTS
FOOD AND DRUG ADMINISTRATION

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Rockville, MD 20852

Transmitted to FAX Number: (609) 252-6000

Attention: Ms. Grace Heckman

Company Name: Bristol-Myers Squibb

Phone: (609) 252-6126

Subject: **Minutes of Telecon w/FDA, March 6, 2002**
Avapro (irbesartan) for Diabetic Nephropathy
IND [redacted]
NDA 20-757/S-021 (WD)

Date: March 15, 2002

Minutes of a Meeting between Bristol-Myers Squibb and the FDA

Date: November 29, 2001

Application: NDA 20-757/SE1-021
Avapro (irbesartan) Tablets

Indication: Treatment of hypertensive patients with type 2 diabetic nephropathy

Applicant: Sanofi-Synthelabo c/o Bristol-Myers Squibb

Subject: Pre-Advisory Committee Meeting

FDA participants

Raymond Lipicky, M.D., HFD-110, Director, Division of Cardio-Renal Drug Products
Douglas Throckmorton, M.D., HFD-110, Deputy Division Director
Norman Stockbridge, M.D., Ph.D., Medical Team Leader
Juan Carlos Pelayo, M.D., HFD-110, Medical Officer
James Hung, Ph.D., HFD-110, Statistician/Team Leader
John Lawrence, Ph.D., HFD-110, Statistician
Edward Fromm, HFD-110, Project Manager

Bristol-Myers Squibb

Deborah Anzalone, M.D., Director, Cardiovascular Clinical Research
John Bedard, M.S., Vice President, Regulatory Science
Brian Daniels, M.D., Vice President, Cardiovascular and Immunology Clinical Research
Grace Heckman, Director, Regulatory Science
Margo Herron, Associate Director, Regulatory Science
Kannan Natarajan, Ph.D., Director, Biostatistics
James Rusnak, M.D., Ph.D., Associate Director, Cardiovascular Clinical Research
Laurie Smaldone, M.D., Senior Vice President, Regulatory Science and Outcomes Research

Sanofi-Synthelabo

Gerald Frangin, M.D., Clinical Research Project Director
Eileen Kahn, M.S., Regulatory Assistant, Dept. of Regulatory Affairs
Gerald Pillion, M.D., Clinical Research Director
Jon Villaume, Ph.D., Senior Director, Dept. of Regulatory Affairs

Background

Bristol-Myers Squibb, on August 3, 2001, submitted an efficacy supplement for irbesartan tablets for the treatment of hypertensive patients with type 2 diabetic nephropathy. The firm was given a priority review because there is currently no approved drug for this indication.

Bristol-Myers Squibb believes that the pivotal trials show that irbesartan provides benefits at both early and late stage diabetic renal disease by delaying the onset of overt proteinuria and delaying the progressive loss of renal function leading to the development of ESRD (end-stage renal disease). They claim this renal protective effect is independent of blood pressure lowering.

The Division asked the sponsor to present their data for irbesartan for type 2 diabetic renal disease at the January 2002 Cardio-Renal Advisory Committee Meeting. The firm agreed to present before the Committee and requested feedback on a draft background package for the meeting as well as the review of the application to date by the Division.

Meeting

Dr. Lipicky opened the meeting by giving the Division's perspective of the application:

- The number of events and other numbers in tables in Dr. Pelayo's review appear to be different than those presented in the firm's briefing document. It appears that the differences concern only the IDNT (The Effects of Irbesartan on Morbidity and Mortality in Hypertensive Patients with Type II Diabetes and Diabetic Nephropathy) study. Dr. Pelayo noted that some tables in the briefing document group number and events in a cumulative manner that seems to be inconsistent with the analysis plan described in the study protocol. Dr. Lipicky pointed out for example, that the Kaplan-Meier graph on page 81 of the draft briefing book is at odds with the table immediately beneath it. He encouraged the firm to talk with Dr. Pelayo to iron out the number differences prior to the Advisory Committee meeting as disagreements over items such as these are very distracting and time consuming when brought up at the Advisory Committee meeting.

  Bristol-Myers Squibb said it would contact Dr. Pelayo to find out which tables have numbers that are in question and try to resolve them as promptly as possible. They asked that if they were unable to bridge the difference in numbers what would be their next option. Dr. Lipicky advised them to contact him directly for assistance. If the Division and the firm were still unable to agree on a table or other numbers then the Advisory Committee could argue the numbers in question. The firm suggested that if agreement could not be reached with the Division on certain numbers, they could list both sets (theirs and the Divisions) of numbers in the briefing book with an explanation as to why there was a difference between the numbers. The Division agreed and said it is possible that definitional differences could explain the disparity.

- Referring to the primary composite endpoint of death, ESRD, and doubling of serum creatinine, Dr. Lipicky said that there appears to be no difference in event rates between the endpoints of death and ESRD. Therefore it appears that the effect of irbesartan on the doubling of serum creatinine was driving the apparent positive result of the study. However, the Division will argue before the Advisory Committee that the endpoint of doubling of serum creatinine should be viewed as a surrogate endpoint. He noted that he has reviewed reprints of published clinical trial results in diabetic nephropathy and has calculated a delta of about 60 events between the control and treated groups in the studies. This number suggests that doubling of serum creatinine is not a valid clinical endpoint.

- The p value of 0.023 obtained for the IDNT study is not persuasive enough by itself to support approval. The firm will have to make an argument before the Advisory Committee that there is other evidence to show irbesartan mechanistically has a positive effect on diabetic nephropathy.

<u>Bristol-Myers/Sanofi-Synthelabo Questions</u>

The firm said they were planning on a presentation before the Advisory Committee of between 45 and 60 minutes and asked if that was acceptable. Dr. Lipicky said it was acceptable.

The firm said they would have nephrologists from the academic community, including investigators of the studies at the Advisory Committee meeting and asked if the Division had invited any nephrologists

to be members of the Committee. Dr. Throckmorton said the Division has invited Dr. Brem and Dr. Kopp to be members of the Committee. Dr. Lipicky added that the firm's invited nephrologists should make a presentation on the benefits of reducing protein in the urine, provided the firm stays within the 45-60 minute timeframe.

Bristol-Myers Squibb said, in response to a query from the Division, they had gathered published articles on diabetic nephropathy for the Division's review. Dr. Throckmorton quickly scanned the articles and said some would be included in the Division's review package to Advisors and Consultants. Other papers appeared to be editorial in nature and would not be included. He invited the firm to look for other published clinical study reports and submit them to the Division as soon as possible.

Summary of Main Action Items

- The firm and the Division will try to iron out differences in numbers (e.g., event rates) between those in the firm's briefing book and the Division's reviews.
- The Division will argue before the Advisory Committee that the p value achieved in the IDNT is not significant enough for one study to support approval for this indication.
- The Division will argue that the endpoint of doubling of serum creatinine drove the positive result seen for the composite endpoint of death, ESRD, and doubling of serum creatinine chosen as the primary endpoint for the IDNT study. We will point out, based on literature and other data, that doubling of serum creatinine should, in fact, be considered a surrogate endpoint.
- The Division will include in its review package to the Advisory Committee published clinical study reports involving diabetic nephropathy. The sponsor was encouraged to send any additional published study reports to the Division that it thinks are relevant.

Minutes Preparation: /S/

Edward Fromm

Concurrence, Chair: /S/

Raymond J. Lipicky, M.D.

drafted/ef: 12-03-01/12-04-01

Rd: JLawrence-12/03/01
JHung-12/03/01
JPelayo-12/03/01
NStockbridge-12/04/01
DThrockmorton-12/04/01

Filing Summary/Meeting Minutes

Date of filing meeting: August 30, 2001

Application: NDA 20-757/SE1-021
Avapro (irbesartan) Tablets
75, 150 and 300 mg

Indication: Treatment of hypertensive patients with type 2 diabetic renal disease

Applicant: Sanofi-Synthelabo
Co-developer and Agent: Bristol-Myers Squibb

Application Date: August 3, 2001

Receipt Date: August 3, 2001

User Fee Goal Date: February 3, 2002 (Priority Review)

Participants:

Douglas Throckmorton, M.D., HFD-110, Deputy Division Director
Norman Stockbridge, M.D., Ph.D., HFD-110, Medical Team Leader
John Lawrence, Ph.D., HFD-110, Statistician
Earl Butler, Ph.D., HFD-45, Pharmacologist
Edward Fromm, HFD-110, Project Manager

Additional Application Information

Therapeutic Classification: SE1 (new indication)

User Fee Paid? Yes (User Fee ID#4173)

Format of Submission? This supplemental NDA was submitted electronically (available through the Electronic Document Room-EDR).

Patent Information Included? Yes

Exclusivity Requested? Yes (3 years)

Debarment Statement Included? Yes

Pediatric Rule Addressed? Yes-The company has requested a waiver for conducting pediatric studies for this indication.

Previous Meetings? July 26, 1995

Deficiencies? Based on an initial look at the submission, no deficiencies were identified.

Assigned Reviewers:

Medical:	Has not been determined
Statistical:	John Lawrence, Ph.D.
Biopharmaceutics:	Angelica Dorantes, Ph.D
Chemistry:	N/A
Pharmacology:	N/A
Microbiologist:	N/A
DSI:	Antoine El-Hage, M.D.

Background

Sanofi-Synthelabo has submitted this efficacy supplement for irbesartan for the treatment of hypertensive patients with type 2 diabetic renal disease. Irbesartan, an angiotensin II receptor blocker, is currently indicated for the treatment of hypertension. Studies for irbesartan for type 2 diabetic renal disease were conducted under IND [redacted]

The application for efficacy and safety is supported by 5 clinical trials, with study CV 131-048 (IDNT, Irbesartan Diabetic Nephropaty Trial) and study EFC 2481 (IRMA 2, Irbesartan in the study of Microalbuminaria in Hypertensive Patients with Type 2 Diabetes Mellitus) being the main supporting trials.

Study CV 131-048 (IDNT), is a study examining irbesartan's effect on morbidity and mortality in hypertensive subjects with type 2 diabetes and diabetic nephropathy. The long-term effects of 300 mg irbesartan were compared to placebo or the calcium channel blocker, amlodipine.

Study EFC 2481 (IRMA 2) looked at the effects of 150 and 300 mg irbesartan versus placebo on the progression to overt proteinuria in type 2 diabetics and microalbuminuria.

The applicant believes that the pivotal trials show that irbesartan provides benefits at both early and late stage diabetic renal disease by delaying the onset of overt proteinuria and delaying the progressive loss of renal function leading to the development of ESRD (end stage renal disease). They claim this renal protective effect is independent of blood pressure lowering.

Meeting

Biopharmaceutics

Reviewer: Angelica Dorantes, Ph.D.

Dr. Dorantes was unable to attend the meeting but indicated afterward that there were no biopharmaceutics issues to review in the application.

Statistical:

Dr. Lawrence identified no filing concerns and said his review could be ready by mid-November if the Division decides to present the application before the December 2001 Cardio-Renal Advisory Committee Meeting.

Medical:

Reviewer: Not determined

Dr. Stockbridge said the medical officer for this application has not been determined but indicated that Dr. Pelayo would be the first choice for doing the review. If he were unable to do it, Dr. Karkowsky would likely do the review.

Dr. Stockbridge said he had briefly looked at the submission and has identified the IDNT and IRMA 2 trials as the main supporting ones of efficacy. The IDNT trial studied approximately 1500 patients and was compared to placebo and amlodipine (3 arms). It appeared, at least nominally, to have a beneficial effect on time to first event of a composite endpoint (all-cause death, ESDR (End Stage Renal Disease and doubling of serum creatinine). Dr. Stockbridge, however, noted two potential problems with the study:

- A fair number of patient withdrawals in the study
- It appears that the drug was not beneficial when studied at North American centers but had a robust effect when studied at foreign sites.

The IRMA 2 trial measured the effects of 150 and 300 mg of irbesartan in reducing the time to progression of frank albuminuria. Dr. Stockbridge said the data might yield information on a key outcome, the reduction of protein excretion 4 weeks after cessation of treatment.

Secondary Medical:

Dr. Throckmorton said a decision on who would do the secondary medical review would be made after the primary medical reviewer has been assigned.

DSI Audits:

Dr. Stockbridge indicated that he would contact DSI with a list of possible study sites to inspect.

Conclusion

The application will be filed. The supplement may be presented at the December 2001 or January 2002 Cardio-Renal Advisory Committee Meeting.

Minutes Preparation: /S/
Edward Fromm

Concurrence Chair: /S/ 9.12.01
Douglas Throckmorton, M.D.

dr: ef/8-31-01

Rd: JLawrence-8/31/01
NStockbridge-8/31/01