

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER: NDA 21-162

CHEMISTRY REVIEW(S)

**ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT**

Application: NDA 21162/000	Priority: 4S	Org Code: 110
Stamp: 29-DEC-1999 Regulatory Due: 29-OCT-2000	Action Goal:	District Goal: 30-AUG-2000
Applicant: BOEHRINGER PHARMS 900 RIDGEBURY RD RIDGFIELD, CT 06877	Brand Name: TELMISARTAN/HYDROCHLOROTHI AZIDE 40/12.5M	
	Established Name:	
	Generic Name: TELMISARTAN/HYDROCHLOROTHI AZIDE 40/12.5M	
	Dosage Form: TAB (TABLET)	
	Strength: 40/12.5 & 80/12.5MG	
FDA Contacts: S. BIRDSONG (HFD-110)	301-594-5300	, Project Manager
S. ZIMMERMAN (HFD-110)	301-594-5300	, Review Chemist
K. SRINIVASACHAR (HFD-110)	301-594-5376	, Team Leader

Overall Recommendation:

ACCEPTABLE on 16-OCT-2000 by M. GARCIA (HFD-322) 301-594-0095

Establishment:	DMF No:
BOEHRINGER INGELHEIM KG	AADA No:
INGELHEIM AM RHEIN, , GM	

Profile: CSN	OAI Status: NONE	Responsibilities: DRUG SUBSTANCE MANUFACTURER FINISHED DOSAGE MANUFACTURER
Last Milestone: OC RECOMMENDATION		
Milestone Date: 06-JUN-2000		
Decision: ACCEPTABLE		
Reason: DISTRICT RECOMMENDATION		
Profile: TCM	OAI Status: NONE	
Last Milestone: OC RECOMMENDATION		
Milestone Date: 16-OCT-2000		
Decision: ACCEPTABLE		
Reason: BASED ON FILE REVIEW DISTRICT RECOMMENDATION		

Establishment:	DMF No:
BOEHRINGER INGELHEIM PHARMA	AADA No:
BIBERACH AN DER RISS, , GM	

Profile: CRU	OAI Status: NONE	Responsibilities: INTERMEDIATE MANUFACTURER
Last Milestone: OC RECOMMENDATION		
Milestone Date: 13-MAR-2000		
Decision: ACCEPTABLE		
Reason: DISTRICT RECOMMENDATION		

Establishment: L	DMF No:
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FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

AADA No:

Profile: TCM OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 18-SEP-2000
Decision: ACCEPTABLE
Reason: DISTRICT RECOMMENDATION

Responsibilities: FINISHED DOSAGE PACKAGER

Establishment:

DMF No:
AADA No:

Profile: TCM OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 31-AUG-2000
Decision: ACCEPTABLE
Reason: DISTRICT RECOMMENDATION

Responsibilities: FINISHED DOSAGE PACKAGER

Establishment:

DMF No:
AADA No:

Profile: CSN OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 04-FEB-2000
Decision: ACCEPTABLE
Reason: BASED ON PROFILE

Responsibilities: DRUG SUBSTANCE
MANUFACTURER

APPEARS THIS WAY
ON ORIGINAL

Methods Validation

As of October 25, 2000, the Methods Validation is pending.

DIVISION OF CARDIO-RENAL DRUG PRODUCTS

Review of Chemistry, Manufacturing, and Controls

NDA # 21-162

DATE REVIEWED: 10/16/00

REVIEW #: 2

REVIEWER: Stuart Zimmerman

SBMISSION TYPE	DOCUMENT	CDER DATE	ASSIGNED DATE
AMENDMENT	28-08-00*	30-08-00	30-08-00
AMENDMENT	29-08-00	30-08-00	31-09-00
AMENDMENT	08-09-00	11-09-00	12-09-00
AMENDMENT	27-09-00	28-09-00	29-09-00
AMENDMENT	06-10-00	10-10-00	12-10-00

Note: This is included in Chemistry Review #1 and #2 for continued review..

NAME & ADDRESS OF APPLICANT:

Boehringer Ingelheim Pharmaceuticals, Inc.
900 Ridgebury Rd./P. O. Box 368
Ridgefield, CT 06877-

DRUG PRODUCT NAME

Proprietary: MICARDIS HCT (given in 8/29/00 submission)
Established: telmisartan/hydrochlorothiazide
Code Name/#: BIBR 277 SE for telmisartan

Chem.Type/Ther.Class: 34S

PHARMACOL. CATEGORY/INDICATION:

Specific angiotension II antagonist/diuretic

DOSAGE FORM:

Tablet

STRENGTHS:

40/12.5 mg & 80/12.5 mg

ROUTE OF ADMINISTRATION:

Oral

Rx/OTC:

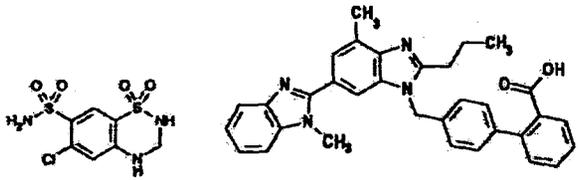
Rx Yes

SPECIAL PRODUCTS:

Yes _ No X

CHEMICAL NAME, STRUCTURAL FORMULA

Hydrochlorothiazide: 6-Chloro-3,4-dihydro-2H-1,2,4-benzothiazide-7-sulfonamide-1,1-dioxide & Telmisartan: 4'[(9Z)-n-Propyl-4-methyl-6-(1-methylbenzimidazol-2-yl)-benzimidazol-1-yl]-methyl]-biphenyl-2-carboxylic acid.



SUPPORTING DOCUMENTS:

- { } for Telmisartan (BIBR 277 SE)
- NDA 20-850 for Telmisartan Tablets

DMF#	TYPE	HOLDER	ITEM REF	CODE ¹	STATUS	DATE REVIEW	NOTE# (Below)
	III			2426F	Adequate	9-21-98	
	II				Adequate	8-31-98	
	III				Adequate	01-22-00	
	III				Adequate	01-17-00	

STATUS OF CONSULTS AND OTHER RELATED REVIEWS:

ITEM	RECOMMENDATION	DATE	REVIEWER'S NAME
Microbiology	NA for oral tablet		
Inspection	Acceptable --	10/16/00	Garcia
Methods Validation	Pending Completion		
OPDRA (Trade Name)	Proposed name Acceptable		Through Edward Froom
Biopharmaceutics	Dissolution Issues Adequate		Angelica Dorantes

21. COMMENTS: This review deals with the various issues relating to the ongoing manufacturing control resolutions as specified in the Chemistry Review #1 in the 8/28/00 NDA Amendment regarding the specification limit for unspecified HCTZ related degradants); certain previously encountered control issues are given a fuller evaluative rationale as discussed under the topic heading for the drug product entitled Degradant & Related Control Issues (In an effort to further reduce this subject degradant specification limit level, the applicant was contacted by telephone and requested to again consider providing for limits that are consistent with what stability results most validly support. The actual language of the finalized comments was considered to be the responsibility of the applicant – owing to clarifying follow-up conversations In this context, several other control issues were also mentioned as given under “Other Related Issues” in this review. The subject FDA deficiency issues are incorporated into this amendment response dated 9/27/00. The applicant is considered to have adequately responded to all of these issues (e.g., adoption of the reduced NMT tolerance limit for the unspecified HCTZ degradants. This total response has been scanned into this Chemistry Review #2 to serve as convenient documentation demonstrating just how the resolution of the issues has been realized (e.g., degree of detail provided) – to serve the needs of future evaluations in this area , The applicant has also provided updated stability data, additional contract packagers, and labeling changes. In general, all the outstanding issues involved have been appropriately dealt with so the only outstanding matter that needs to be expressed to the applicant pertains to the fact that the validation of the analytical methods is a pending issue that will not withhold approval.

22. CONCLUSIONS AND RECOMMENDATIONS: This NDA 21-162 may be approved from the standpoint of CMC considerations since there are no more pending issues...

|S|
Stuart Zimmerman, Ph. D.

cc. Orig.NDA 21-162
HFD-110/Division File
HFD-110/SZimmerman
HFD-110/PM/SBirdsong
HFD-110/KSrinivasachar
HFD-810/JSimmons DNDC1 Director
R/D Init by: KSrinivasachar

|S|
10-17-00

DIVISION OF CARDIO-RENAL DRUG PRODUCTS

Review of Chemistry, Manufacturing, and Controls

NDA #21-162 **DATE REVIEWED: 8/28/00**

REVIEW #: 1 **REVIEWER: Stuart Zimmerman**

SBMISSION TYPE DOCUMENT CDER DATE ASSIGNED DATE

ORIGINAL	29-12-99	30-12-99	30-12-99
AMENDMENT	27-04-00	28-04-00	29-04-00
AMENDMENT	05-05-00	05-08-00	09-05-00
AMENDMENT	24-05-00	25-05-00	27-05-00
AMENDMENT	19-06-00	19-06-00	20-07-00
AMENDMENT	18-07-00	19-07-00	20-07-00
AMENDMENT	27-07-00	28-07-00	29-07-00
AMENDMENT	28-08-00	28-08-00	28-08-00

INAME & ADDRESS OF APPLICANT:

Boehringer Ingelheim Pharmaceuticals, Inc.
900 Ridgebury Rd./P. O. Box 368
Ridgefield, CT 06877-

DRUG PRODUCT NAME

Proprietary: MICARDIS PLUS (given in 5/5/00 submission) – Note that this will be changed
Established: telmisartan/hydrochlorothiazide
Code Name/#: BIBR 277 SE for telmisartan

CHEM. TYPE/THER. CLASS: 34S

PHARMACOL. CATEGORY/INDICATION: Specific angiotension II antagonist/diuretic

DOSAGE FORM:

Tablet

STRENGTHS:

40/12.5 mg & 80/12.5 mg

ROUTE OF ADMINISTRATION:

Oral

Rx/OTC:

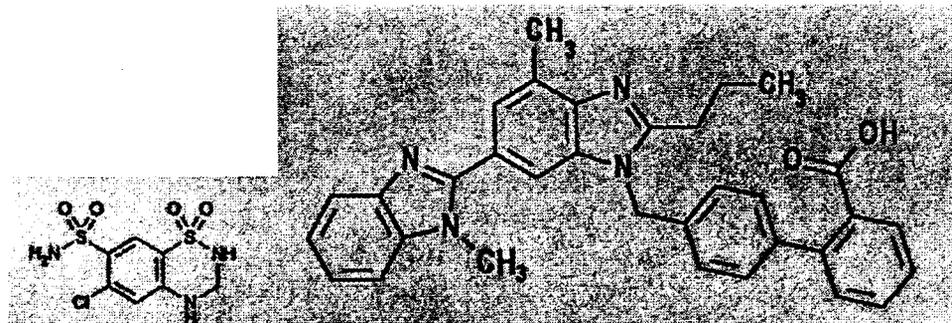
Rx Yes

SPECIAL PRODUCTS:

Yes No X

CHEMICAL NAME, STRUCTURAL FORMULA

Hydrochlorothiazide: 6-Chloro-3,4-dihydro-2H-1,2,4-benzothiazide-7-sulfonamide-1,1-dioxide & Telmisartan: 4'[(9Z)-n-Propyl-4-methyl-6-(1-methylbenzimidazol-2-yl)-benzimidazol-1-yl]-methyl]-biphenyl-2-carboxylic acid.



SUPPORTING DOCUMENTS:

- IND for Telmisartan (BIBR 277 SE)
- NDA 20-850 for Telmisartan Tablets

DMF#	TYPE	HOLDER	ITEM REF	CODE ¹	STATUS	DATE REVIEW	NOTE# (Below)
	III				Adequate	9-21-98	
	II		HCTZ		Adequate	8-31-98	
	III				Adequate	01-22-00	
	III				Adequate	01-17-00	

STATUS OF CONSULTS AND OTHER RELATED REVIEWS:

ITEM	RECOMMENDATION	DATE	REVIEWER'S NAME
Microbiology	NA for oral tablet		
Inspection	Pending Request Outcome		
Methods Validation	Awaiting Biopharm Rev. Input		
OPDRA (Trade Name)	Pending finalized outcome	8/3/00	Through Edward Froom
Biopharmaceutics	Pending Finalized Evaluation		Angelica Dorantes

21. COMMENTS: Unique Control Issues Recognized for this NDA Bilayered Tablet Formulation

Telmisartan is an orally active, potent, specific angiotensin II receptor blocker which acts selectively on AT₁ receptor subtype. Hydrochlorothiazide is a diuretic; the mechanism of action of the antihypertensive effect of thiazides is not fully understood. Together, these drugs lower blood pressure by two mechanisms of action.

It is recognized that this dosage formulation is a bi-layer tablet that has certain potential stability problems that have been found to exist in the single entity drug product, NDA 20-850 which center around the fact that the HCTZ portion of the tablet is likely to undergo base catalyzed degradation to the well-known degradant. This problem involves the slow migration of base from the telmisartan layer into the HCTZ layer. It is enhanced by the presence of water in the tablet so it is also very important to have good control (low specification values) for the amount of water present in the tablet. There is also the related problem that the tablet is hygroscopic and has a tendency to pick up moisture – if and when it is exposed to the atmosphere – which causes the tablet to soften and crumble. In order to guard against this from happening, attention is given to the use of a very protective blister packaging and instructions to the patient to keep the tablet in the blister package until it is used. There is also the related concern that in order to be sure that the package meets the child resistant packaging requirements, it must be provided with a peel-push opening mechanism whereby an adhesive backing must first be removed before the blister may be pushed out in the normal manner. This latter need has an impact for the evaluation of the applicant's stability data since the initial so-called "primary"

stability batches involved blister packaging materials that were not optimized for this particular tablet formulation, but rather were just a convenient carry-over application from the previously approved NDA 20-850. It was also realized that there was a problem in the cavity size for this unoptimized "primary blister" since it was initially too big so it allowed children to push through the blister backing with ease. This blister package change impacted on the nature of the stability data involved since it was not possible to provide for long-term data in the marketed package without a delay in the NDA. In this regard, it was considered to be acceptable to allow the applicant to use the "primary" stability data to support the long-term stability profile with a commitment to then provide for 3 months data in the revised blister package after it became available. This matter was considered in the L... This approach was followed by special evaluative attention is given to those amendments that provide for this updated stability data. Such data proved to be important to consider in terms of the revision of the applicant's specifications for the tolerance limits for certain classifications of unspecified degradants related to both of the drug components involved in the drug product. In this context, it was found that there were a number of basic analytical issues that needed to be resolved before the whole degradant control question could be closed.

22. CONCLUSIONS AND RECOMMENDATIONS: The applicant has been contacted in a telecon with respect to a number of deficiency issues which were then addressed in a response (i.e., Amendment dated 8/28/00). In this regard, reference is made to the "Draft Letter" Review Section H that includes both the context of the FDA issues and the Applicant's response. In this context, it is important to understand that the evaluative rationale for certain follow up deficiency issues is consolidated and given more attention :

While the applicant's response to the FDA comments 1, 2, 3, and 5 are considered to be acceptable, the answer to comment #4 given by the applicant did not resolve the FDA issue for the reduction of the specification limit of NMT for those unspecified degradants related to the HCTZ drug component to a value of NMT as may be reflected from the current stability data. Hence it was considered to be necessary to provide a more intense and continued assessment of this specification issue as well as other related analytical questions that were also found to be in need of resolution. Hence, the Chemistry Review #2 must be closely considered to provide an appropriate evaluative perspective concerning the questions that are raised in this Chemistry Review #1.

in this complexly formulated bilayered tablet. In summary, the scope of this Chemistry Review #1 deals with the evaluative events that carry up to the applicant's response dated 8/28/00. Then, Chemistry Review #2 becomes concerned with the open issue related to the controls for this unspecified HCTZ degradant as well as dealing with certain newly related issues and bringing the NDA evaluation to a close.

/s/
Stuart Zimmerman, Ph. D.

cc. Orig.NDA 21-162

HFD-110/Division File

HFD-110/SZimmerman

HFD-110/PM/SBirdsong

HFD-810/JSimmons DNDC1 Director

R/D Init by: KSrinivasachar

/s/
10-16-00