CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 20-818

CHEMISTRY REVIEW(S)

SEP 9 1997 Boulevard

DIVISION OF CARDIO-RENAL DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

NDA #: 20-818 **CHEM.REVIEW #:** 1 **REVIEW DATE:** 8/29/97

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
Original NDA	March 28,1997	April 1, 1997	April 3, 1997
Amendment	6/25/97	7/2/97	7/4/97(?)
Amendment	8/22/97	8/27/97	8/29/97 (?)

NAME & ADDRESS OF APPLICANT: Novartis Pharmaceuticals Corporation
59 Route 10
East Hanover, NJ 07936-1080

DRUG PRODUCT NAME

Proprietary: Diovan HCT

Nonproprietary/USAN: Valsartan (CGP 48933) and Hydrochlorothiazide, USP

Code Name/#: CGP 63170 (80:12.5)
CGP 63171 (160:12.5)

ANDA Suitability Petition/DESI/Patent Status:

No specific information is provided for this new combinational agent other than that it is the subject of the US Patent Number 5,399,578 (See Vol.#1.1, p.# 001)

PHARMACOL.CATEGORY/INDICATION: Valsartan is an orally active angiotensin II antagonist and Hydrochlorothiazide is a diuretic.

DOSAGE FORM: Tablets
STRENGTHS: 80mg/12.5mg and 160mg/12.5mg
ROUTE OF ADMINISTRATION: Oral
DISPENSED: _X_ Rx _____ OTC

STRUCTURAL FORMULA, CHEMICAL NAME, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Refer to Appendix #6 for this information for these previously approved drug products.

Chemical Name(Valsartan):
N-(1-oxopentyl)-N-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-L-Valine.

RELATED DOCUMENTS (Valsartan/ Hydrochlorothiazide): NDA 20-665 and NDA 11-193 (approved)

Pharmacology similar drugs (Valsartan) Refer to the Chemist's Review #1 for NDA 20-665.

REMARKS/COMMENTS: This review is conducted in an expedited manner to meet the deadline for completion at the end of August, 1997. In this regard, there are certain evaluative areas that need to be completed which are not considered to be of high priority, such as: methods validation, labeling details, and DMF reviews where information is currently being generated by the DMF holder - Also, certain information that is just a repeat of what is offered in the review is handled by referencing it as an Appendix to this review; this approach will help to capture critical details without concern for errors resulting from scanning or the like.

Concerning the need to evaluate information that has been provided to the FDA in another context and approved in a similar context, it is considered to be appropriate to only cite the evaluative basis already documented rather than to conduct a parallel evaluation. In this regard, it is recognized that this NDA is for a combination drug product and that both active ingredients have been approved in the past under several supporting NDAs. A more detailed understanding of the various evaluative issues involved may be derived from an examination of the primary FDA reviews conducted by other reviewers. The applicant already has a large amount of regulatory experience (e.g., approvals for the active ingredients. For example, for Valsartan, there is the approved NDA 20-665 which was reviewed extensively by Dr. C. Coughlin. Also, for Hydrochlorothiazide, there is available the applicant's supporting NDA 11-793 for Esidrix (See Vol.#1.1, p. #38).

With such cross-referencing to these supporting NDAs and their related DMFs, it is to be expected that the certain CMC control aspects would remain unchanged. Attempts will be made to identify those areas where differences exist and appropriate evaluations will be made for any such newly considered information.

With respect to the above, the following review topics are considered to be critical to this review: (1) Manufacturer(s) since these may be more specific with respect to this NDA 20-818 in terms of the micronization step involved, (2) Regulatory Specifications/Analytical Methods relating to any tests which are not compendial (e.g., the newly instituted particle size specification and test method for Hydrochlorothiazide bulk drug substance)

D. CONCLUSIONS: This NDA is considered to be approvable in terms of the information provided. There are a number of control issues which are outstanding in terms of needing additional evaluation, such as the updated stability data to be reported in November of this year. Other more minor control considerations are to be resolved on a continuing basis with both the applicant and the DMF holders involved. Assessment outcome results will be reported in the Chem. Review #2. Since the applicant has been informed of the various deficiencies that have come up on a continuing basis, there are no items to list in the action leter at this time.

The L & N committee found the trademark Diovan HCT unacceptable because HCT has been used to designate hydrocrotisone and hematocrit (i.e., refer to Appendix # 14) as well as hydrochlorothiazide. However, Norvartis has used HCT with Lopressor and Lotensin. Therefore, it is recommended that this name be accepted.

Stuart Zimmerman, Ph.D.

cc:
Orig. NDA 20-818
HFD-110/Division File
HFD-110/Stuart Zimmerman
HFD-110/Project Manager
HFD-110/Endorsed by R. Wolters
HFD-810/Hoiberg/DNDC Director

9/9/97

NOV 21 1997

CHEM. REV. #2 for NDA 20-818

DIVISION OF CARDIO-RENAL DRUG PRODUCTS

Review of Chemistry, Manufacturing, and Controls

NDA#: 20-818 CHEM.REVIEW # 2 REVIEW DATE: 11/20/97

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
AMENDMENT *	10/13/97	10/16/97	10/20/97
AMENDMENT	11/07/97	11/10/97	11/13/97

* This primarily provides for updated stability data on the various packaging configurations for up to one year.

NAME AND ADDRESS OF APPLICANT

Novartis Pharmaceuticals Corporation
59 Route 10
East Hanover, NJ 07936-1080

DRUG PRODUCT NAME:

Proprietary: Diovan HCT
Nonproprietary/USAN:Valsartan and Hydrochlorothiazide, USP
Code Name (#): see Chem Rev. #1

ANDA Suitability Petition/DESI/Patent Status: No change from Chem. Rev, #1

DOSAGE FORM: Tablets
STRENGTHS: 80mg/12.5mg and 160mg/12.5mg
ROUTE OF ADMINISTRATION : Oral
DISPENSED: Rx

PHARMACOL. CATEGORY/INDICATION: Valsartan is an orally active angiotensin II antagonist and Hydrochlorothiazide is a diuretic,

STRUCTURAL FORMULA - etc. No change from Chem Rev. #1

C. **REMARKS**: This review evaluates those issues which are outstanding from the Chem. Rev. #1. Since not all review categories are relevant, only those which remain active will be the subject of this review. Supporting information is attached in the various Appendixes involved.

D. **CONCLUSIONS**: This NDA is considered to be adequate for an approval action in terms of the CMC portion of the information that has been submitted for evaluation. Of course, a finalized decision awaits any additional information provided (e.g., updated labeling) which normally comes later in the review process.

Stuart Zimmerman

Stuart Zimmerman Ph.D.

cc:

Orig. NDA 20-818

HFD- 110/Div File

HFD -110/SZimmerman

HFD -110/ Project Manager

HFD - 110/Endorsed by RWolters

HFD - 810/CHoiberg/DNDC Director

11-21-97

K. Bargeman

JAN 22 1998

DIVISION OF CARDIO-RENAL DRUG PRODUCTS

Review of Chemistry, Manufacturing, and Controls

NDA#: 20-818 **CHEM.REVIEW # 3** **REVIEW DATE:** 1/13/98

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
AMENDMENT *	12/12/97	12/15/97	12/16/97

* This primarily provides for updated stability data on the various packaging configurations for up to one year.

There is another amendment dated 12/23/97 which does deal with the change in the specification for the HCTZ; however, this is not directed to the chemist for review.

NAME AND ADDRESS OF APPLICANT:
Novartis Pharmaceuticals Corporation
59 Route 10
East Hanover, NJ 07936-1080

DRUG PRODUCT NAME:
Proprietary: Diovan HCT
Nonproprietary/USAN: Valsartan and Hydrochlorothiazide, USP
Code Name (#): see Chem Rev. #1

ANDA Suitability Petition/DESI/Patent Status: No change from Chem. Rev, #1

DOSAGE FORM: Tablets
STRENGTHS: 80mg/12.5mg and 160mg/12.5mg
ROUTE OF ADMINISTRATION : Oral
DISPENSED: Rx

PHARMACOLOGICAL CATEGORY/INDICATION: Valsartan is an orally active angiotensin II antagonist and Hydrochlorothiazide is a diuretic,

STRUCTURAL FORMULA - etc. No change from Chem Rev. #1

B. REMARKS: This review evaluates those additional issues which have evolved since Chem. Rev. #2. Since not all review categories are relevant, only those which remain active will be the subject of this review. Supporting information is attached in three Appendixes involved. It is informative to reference the evaluative status of certain critical approval benchmarks for the following aspects. (1) about the regulatory status of the pre-approval inspection, reference is made to Appendix #9 of Chem Rev. #2 and the documented acceptable decision by the Office of Compliance on 9/19/97: (2) The most recent Method's Validational interactions are given in Appendix #7 of Chem Rev #2 (11/20/97) after the methods had been submitted to two laboratories; (3) Regarding the acceptability of the trademark, Diovan HCT, it was noted in Chem Rev #1 under the Conclusion section that this name was turned down by the L & N committee, but then considered to be acceptable by HFD-110 since Novartis has used HCT with Lopressor and Lotensin; (4) Concerning the environmental requirements, statements are provided relating to acceptability in Appendix #8 in Chem Rev #1.

D.CONCLUSIONS: This NDA is now considered to be adequate for an approval action in terms of the CMC portion of the information that has been submitted for evaluation. The FDA position concerning the dissolution rate specification for the HCTZ is now resolved (i.e., the requirement for Q of NLT dissolved in 30 min.- see **Appendix #0**). It is appropriate to put into an approveable letter the understanding that a *standalone stability protocol* will be developed in the future and submitted as a supplement for approval so there will be available an *approved* stability protocol to support any future changes in the expiry date.

Stuart Zimmerman Ph.D.
WPF: 20818cr3.J13 (Office Code: E-76)

cc:
Orig. NDA 20-818
HFD- 110/Div File
HFD -110/SZimmerman
HFD -110/ Project Manager
HFD - 110/Endorsed by SHORT
HFD - 810/CHoiberg/DNDC Director

James O Short
1-21-98