CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER(S)
NDA 19-778/S-034

Trade Name: Prinzide Tablets

Generic Name(s): (lisinopril/hydrochlorothiazide)

Sponsor: Merck & Co., Inc.

Approval Date: July 2, 2002

Indication: Provides for an alternate manufacturing, testing, and packaging site

CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

NDA 19-778/S-034

Approval Letter

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 19-778/S-034

Merck & Co., Inc.
Attention: Michael C. Elia, Ph.D.
P.O. Box 4, BLA-20
Sumneytown Pike
West Point, PA 19486

Dear Dr. Elia:

Please refer to your supplemental new drug application dated December 31, 2001, received January 2, 2002, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Prinzide (lisinopril/hydrochlorothiazide) Tablets 10/12.5 mg, 20/12.5 mg and 20/25 mg.

This "Changes Being Effected in 30 days" supplemental new drug application provides for Merck Frosst in Kirkland, Quebec as a alternate manufacturing/testing/packaging site for the 10/12.5 mg, 20/12.5 mg and 20/25 mg strengths of PRINZIDE™ Tablets.

We have completed the review of this supplemental application, and it is approved.

Please submit final printed labeling (FPL) for PRINZIDE™ identical to the submitted draft labeling in your next annual report.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, call Ms. Sandra L. Birdsong, Regulatory Health Project Manager, at (301) 594-5312.

Sincerely,

/S/

{See appended electronic signature page}

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

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/s/

Kasturi Srinivasachar
7/2/02 09:54:31 AM

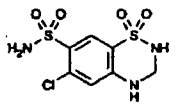
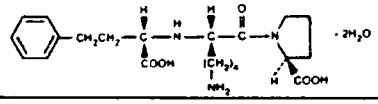
CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

NDA 19-778/S-034

Chemistry Review(s)

CHEMIST'S REVIEW	1. ORGANIZATION HFD-110/810	2. NDA Number 19-778
3. Name and Address of Applicant (City & State) Merck & Co. Inc. P.O. Box 4, BLA-20 West Point PA 19486		4. Supplement(s) Number(s) Date(s) S-034 12/31/01
5. Drug Name Prinzide	6. Nonproprietary Name lisinopril and hydrochlorothiazide	Amendments - Dates
8. Supplement BasicallyProvides For the addition of Merck Frosst, Kirkland, Quebec, Canada as an alternate manufacturing/testing/packaging site for Prinzide Tablets (10/12.5 mg, 20/12.5 mg and 20/25 mg)		
9. Pharmacological Category Angiotensin converting enzyme inhibitor and diuretic (HCT)	10. How Dispensed Rx	Related NDAs: NDA 19-558/S-041
12. Dosage Form(s) TCM	13. Potencies 10/12.5, 20/12.5 & 20/25mg	
14. Chemical Name and Structure: 2H-1,2,4-Benzothiadiazine-7-sulfonamide, 6-chloro-3,4-dihydro-, 1,1-dioxide (HCT):  PRINIVIL® (Lisinopril), a synthetic peptide derivative, is an oral long-acting angiotensin converting enzyme inhibitor. Lisinopril is chemically described as (S)-1-[N²-(1-carboxy-3 phenylpropyl)-L-lysyl]-L-proline dihydrate. Its empirical formula is $C_{21}H_{31}N_3O_5 \cdot 2H_2O$ and its structural formula is: 		15. Records/Reports Current Yes No Reviewed Yes No

Comments: This is a CBE-30 submission. that relates to a similar submission for NDA 19-558 /S-041 for which certain common evaluative rationales are documented (e.g., rationale for acceptance of the changes in the labeling involved).The acceptance of the environmental request for a waiver is also likewise applicable for this related supplement The EES report is satisfactory (see attached scan).

17. Conclusions and Recommendations:

Send approval letter and state/confirm that the revised labeling (FPL) should be submitted in the annual report as indicated in the application.

18. REVIEWER

Name	Signature	Date Completed
Stuart Zimmerman, Ph.D.	S	6/27/02

: File Name: AAA W(6-27-02)S034(12-31-02) NDA19778 AP DATE: 02/16/89

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pages of trade

secret and/or

confidential

commercial

information

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/s/

Stuart Zimmerman
7/1/02 11:27:19 AM
CHEMIST

Kasturi Srinivasachar
7/1/02 12:11:09 PM
CHEMIST

CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

NDA 19-778/S-034

Clinical Pharmacology and Biopharmaceutics Review

CLINICAL PHARMACOLOGY and BIOPHARMACEUTICS REVIEW
Division of Pharmaceutical Evaluation I

NDA 19-778 **SUBMISSION DATE:** December 31, 2001
Supplement SCM-034

PRINZIDE® Tablets, 10/12.5, 20/12.5, 20/25 mg
(Lisinopril/HCTZ)
Merck & Co., Inc.
West Point, PA **REVIEWER:** Angelica Dorantes, Ph.D.

TYPE OF SUBMISSION: Supplement: Changes Being Effected in 30 Days/Alternate Manufacturing Site

BACKGROUND:

PRINZIDE® (lisinopril/HCTZ) 20/12.5 and 20/25 mg Tablets were approved on February 16, 1989 and PRINZIDE® (lisinopril/HCTZ) 10/12.5 mg Tablets were approved on November 18, 1993 for the treatment of hypertension.

SUBMISSION:

Supplement SCM-034 to NDA 19-778 dated December 31, 2001 provides CMC data to support an alternate manufacturing/testing/packing site. In this supplement the sponsor wishes to affiliate Merck Frosst located in Kirkland, Quebec, Canada as an additional manufacturing/testing/packing site for PRINZIDE® 10/12.5, 20/12.5 and 20/25 mg Tablets. It should be noted that the Merck Plant located in Wilson, NC, USA is the current manufacturing/testing/packing facility for PRINZIDE® 10/12.5, 20/12.5 and 20/25 mg Tablets.

ISSUES:

1. On January 29, 2002, the Office of clinical Pharmacology and Biopharmaceutics/Division of Pharmaceutical Evaluation 1 (OCPB/DPE1) was consulted by Dr. Stuart Zimmerman (Reviewing Chemist of DCRDP) regarding the dissolution data submitted to support the additional manufacturing/testing/packing site for PRINZIDE® 10/12.5, 20/12.5 and 20/25 mg Tablets.

   The following information was provided according to the SUPAC-IR Guidance: Site Change; Level 3; Case B.

   - Dissolution profile data in the compendial medium for PRINZIDE® 10/12.5, 20/12.5 and 20/25 mg Tablets manufactured at Merck Frosst, Canada and at MMD-Wilson, USA.
   - Similarity factors (f_2) data.

□

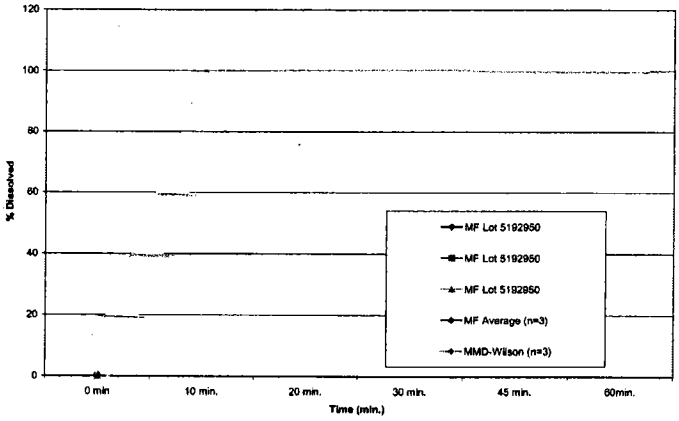
REVIWER COMMENTS:

1. It should be noted that the currently approved dissolution method and specifications are as follow:

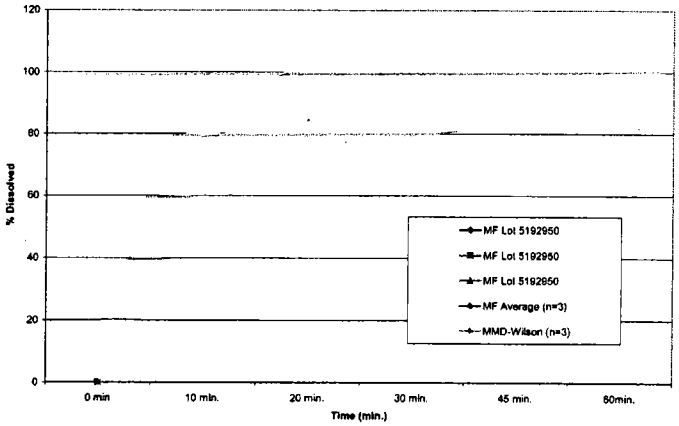
	PRINZIDE TABLETS
Apparatus	2 (Paddles)
Medium	0.1 N HCL
Medium Temperature	37°C
Dissolution Volume	900 ml
Rotation Speed (rpm)	50
Sampling Times	30 min and 45 min
Lisinopril Specification	Q = 80% in 30 minutes
HCTZ Specification	Q = [illegible] % in 45 minutes

2. The Dissolution profile comparisons for lisinopril and HCTZ for PRINIZIDE 10/12.5, 20/12.5, and 20/25 mg Tablets are presented below.

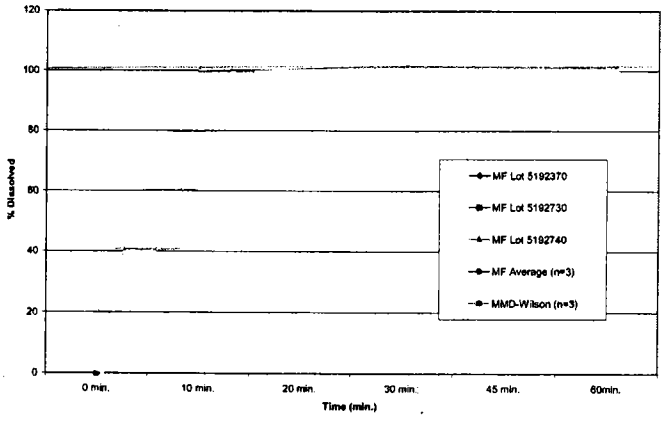
PRINZIDE 10/12.5 mg Merck Frosst (MF) vs. MMD-Wilson: Lisinopril



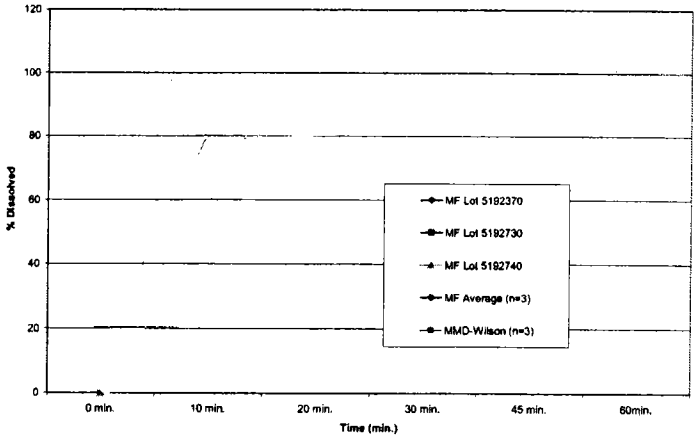
PRINZIDE 10/12.5 mg Merck Frosst (MF) vs. MMD-Wilson: Hydrochlorothiazide

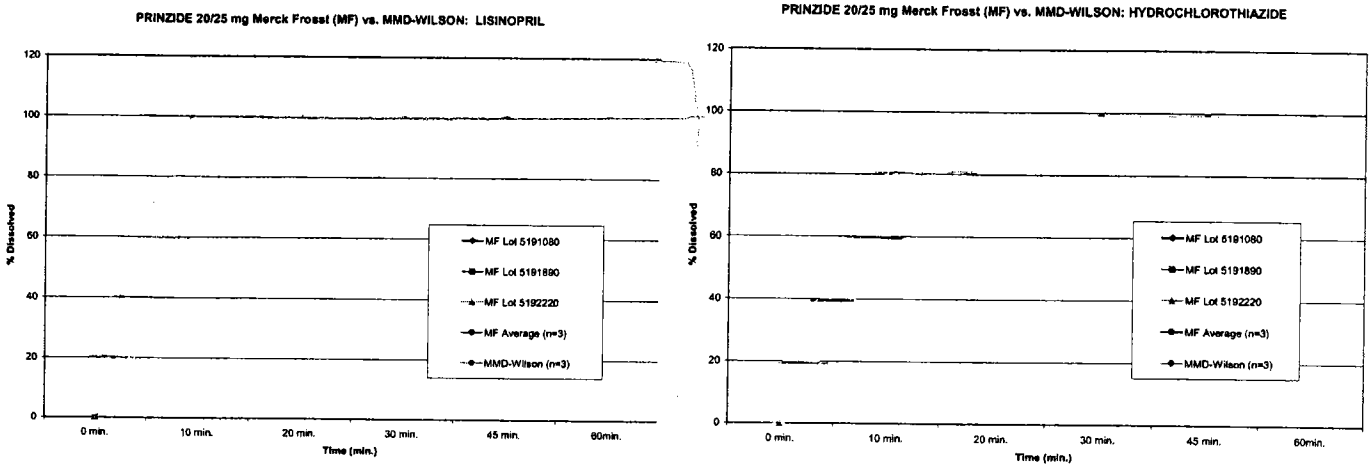


PRINZIDE 20/12.5 mg Merck Frosst (MF) vs. MMD-WILSON: LISINOPRIL



PRINZIDE 20/12.5 mg Merck Frosst (MF) vs. MMD-WILSON: HYDROCHLOROTHIAZIDE





3. Mean dissolution data and similarity factors (f_2) for PRINZIDE 10/12.5, 20/12.5, and 20/25 mg Tablets are presented in the next tables. It should be noted that the dissolution profiles of the lots manufactured at Merck-Frosst were compared with the mean profiles of three lots manufactured at Merck-Wilson using the equation that defines the similarity factor (f_2) as described in the SUPAC-IR Guidance.

	PRINZIDE 10/12.5 MG TABLETS (N=12)											
	Merck Frosst: Percent Dissolved of Lisinopril					Merck Wilson: Percent Dissolved of Lisinopril						
Lot No.	10 min	20 min	30 min	45 min	60 min	Lot No.	10 min	20 min	30 min	45 min	60 min	f_2
5192950	94.6	98.2	98.1	98.2	98.1	902177	91	96	98	100	99	84
5192960	98.1	100.1	100.2	100.3	100.4	902178	90	95	97	98	98	69
5192970	97.2	99.3	99.4	99.3	99.3	902179	93	96	98	98	98	74
						Mean	91.3	95.7	97.7	98.7	98.3	
	Merck Frosst: Percent of Hydrochlorohiazide					Merck Wilson: Percent of Hydrochlorohiazide						
Lot No.	10 min	20 min	30 min	45 min	60 min	Lot No.	10 min	20 min	30 min	45 min	60 min	f_2
5192950	82.4	98.8	99.7	99.5	99.5	902177	72	84	88	91	93	47
5192960	84.8	99.3	100.1	100.1	100.0	902178	82	90	92	93	94	46
5192970	82.3	97.1	97.9	98.5	98.7	902179	67	77	81	83	85	49
						Mean	73.7	83.7	87	89	90.7	

	PRINZIDE 20/12.5 MG TABLETS (N=12)										
	Merck Frosst: Percent Dissolved of Lisinopril					Merck Wilson: Percent Dissolved of Lisinopril					
Lot No.	10 min	20 min	30 min	45 min	60 min	Lot No.	10 min	20 min	30 min	45 min	60 min	f_2
5192375	94.0	99.3	99.5	99.3	99.2	901946	89	95	96	97	97	74
5192370	92.0	98.4	98.6	98.6	98.8	901947	96	98	98	98	98	81
5192740	96.1	99.9	99.8	99.9	99.9	901964	85	92	96	97	97	69
						Mean	**90.0**	**95.0**	**96.7**	**97.3**	**97.3**	
	Merck Frosst: Percent of Hydrochlorohiazide					Merck Wilson: Percent of Hydrochlorohiazide						
Lot No.	10 min	20 min	30 min	45 min	60 min	Lot No.	10 min	20 min	30 min	45 min	60 min	f_2
5192375	79.3	95.4	97.0	97.6	97.8	901946	75	88	92	94	96	62
5192370	77.0	95.6	96.9	97.4	97.8	901947	87	94	96	96	97	63
5192740	82.3	97.0	97.8	98.4	98.4	901964	65	79	85	88	89	58
						Mean	**75.7**	**87.0**	**91.0**	**92.7**	**94.0**	

	PRINZIDE 20/25 MG TABLETS (N=40)					PRINZIDE 20/25 MG TABLETS (N=12)						
	Merck Frosst: Percent Dissolved of Lisinopril					Merck Wilson: Percent Dissolved of Lisinopril						
Lot No.	10 min	20 min	30 min	45 min	60 min	Lot No.	10 min	20 min	30 min	45 min	60 min	f_2
5191080	94.3	99.4	99.5	99.6	99.6	901941	96	100	100	100	100	83
5191890	91.4	99.4	99.4	99.6	99.7	902013	85	94	96	97	98	92
5192220	92.9	99.1	99.1	99.0	99.2	902014	91	98	100	100	100	89
						Mean	**90.7**	**97.3**	**98.7**	**99.0**	**99.3**	
	Merck Frosst: Percent of Hydrochlorohiazide					Merck Wilson: Percent of Hydrochlorohiazide						
Lot No.	10 min	20 min	30 min	45 min	60 min	Lot No.	10 min	20 min	30 min	45 min	60 min	f_2
5191080	79.6	97.9	98.6	98.9	99.1	901941	74	83	87	89	90	52
5191890	77.6	97.7	98.6	99.1	99.2	902013	66	81	85	89	90	53
5192220	79.5	98.0	98.7	98.8	99.2	902014	81	92	94	95	96	52
						Mean	**73.7**	**85.3**	**88.7**	**91.0**	**92.0**	

4. The overall dissolution data and f_2 results for PRINZIDE® 10/12.5, 20/12.5 and 20/25 mg Tablets, showed that the dissolution profiles of lisinopril for the lots manufactured at Merck Frosst and at Merck Wilson are similar (f_2 values are within the range of 50 to 100). With respect to HCTZ the f_2 values for PRINZIDE® 20/12.5 and 20/25 mg tablets are within the acceptance range, however, the f_2 value for the 10/12.5 mg tablet is below the acceptance range (i.e., 46 to 49).

□

5. It should be noted that there is higher variability for HCTZ-dissolution data for the lots manufactured at Merck-Wilson than for the lots manufactured at Merck-Frosst. Also, it should be noted that the mean HCTZ-dissolution profiles for the 10/12.5, 20/12.5, and 20/25 mg tablets manufactured at Merck-Wilson are overall different (lower values) than those lots manufactured at Merck-Frosst.

6. The sponsor states that the fact that the 10/12.5 mg tablet did not pass the f2 test, will not affect the efficacy/safety of the product. Reference is made to a study of 31 HCTZ products with times to reach 60% dissolution varying from 1.5 to 195 minutes with essentially no correlation between dissolution and bioavailability (i.e., all products were bioavailable compared to an oral suspension). For HCTZ, diuresis begins within two hours of oral use and peaks in about four hours with effects lasting six to twelve hours. HCTZ is not metabolized but is eliminated rapidly by the kidney. When plasma levels have been followed for at least 24 hours, the plasma half-life has been observed to vary between 5.6 and 14.8 hours. At least 61 percent of the oral dose is eliminated unchanged within 24 hours.

RECOMMENDATION:

The Office of Clinical Pharmacology and Biopharmaceutics/Division of Pharmaceutical Evaluation I (OCPB/DPEI) has reviewed the dissolution information provided in NDA 19-778, Supplement SCM-034 submitted on December 31, 2001. OCPB/DPEI considers that Merck & Co. has provided appropriate dissolution information to support the approval of Merck-Frosst, Canada site as an additional manufacturing/testing/packing site for PRINZIDE® 20/12.5 and 20/25 mg Tablets. With respect to the 10/12.5 mg tablets that did not pass the f_2 test, OCPB agrees with the sponsor' opinion that a slightly faster dissolution will not affect the safety and efficacy of the HCTZ component. Therefore, from the OCPB's viewpoint the Canada site is also acceptable for the manufacturing/testing/packing site of PRINZIDE® 10/12.5 mg Tablets.

Please convey the Recommendation as appropriate to the sponsor. /S/

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

/S/

RD/FT Initialed by Chandra Sahajwalla, Ph.D. _____

cc: NDA 20-778, HFD-110 (Zimmerman), HFD-860 (Dorantes, Mehta), and CDR (Biopharm).

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/s/

Angelica Dorantes
2/4/02 08:03:33 PM
BIOPHARMACEUTICS

Chandra Sahajwalla
2/5/02 09:33:03 AM
BIOPHARMACEUTICS

CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

NDA 19-778/S-034

Administrative Documents

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO *(Division/Office)*: Biopharm, HFD-110			FROM: Stuart Zimmerman, HFD -810	
DATE: 5/29/02	IND NO.:	NDA NO.: 19-778	TYPE OF DOCUMENT: SCM -034	DATE OF DOCUMENT: 12/31/01
NAME OF DRUG: Prinzide Tablets	PRIORITY CONSIDERATION: CBE Goal Date 7/2-02		CLASSIFICATION OF DRUG: NA for supplement	DESIRED COMPLETION DATE: 6/21/02

NAME OF FIRM: Merck Research Labs

REASON FOR REQUEST

I. GENERAL

NEW PROTOCOL
☐ PROGRESS REPORT
☐ NEW CORRESPONDENCE
☐ DRUG ADVERTISING
☐ ADVERSE REACTION REPORT
☐ MANUFACTURING CHANGE/ADDITION
☐ MEETING PLANNED BY
☐ PRE--NDA MEETING
☐ END OF PHASE II MEETING
☐ RESUBMISSION
☐ SAFETY/EFFICACY
☐ PAPER NDA
☐ CONTROL SUPPLEMENT
☐ RESPONSE TO DEFICIENCY LETTER
☐ FINAL PRINTED LABELING
☐ LABELING REVISION
☐ ORIGINAL NEW CORRESPONDENCE
☐ FORMULATIVE REVIEW
☐ OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW ☐ END OF PHASE II MEETING ☐ CONTROLLED STUDIES ☐ PROTOCOL REVIEW ☐ OTHER:	☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER:

III. BIOPHARMACEUTICS

~~☐NNNNNN~~ DISSOLUTION
☐ BIOAVAILABILTY STUDIES
☐ PHASE IV STUDIES
☐ DEFICIENCY LETTER RESPONSE
☐ PROTOCOL-BIOPHARMACEUTICS
☐ IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
☐ SUMMARY OF ADVERSE EXPERIENCE
☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

☐ CLINICAL ☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS: This submission has some f_2 factors below the 50 % value for the HCTZ drug in this combination drug product. This requires a biopharm review to be conducted. This is an electronic submission so it can be accessed from the server, but I have a copy that you can use if you need to do so.

SIGNATURE OF REQUESTER:	METHOD OF DELIVERY (Check one): Ξ E- MAIL ☐ HAND
SIGNATURE OF RECEIVER:	SIGNATURE OF DELIVERER:

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/s/

Stuart Zimmerman
5/29/02 08:45:21 AM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 19-778/S-034

Merck & Co., Inc.
Attention: Michael C. Elia, Ph.D., DABT
Sumneytown Pike
P.O. Box 4, BLA-20
West Point, PA 19486

Dear Dr. Elia:

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: Prinzide (lisinopril/hydrochlorothiazide) Tablets

NDA Number: 19-778

Supplement number: S-034

Date of supplement: December 31, 2001

Date of receipt: January 2, 2002

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 March 3, 2002 in accordance with 21 CFR 314.101(a).

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:

Ms. Sandra Birdsong
Regulatory Project Manager
(301) 594-5334

Sincerely yours,

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

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/s/

Natalia Morgenstern
1/15/02 10:47:56 AM