CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20-758/S-003

MEDICAL REVIEW(S)

JUN 2 4 1998

DIVISION OF CARDIO-RENAL DRUG PRODUCTS

Clinical Review

NDA: 20-758

Sponsor: Bristol-Myers Squibb PRI

Submission: SCF-003 (June 5, 1998): proposed label for Avapro HCT (irbesartan/hydrochlorothizide).

Review date: June 24, 1998

Reviewer: N. Stockbridge, M.D., Ph.D., HFD-110

Summary: The submission is a response to an approvable letter dated April 24, 1998. Based upon a teleconference with the reviewer, the sponsor has submitted revisions to the DOSAGE AND ADMINISTRATION section. Upon discussion with the Division Director, this review contains newly revised wording.

Distribution: NDA 20-758

HFD-110/Project Manager

HFD-110/Stockbridge

1 Dosage and Administration

The sponsor's proposed language is as follows:

> **Dose Titration by Clinical Effect**
>
> A patient whose blood pressure is inadequately controlled with irbesartan monotherapy or hydrochlorothiazide may be switched to Avapro HCT (irbesartan 150 mg/ HCTZ 12.5 mg or irbesartan 300 mg/HCTZ 12.5 mg) once daily.
>
> Dosage should be individualized for patient management and guided by clinical response. Based on clinical trials, a dose of 300 mg irbesartan monotherapy once daily can be expected to reduce systolic/diastolic blood pressure by 8-12/5-8 mmHg (placebo subtracted). By comparison, patients receiving Avapro HCT once daily can be expected to reduce systolic/diastolic blood pressure (placebo subtracted) by 13-15/7-9 mmHg with a dose of irbesartan 150 mg/hydrochlorothizide 12.5 mg and by 14/9-12 mmHg with irbesartan 300 mg/hydrochlorothiazide 12.5 mg. A dose of irbesartan 300 mg/hydrochlorothiazide 25 mg (two 150 mg/12.5 mg tablets) can be expected to reduce systolic/diastolic blood pressure by 19-21/11-12 mmHg (placebo-subtracted).
>
> The maximal antihypertensive effect of Avapro HCT is attained within 2-4 weeks. There are no controlled studies evaluating doses of irbesartan greater than 300 mg in combination with 25 mg hydrochlorothiazide.

The current proposal of the Division is to retain the proposed label's option to start at a dose greater than the smallest combination, but to eliminate the quantitative information, since, at best, it represents an average response and these data are represented in the Clinical Trials section.

The Division's new proposal is to replace all three paragraphs as follows:

> **Dose Titration by Clinical Effect**
>
> A patient whose blood pressure is inadequately controlled by irbesartan or hydrochlorothiazide alone may be switched to once-daily Avapro HCT. Recommended doses of Avapro HCT, in order of increasing mean effect, are (irbesartan/HCTZ) 150-mg/12.5-mg, 300/12.5, and 300/25 (two 150/12.5 tablets). The largest incremental effect will likely be in the transition from monotherapy to 150/12.5. It takes 2 to 4 weeks for the blood pressure to stabilize after a change in the dose of irbesartan or Avapro HCT.

2 How Supplied

The Division proposes that the text for the HOW SUPPLIED section be replaced as follows:

Avapro HCT tablets are peach, biconvex, and oval, with a heart on the obverse and 2775 or 2776 on the reverse, supplied as follows:

Irbesartan (mg)	HCTZ (mg)	NDC0087-xxxx-xx for unit of use			
		Bottle of			Blister of
		30	90	500	100
150	12.5	2775-31	2775-32	2775-15	2775-35
300	12.5	2776-31	2776-32	2776-15	2776-35

APR 10 1998

DIVISION OF CARDIO-RENAL DRUG PRODUCTS
MEDICAL OFFICER'S REVIEW

NDA: 20-758 (irbesartan-HCTZ)

Sponsor: Sanofi/Bristol-Myers Squibb.

Submission: S-003: Addition of new dosage strength (300/12.5).

Review date: 10 April 1998.

Reviewer: N. Stockbridge, M.D., Ph.D.

1. The biopharmaceutical review (dated 27 March 1998) found no problem with the proposed new tablet strength.

2. The chemistry review (dated 10 April 1998) found no problem with the proposed new tablet strength.

3. No new clinical data were supplied.

4. The sponsor proposes the following change in the "Dose titration by clinical effect" paragraph of the label:

Old:

"A patient whose blood pressure is inadequately controlled with irbesartan monotherapy (see above) or hydrochlorothiazide may be switched to TRADENAME (irbesartan 150 mg/hydrochlorothiazide 12.5 mg) once daily. The combination irbesartan 150 mg/hydrochlorothiazide 12.5 mg may produce antihypertensive effects somewhat greater than those of either irbesartan 300 mg alone or hydrochlorothiazide 25 mg alone. If blood pressure remains uncontrolled after about 2-4 weeks of therapy, the dose may be increased to two tablets once daily."

New:

"A patient whose blood pressure is inadequately controlled with irbesartan monotherapy (see above) or hydrochlorothiazide may be switched to combination therapy with TRADENAME. Dosage must be guided by clinical response. Controlled clinical trials showed that the addition of 12.5 mg hydrochlorothiazide to 150 mg or 300 mg of irbesartan will typically be associated with additional reduction in seated diastolic pressure at 24 hours after dosing (see CLINICAL PHARMACOLOGY: Clinical Studies)."

Thus the proposed language does not provide appropriate counsel that the next step after maximum monotherapy is the LOWEST combination dose (as this will still produce greater antihypertensive effects than monotherapy), nor does it provide counsel regarding an appropriate titration interval.

The medical officer recommends:

"A patient whose blood pressure is inadequately controlled with irbesartan monotherapy (see above) or hydrochlorothiazide may be switched to combination therapy with TRADENAME. Dosage must be guided by clinical response. Controlled clinical trials showed that the combination of irbesartan 150 mg and hydrochlorothiazide 12.5 mg produces antihypertensive effects greater than irbesartan 300 mg alone or HCTZ 25 mg alone; this, then, is the appropriate next titration step. If blood pressure remains uncontrolled after about 2-4 weeks of therapy, the dose may be increased to irbesartan 300 mg/HCTZ 12.5 mg and then to irbesartan 300 mg/HCTZ 25 mg (two 150/12.5 tablets) once daily."

N. Stockbridge, M.D., Ph.D.

cc: NDA 20-758
HFD-110
HFD-110/CSO
HFD-110/Stockbridge

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20-758/S-003

CHEMISTRY REVIEW(S)

AUG 10 1998

CHEMIST'S REVIEW	1. ORGANIZATION HFD-110	2. NDA Number 20-758
3. Name and Address of Applicant (City & State) Sanofi Pharmaceuticals, Inc. 90 Park Avenue New York, NY 10016		4. Supplement(s) Number(s) Date(s) SCF-003 12/22/97
5. Drug Name AVAPRO HCT	6. Nonproprietary Name Irbesartan Hydrochlorothiazide	8. Amendments & Other (reports, etc) - Dates AF - 7/31/98
7. Supplement Provides For: A new strength of irbesartan 300 mg/hydrochlorothiazide 12.5 mg tablets.		
9. Pharmacological Category Angiotensin II receptor antagonist/diuretic	10. How Dispensed [X] Rx [ ] OTC	11. Related IND(s)/ NDA(s)/DMF(s)
12. Dosage Form(s) Tablets	13. Potency(ies) 75/12.5, 150/12.5 & 300/12.5 mg	
14. Chemical Name and Structure 2-Butyl-3-[[2'-(1*H*-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1,3-diazaspiro[4,4]non-1-en-4-one and 6-Chloro-3,4-dihydro-2*H*-1,2,4-benzo-thiadiazine-7-sulfonamide 1,1-dioxide		15. Records/Reports Current [ ] Yes [ ] No Reviewed [ ] Yes [ ] No

16. Comments:

FPL is submitted in this amendment to S-003.

Insert - 1030329 Issued July 1998 - satisfactory for DESCRIPTION and HOW SUPPLIED sections.

These revisions included Dr. Stockbridge's comments relayed on July 28, 1998 by Ms. Bongiovanni, addition of "and" between "300/12.5 mg," and "300/25 mg (two 150/12.5 mg tablets)" in the section "Dose Titration by Clinical Effect"; and replacement of "and" with "or" between "2775" and "2776" in the "HOW SUPPLIED" section.

The designation of "Rx only" at the top of the package insert has been deleted.

17. Conclusions and Recommendations:

Satisfactory for DESCRIPTION and HOW SUPPLIED sections.

18. REVIEWER

Name	Signature	Date Completed
Danute G. Cunningham	Danute G. Cunningham	August 6, 1998

Distribution: [X] Original Jacket [ ] Reviewer [ ] Division File [ ] CSO

20758S03.AM3

K. Swinyard 8-10-98

JUL 29 1998

CHEMIST'S REVIEW	1. ORGANIZATION HFD-110	2. NDA Number 20-758
3. Name and Address of Applicant (City & State) Sanofi Pharmaceuticals, Inc. 90 Park Avenue New York, NY 10016.		4. Supplement(s) Number(s) Date(s) SCF-003 7/16/98 (AL)
5. Drug Name AVAPRO HCT	6. Nonproprietary Name Irbesartan Hydrochlorothiazide	8. Amendments & Other (reports, etc) - Dates
7. Supplement Provides For: Labeling revision.		
9. Pharmacological Category Angiotensin II receptor antagonist/diuretic	10. How Dispensed [X] Rx [ ] OTC	11. Related IND(s)/ NDA(s)/DMF(s)
12. Dosage Form(s) Tablets	13. Potency(ies) 75/12.5, 150/12.5 & 300/12.5 mg	
14. Chemical Name and Structure 2-Butyl-3-[[2'-(1*H*-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1,3-diazaspiro[4,4]non-1-en-4-one and 6-Chloro-3,4-dihydro-2*H*-1,2,4-benzo-thiadiazine-7-sulfonamide 1,1-dioxide		15. Records/Reports Current [ ] Yes [ ] No Reviewed [ ] Yes [ ] No

16. Comments:

Substitute AVAPRO HCT for TRADENAME. DESCRIPTION section - satisfactory. HOW SUPPLIED section - satisfactory, although did not use the suggested phrase.

17. Conclusions and Recommendations:

DESCRIPTION and HOW SUPPLIED sections - satisfactory

18. REVIEWER

Name	Signature	Date Completed
Danute G. Cunningham	Danute G. Cunningham	July 21, 1998

Distribution: [X] Original Jacket [ ] Reviewer [ ] Division File [ ] CSO

20758S03.AM2

K. Srinivasachar 7-27-98

APR 10 1998

CHEMIST'S REVIEW	1. ORGANIZATION HFD-110	2. NDA Number 20-758
3. Name and Address of Applicant (City & State) Sanofi Pharmaceuticals, Inc. 90 Park Avenue New York, NY 10016		4. Supplement(s) Number(s) Date(s) SCF-003 12/22/97
5. Drug Name Irbesartan/Hydrochlo-thiazide	6. Nonproprietary Name Irbesartan Hydrochlorothiazide	8. Amendments & Other (reports, etc) - Dates
7. Supplement Provides For: New strength of Irbesartan 300 mg /Hydrochlorothiazide 12.5 mg tablets. In addition, change in dissolution specifications is proposed.		
9. Pharmacological Category Angiotensin II receptor antagonist/diuretic	10. How Dispensed ☒ Rx ☐ OTC	11. Related IND(s)/ NDA(s)/DMF(s)
12. Dosage Form(s) Tablets	13. Potency(ies) 75/12.5 mg, 150/12.5 mg	
14. Chemical Name and Structure		15. Records/Reports Current ☐ Yes ☐ No Reviewed ☐ Yes ☐ No

16. Comments:

Bioequivalence was reviewed by Biopharmaceutics on 3/27/98.

Irbesartan/Hydrochlorothiazide Tablets, 75/12.5 mg and 150/12.5 mg, were approved on September 30, 1997.

Details on formulation, manufacturing, packaging and quality control of a new strength of irbesartan/hydrochlorothiazide (300/12.5 mg) tablets are included on the following pages.

New dissolution specifications are submitted.

Cont'd

17. Conclusions and Recommendations:

EER requested on 1/9/98. Acceptable on 4/9/98.

Approved.

18. REVIEWER

Name	Signature	Date Completed
Danute G. Cunningham	Danute G. Cunningham	April 10, 1998

Distribution: ☒ Original Jacket ☐ Reviewer ☐ Division File ☐ CSO

20758S03.SUP

PM Sheet 4/10/98

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20-758/S-003

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

MAR 27 1998

CLINICAL PHARMACOLOGY/BIOPHARMACEUTICS REVIEW

NDA 20-758 (SCF 003)
DRUG: irbesartan/HCTZ 75/12.5, 150/12.5, 300/12.5 mg tablets
SPONSOR: Bristol-Myers Squibb
TYPE OF SUBMISSION: In-vitro dissolution specs, labeling changes,
DATE OF SUBMISSION: 12/22/97
REVIEWERS: Ameeta Parekh, Ph.D.

BACKGROUND:

Irbesartan/HCTZ combination tablet is approved as an antihypertensive when patients have failed to achieve the desired response with monotherapy. A maximum of 2 tablets of 150/12.5 of irbesartan/HCTZ for once daily administration for hypertension are currently approved. While the original NDA approval was for 75/12.5 and 150/12.5 mg tablet strengths, a supplemental application with an additional combination strength, 300/12.5 mg, was reviewed by the Division in 1/98. Bioequivalence was established between 300/12.5 combination tablet and coadministered 300 mg capsule and 12.5 mg tablet of irbesartan and HCTZ respectively (clinically tested).

Based on the in-vitro dissolution data provided on 75/12.5 and 150/12.5 mg combination tablets in the original NDA, a specification of for irbesartan and for HCTZ was recommended. The method used was the as dissolution medium. In the current supplement, in addition to the dissolution data for 300/12.5 mg tablets, dissolution on stability lots for all strengths has also been provided. Based on this additional in-vitro dissolution, the sponsor is proposing a specification of for irbesartan and HCTZ for all strengths. Additionally, labeling changes have been submitted for review, which address the addition of a new combination strength to this NDA.

RESULTS AND DISCUSSION:

The in-vitro dissolution data provided on all proposed strengths of combination tablets address the sponsor's concern that several stability lots fail at with irbesartan specification of Based on this data (attached), the sponsor is requesting a specification of for both irbesartan and HCTZ. There would be some lots that would still fail the dissolution with the specification, and dissolution will need to be conducted for these lots, however if the specification is set at many more lots will need the testing and the sponsor is requesting the Agency to help with minimizing this. It is noted that in the original application, dissolution data was provided on lots N95094, N95095, 8MLJ142 and 8MLJ346 for 150/12.5 mg combination tablet. At lots N95095 and 8MLJ346 dissolution ranged respectively while at these were higher than These lots were identical formulation as the lot tested in bio-study and were 14 and 10 days old respectively at the time of dissolution testing. Based on this and the additional data provided on the stability

of all combination strengths, the rapid solubility of the tablet in vivo (based on plasma profiles from fasted and fed studies in the NDA), specifying 30 minutes for both irbesartan and HCTZ for in-vitro testing should not introduce therapeutically inadequate product on the market. The requested specification by the sponsor is acceptable.

RECOMMENDATION:

The Office of Clinical Pharmacology and Biopharmaceutics has reviewed the supplemental application requesting for dissolution specification to be

for both irbesartan and HCTZ

The amended labeling to include the new combination strength has also been reviewed . The proposed specifications and the labeling changes are acceptable.

Ameeta Parekh 3/27/98

Ameeta Parekh, Ph.D.
Division of Pharmaceutical Evaluation I

FT Initialed by Patrick Marroum, Ph.D. 3/27/1998.

cc: NDA 20-758, HFD-110 (Bongiovanni), HFD-860 (Parekh), CDR (Attn: Barbara Murphy)

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20-758/S-003

ADMINISTRATIVE DOCUMENTS

JUL 14 1998

RHPM Review of Labeling

NDA:	20-758/SLR-003 Avapro HCT (irbesartan/hydrochlorothiazide) 75/12.5 and 150/12.5 mg Tablets
Date of submission:	June 5, 1998
Date of receipt:	June 8, 1998
Applicant:	Bristol-Myers Squibb, agent for Sanofi Pharmaceuticals

Background: Bristol-Myers Squibb/Sanofi submitted a supplement on December 22, 1997 to NDA 20-758 that provided for a new tablet strength, 300 mg irbesartan/12.5 mg hydrochlorothiazide, with draft labeling revised under DESCRIPTION, DOSING AND ADMINISTRATION, Dose Titration by Clinical Effect, and HOW SUPPLIED, and a new dissolution specification for irbesartan of for the 75/12.5 and 150/12.5 mg tablets.

We issued an approvable letter dated April 24, 1998, asking for final printed labeling revised as indicated in the letter.

Norman Stockbridge, M.D. spoke to Bristol-Myers Squibb by telephone on May 8, 1998, and the group discussed possible alternative wording for the DOSING AND ADMINISTRATION section of the labeling. BMS/Sanofi submitted proposed revisions to the DOSAGE AND ADMINISTRATION section of the labeling and a new revision to the CLINICAL PHARMACOLOGY, Clinical Studies subsection in a submission dated June 5, 1998.

Dr. Stockbridge consulted with Dr. Lipicky and, in his review dated June 24, 1998, recommended the following wording for the DOSAGE AND ADMINISTRATION and HOW SUPPLIED sections: he agreed with the submitted revisions to the DESCRIPTION and CLINICAL PHARMACOLOGY sections.

DOSING AND ADMINISTRATION, Dose Titration by Clinical Effect:

> A patient whose blood pressure is inadequately controlled by irbesartan or hydrochlorothiazide alone may be switched to once-daily Avapro HCT. Recommended doses of Avapro HCT, in order of increasing mean effect, are (irbesartan/hydrochlorothiazide) 150 mg/12.5 mg, 300/12.5 and 300/25 (two 150/12.5 tablets). The largest incremental effect will likely be in the transition from monotherapy to 150/12.5. It takes 2 to 4 weeks for the blood pressure to stabilize after a change in the dose of Avapro HCT.

HOW SUPPLIED

Avapro HCT tablets are peach, biconvex, and oval, with a heart on the obverse and 2775 or 2776 on the reverse, supplied as follows:

Irbesartan (mg)	HCTZ (mg)	NDC 0087-xxxx-xx for unit of use			
		Bottle of			Blister of
		30	90	500	100
150	12.5	2775-31	2775-32	2775-15	2775-35
300	12.5	2776-31	2776-32	2776-15	2776-35

Review: The submitted draft labeling has been revised as noted above.

Recommendation: I will prepare an approvable letter for Dr. Lipicky's signature with the revisions to the DOSAGE AND ADMINISTRATION and HOW SUPPLIED sections as noted above. This supplement falls under 21 CFR 314.70 (b), Supplements requiring FDA approval before the change is made.

Kathleen F. Bongiovanni

7-13-98

cc: 20-758/S-003
HFD-110
HFD-110/KBongiovanni
HFD-110/SBenton
HF-2/MedWatch
kb/7/13/98.

AUG 3 1 1998

RHPM Review of Labeling

NDA:	20-758/SLR-003 Avapro HCT (irbesartan/hydrochlorothiazide) 75/12.5 and 150/12.5 mg Tablets
Date of submission:	July 31, 1998
Date of receipt:	August 3, 1998
Applicant:	Bristol-Myers Squibb, agent for Sanofi Pharmaceuticals

Background: Bristol-Myers Squibb/Sanofi submitted a supplement dated December 22, 1997 to NDA 20-758 that provided for a new tablet strength, 300 mg irbesartan/12.5 mg hydrochlorothiazide, with draft labeling revised under DESCRIPTION, DOSING AND ADMINISTRATION, Dose Titration by Clinical Effect, and HOW SUPPLIED, and a new dissolution specification for irbesartan of Q=80% in 30 minutes for the 75/12.5 and 150/12.5 mg tablets.

We issued an approvable letter dated April 24, 1998, asking for final printed labeling revised as indicated in the letter; the firm responded with a submission dated June 5, 1998 with proposed labeling revisions. We issued a second approvable letter on July 14, 1998, asking for final printed labeling revised as indicated in the letter. The firm sent in revised draft labeling in a submission dated July 16, 1998. Drs. Lipicky and Stockbridge agreed that the labeling was acceptable, with two minor changes: the addition of the word "and" after 300/12.5 in the proposed revision under DOSAGE AND ADMINISTRATION, and the replacement of "and" with "or" under HOW SUPPLIED, between 2775 and 2776. I communicated this to Ms. Grace Heckman of BMS in a telephone conversation on July 28, 1998 and asked for final printed labeling. The firm has responded with final printed labeling in a submission dated July 31, 1998.

Review: The submitted final printed labeling has been revised as follows:

The designation "Rx only" at the top of the package insert has been deleted.

DESCRIPTION: In the fourth paragraph, "Avapro HCT is available for oral administration in tablets containing 150 mg of irbesartan and" has been replaced with "Avapro HCT is available for oral administration in tablets containing 150 mg or 300 mg of irbesartan combined with."

CLINICAL PHARMACOLOGY, Clinical Studies, Irbesartan-Hydrochlorothiazide: In the second paragraph, the third sentence has been revised to read, "Once-daily dosing with 150 mg irbesartan and 12.5 mg of hydrochlorothiazide, 300 mg irbesartan and 12.5 mg of hydrochlorothiazide, or irbesartan 300 mg and hydrochlorothiazide 25 mg produced mean placebo-adjusted blood pressure reductions at trough (24 hours post-dosing) of about 13-15/7-9, 14/9-12, and 19-21/11-12 mmHg, respectively."

DOSING AND ADMINISTRATION, Dose Titration by Clinical Effect: The two paragraphs in this subsection have been replaced with the following: A patient whose blood pressure is inadequately controlled by irbesartan or hydrochlorothiazide alone may be switched to once daily Avapro HCT. Recommended doses of Avapro HCT, in order of increasing mean effect, are (irbesartan/hydrochlorothiazide) 150/12.5, 300/12.5, and 300/25 (two 150/12.5 tablets). The largest incremental effect will likely be in the transition from monotherapy to 150/12.5 (See CLINICAL PHARMACOLOGY, Clinical Studies). It takes 2 to 4 weeks for the blood pressure to stabilize after a change in the dose of Avapro HCT.

HOW SUPPLIED: The information above the Storage subsection has been replaced by the following:

Avapro HCT (irbesartan-hydrochlorothiazide) Tablets are peach, biconvex, and oval with a heart debossed on one side and 2775 or 2776 on the reverse, supplied as follows:

Irbesartan (mg)	HCTZ (mg)	NDC 0087-xxxx-xx for unit of use			
		Bottle of			Blister of
		30	90	500	100
150	12.5	2775-31	2775-32	2775-15	2775-35
300	12.5	2776-31	2776-32	2776-15	2776-35

Recommendation: I will prepare an approval letter for Dr. Lipicky's signature. This supplement falls under 21 CFR 314.70 (b), Supplements requiring FDA approval before the change is made.

Kathleen F. Bongiovanni

8-25-98

cc: 20-758/S-003
HFD-110
HFD-110/KBongiovanni
HFD-110/SBenton
HF-2/MedWatch
kb/8/12/98, 8/25/98.