

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
22-314

OTHER REVIEW(S)

RHPM Overview – AP action
NDA 21-990
Exforge HCT (amlodipine, valsartan, hydrochlorothiazide) Tablets
5/160/12.5, 10/160/12.5, 5/160/25, 10/160/25 and 10/320/25 mg

Sponsor: Novartis Pharmaceuticals Corporation
Classification: Standard
Submission Date: June 30, 2008
Receipt Date: June 30, 2008
User Fee Goal Date: April 30, 2009

Background

This original NDA provides for Exforge HCT (amlodipine, valsartan, hydrochlorothiazide) fixed combination tablets for the treatment of hypertension. Amlodipine besylate is a calcium channel blocker approved for the treatment of hypertension (Norvasc; NDA 19-787). Valsartan is an angiotensin receptor blocker also approved for the treatment of hypertension (Diovan; NDA 21-283 and 20-665). Hydrochlorothiazide (HCTZ) is a diuretic approved for hypertension (Esidrix; NDA 11-793). Diovan HCT (valsartan/HCTZ) Tablets were approved originally on 3/6/98 (NDA 20-818) and Exforge (amlodipine and valsartan) Tablets were originally approved on 6/20/07 (NDA 21-990) for the treatment of hypertension.

This NDA for Exforge HCT was submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act and contains full reports of safety and effectiveness of the combination drug. However, for the preclinical data, reference is made to certain information previously submitted to the Agency for Norvasc (amlodipine besylate) Tablets. The sponsor has submitted a paragraph II certification.

In support of approval, the submission includes quality, pre-clinical, clinical pharmacology, and clinical/statistical data. The clinical development program included 10 clinical studies (including one pivotal Phase 3 study, VEA489A2302), bioequivalence studies, a food effect study, and a pharmacokinetic drug-drug interaction study. The following dosage strengths of are being proposed: 5/160/12.5, 10/160/12.5, 5/160/25, 10/160/25, and 10/320/25 mg.

The clinical development of Exforge HCT was conducted under IND 74,490. The pivotal trial (Study VEA489A2302) was an 8-week, multicenter, randomized, double-blind, parallel group study to evaluate the efficacy and safety of the triple combination compared to the dual combinations in patients with moderate to severe hypertension. According to the sponsor, the triple combination produced clinically and statistically significant greater reductions in MSDBP and MSSBP compared to the dual combinations, and no new or unexpected safety issues were identified with triple therapy compared to any of the dual therapies.

Cross-Discipline Team Leader Review

In his 4-7-09 review, Dr. Marciniak wrote the following:

13.1. Recommended regulatory action

I recommend Exforge HCT be approved for the treatment of hypertension in adults. This triple combination produced greater reductions in blood pressure than all of the dual combinations of its components. Its safety profile showed only minor increases in dizziness and some suggestion of decreased rates of edema compared to some of the dual combinations. Because this product is a triple combination of antihypertensives each with its own adverse effect profile, I do not recommend that it be labeled for initial use. The labeling should reflect that its use should be limited to patients still uncontrolled on any two of its components at maximum doses or titrated to all of its components by monotherapy or monotherapy and dual combination use.

Joint Clinical/Statistical Review

A joint clinical/statistical review was completed by Dr. Lemtouni (efficacy), Dr. Pendse (safety), and Dr. Liu (statistics). Their 4-23-09 review states the following:

1.1 Recommendation on Regulatory Action

From a clinical and statistical perspective we recommend that Exforge HCT, the triple combination of valsartan, amlodipine, and hydrochlorothiazide, be approved for the treatment of hypertension in adults.

The triple combination was shown to be significantly more effective than any of the double combinations, and relatively safe in comparison to the double combinations as well. One thing to keep in mind is that the generalizability of the findings from this study may be limited. This is due to the fact that the inclusion/exclusion criteria with regard to hypertension severity, responsiveness to antihypertensive drugs, and co-morbidities might have led to a population that would most respond to the anti-hypertensive effect of the triple combination with few adverse events as observed here. It is not known whether African Americans or subjects who are older and/or have concomitant cardiac conditions, all of whom were under-represented in the study population, would benefit or exhibit a benefit to risk profile as favorable as that observed in this study. In our opinion, the label should include language regarding the under-representation of these sub-populations.

Clinical Pharmacology Review

In her 2-27-09 review, Dr. Menon-Andersen wrote the following:

1.1 Recommendation

The Office of Clinical Pharmacology (OCP/DCP1) reviewed original NDA 22-314.

Clinical Pharmacology: The results of the bioequivalence studies submitted in the application established an adequate link between the results of the pivotal efficacy trial conducted with the free combination, and the final market image tablet (to-be-marketed formulation). Further, it was shown that there was no clinically significant pharmacokinetic drug interaction between the components of the FDC, and that food did not affect the pharmacokinetics of Exforge HCT.

Labeling: The clinical pharmacology information included in the proposed labeling is acceptable.

BE Audit Report: The DSI reports for the audits for the analytical and clinical sites of bioequivalence studies VEA489A2305 and VEA489A2305 will be submitted in April 2009. OCP will review the reports once submitted, and OCP's recommendations will be documented as an amendment to this current OCP review.

The NDA is considered acceptable from a clinical pharmacology perspective.

Note: In their DSI audit report dated 4-14-09, DSI wrote the following conclusion:

DSI recommends data from Study VEA489A2306 be accepted for review.

For Study VEA489A2305, DSI recommends the following:

- The firm should provide stability data to demonstrate analyte stability for the processing conditions mentioned in item #1. If the sample integrity question is not resolved, DSI is of the opinion that data from these samples should be excluded from bioequivalence determination.
- Data from the 11 samples mentioned in items #2 and #3 should be excluded from bioequivalence determination.

Per an email dated 4-17-09, Drs. Menon-Andersen and Dorantes both agreed that they “do not think the results of the DSI audit have a significant impact on the results of study VEA489A2305” and that no further recommendations from OCP will need to be documented as an amendment to Dr. Menon-Andersen’s original review.

Pharmacology review

In his 11-6-08 review, Dr. Jagadeesh recommended that the NDA was “Approvable” and wrote the following:

...The pharmacokinetics of valsartan, HCTZ and amlodipine in rats (likewise in humans) are similar when administered alone or when administered as the double or triple combinations. Systemic exposures (AUCs) to valsartan:amlodipine:HCTZ in rats treated with the combination were compared to systemic exposures in humans treated at the highest combination doses of valsartan (320 mg), amlodipine (10 mg) and HCTZ (25 mg). Exposures to 8 mg valsartan/0.5 mg amlodipine/1.25 mg HCTZ/kg/day in rats (highest dose not resulting in glandular stomach erosion or JGA hyperplasia) were far lower than exposure in humans (0.06 to 0.13 times, based on AUC values), indicating the absence of a safety margin for humans. However, the combination product can still be used safely in humans for the treatment of hypertension because the target organ toxicities are monitorable and attributable to the individual drugs of the combination, drugs which are currently approved for use in this patient population and have often been used concomitantly.

Quality reviews

Dr. Soldatova completed two reviews dated 3-3-09 and 4-20-09. In her review dated 4-20-09, Dr. Soldatova wrote the following:

A. Recommendation and Conclusion on Approvability

NDA 22-314 for Exforge HCT Tablets is recommended for APPROVAL from a Chemistry, Manufacturing and Controls standpoint. Based on the drug product stability data including ONDQA Biopharmaceutics recommendation on dissolution specification, shelf-life of 24 months is recommended for all the strengths, 5/160/12.5 mg, 10/160/12.5 mg, 5/160/25 mg, 10/160/25 mg, 10/320/25 mg in 30, 90 and 100 count — (90 cc and 175 cc) bottles; and shelf life of 12 months is recommended for all dosage strengths in J — blister packs. —

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The Exforge HCT tablets in 100 count (175 cc) bottles and in unit dose blister packages are not planned to be marketed at this time. The overall Acceptable recommendation was assigned by OC for all drug substance and drug product facilities. The applicant has committed to provide complete updated specifications for five strengths of Exforge HCT tablets as a post-approval submission.

List Of Comments To Be Communicated in the Action Letter

1. A 24-month expiration period is granted for all strengths of the drug product packaged in 30 count (90 cc), 90 count and 100 count (175 cc) — bottles stored under controlled room temperature conditions. A 12-month expiration period is granted for all strengths of the drug product packaged in blisters stored under controlled room temperature conditions.

3. The bottle labels for the Exforge HCT tablets in 100 count — bottles should be submitted as a labeling supplement before marketing them.

4. We acknowledge your commitment to update and submit the final agreed upon drug

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product specification documents in the first annual report. Include “non-scored” in the drug product description in the specification to be consistent with drug product description in sections 3 and 16 of the package insert.

See also Dr. Ramesh Sood’s Branch Chief Memo dated 4-20-09.

Environmental Assessment

The sponsor submitted an Environmental Assessment (EA) pursuant to 21 CFR Part 25, which was found to be acceptable. See OPS review dated 3-4-09 and 3-5-09 (FONSI).

EES Report

The Office of Compliance provided on 4-7-09 an overall recommendation of “Acceptable” for the manufacturing sites inspected. See Dr. Soldatova’s Quality review dated 4-20-09.

Safety Update

In her 4-9-09 safety update review, Dr. Pendse concluded that *“There are no significant new safety concerns for valsartan/HCTZ/amlodipine that would preclude an approval action.”*

Financial Disclosure

In her 4-9-09 financial disclosure review, Dr. Pendse wrote that “...Bias was minimized, however, with the use of multiple countries/study sites and investigators, by the independent data monitoring by Novartis, and by the use of the randomized, double-blind, active-controlled design.”

Division of Scientific Investigations

It was agreed by the medical officer and statistician after the NDA Filing Meeting that no clinical site inspections of the pivotal study were needed. Per Dr. Lemtouni, half the population comes from the US and the effect is highly significant in the US. The site of concern (Russia) was less than 10% of the overall population. Argentina enrolled about 15%. These two countries, because of their small numbers, are unlikely to be driving the findings. Per Dr. Liu, after excluding Russia and Argentina, the overall efficacy remains the same; the triple combination of valsartan/HCTZ/amlodipine was statistically superior to the dual combinations ($p < 0.0001$).

See Clinical Pharmacology Review section above regarding DSI inspections of the two bioequivalence studies.

Pediatrics

The sponsor requested a waiver from the pediatric requirement, as discussed during the 5-9-07 Pre-NDA meeting. During the NDA Filing Meeting, the Division agreed that a pediatric waiver should be granted because the drug product is a combination antihypertensive drug.

A PeRC Committee meeting was held on 1-14-09 and the PeRC agreed with the Division to grant a full pediatric waiver for the following reasons:

The product fails to represent a meaningful therapeutic benefit over existing therapies for pediatric patients and is unlikely to be used in a substantial number of all pediatric age groups or the pediatric age group(s) for which a waiver is being requested.

Justification: Exforge HCT is a combination antihypertensive agent. There are single agent products studied and labeled for use in pediatrics, and most pediatric patients are not treated with combination antihypertensives (supported by **The Fourth Report on the Diagnosis, Evaluation, and Treatment of High Blood Pressure in Children and Adolescents**, *Pediatrics* 2004; 114;555-576).

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/s/

Quynh Nguyen
4/29/2009 11:33:28 AM
CSO

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/s/

Norman Stockbridge
4/25/2009 09:30:16 AM
MEDICAL OFFICER



**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology**

Date: April 17, 2009

To: Dr. Norman Stockbridge, MD Director
Division of Cardiovascular and Renal Products

Thru: Carlos Mena-Grillasca, R.Ph., Acting Team Leader
Denise Toyer, PharmD, Deputy Director
Division of Medication Error Prevention and Analysis

From: Walter Fava, R.Ph., Safety Evaluator
Division of Medication Error Prevention and Analysis

Subject: Label and Labeling Review

Drug Name(s): Exforge HCT (Amlodipine, Valsartan, Hydrochlorothiazide)
Tablets
5 mg/160 mg/12.5 mg,
5 mg/160 mg/25 mg,
10 mg/160 mg/12.5 mg,
10 mg/160 mg/25 mg,
10 mg/320 mg/25 mg

Application Type/Number: NDA 22-314

Applicant/Applicant: Novartis

OSE RCM #: 2008-1345

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EXECUTIVE SUMMARY

This review was written in response to a request from the Division of Cardiovascular and Renal Products to evaluate the container labels, carton and package insert labeling for the product Exforge HCT (NDA# 22-314), to identify areas that could lead to medication errors. To identify vulnerabilities that could lead to medication errors, the Division of Medication Error Prevention and Analysis (DMEPA) uses Failure Mode and Effects Analysis (FMEA)¹. Additionally, we completed an AERS search for medication error cases associated with the use of the product, Exforge (Amlodipine/Valsartan), which is currently marketed. However, our search yielded no cases relevant to this review.

Our findings indicate that the presentation of information in the labels and labeling introduces vulnerability to confusion that could lead to medication errors. We would be willing to meet with the Division for further discussion, if needed. Please copy the Division of Medication Error Prevention and Analysis on any communication to the Applicant with regard to this review. If you have further questions or need clarifications, please contact Sean Bradely, OSE Project Manager, at 301-796-1332.

1 MATERIALS REVIEWED

For this product the Applicant submitted on June 28, 2008, the following labels and labeling for DMEPA review. (see Appendix A, B, C, D, and E for images):

- Retail Container Labels (30 and 90 tablets): 5 mg/160 mg/12.5 mg, 5 mg/160 mg/25 mg, 10 mg/160 mg/12.5 mg, 10 mg/160 mg/25mg, 10 mg/320 mg/25 mg
- _____
- _____
- Unit Dose Carton Labeling : 5 mg/160 mg/12.5 mg, 5 mg/160 mg/25 mg, 10 mg/160 mg/12.5 mg, 10 mg/160 mg/25mg, 10 mg/320 mg/25 mg
- Unit Dose Blister Labels: 5 mg/160 mg/12.5 mg, 5 mg/160 mg/25 mg, 10 mg/160 mg/12.5 mg, 10 mg/160 mg/25mg, 10 mg/320 mg/25 mg
- Prescribing Information (no image)

We also compared the Exforge HCT labels and labeling to labels and labeling for Exforge which was submitted to the Agency on December 5, 2006 and August 14, 2008 (See Appendix F).

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¹ Institute for Healthcare Improvement (IHI). Failure Mode and Effects Analysis. Boston. IHI:2004.

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 x Draft Labeling (b4)

 Draft Labeling (b5)

 Deliberative Process (b5)

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/s/

Walter Fava
4/17/2009 10:00:21 AM
DRUG SAFETY OFFICE REVIEWER

Carlos M Mena-Grillasca
4/17/2009 10:07:48 AM
DRUG SAFETY OFFICE REVIEWER

Denise Toyer
4/17/2009 10:18:14 AM
DRUG SAFETY OFFICE REVIEWER

Internal Consult

******Pre-decisional Agency Information******

To: Quynh Nguyen, Pharm.D, Project Manager
Division of Cardiovascular and Renal Products
Office of New Drugs

From: Lisa Hubbard, R.Ph., Regulatory Review Officer
Division of Drug Marketing, Advertising, and Communications (DDMAC)
Office of Medical Policy (OMP)

Through: Jialynn Wang, Pharm.D., Group Leader, DDMAC, OMP

Date: March 31, 2009

Re: NDA # 22-314
Exforge HCT (amlodipine, valsartan, hydrochlorothiazide) Tablets
Comments on draft label

DDMAC has reviewed the proposed product labeling (PI) for Exforge HCT (amlodipine, valsartan, hydrochlorothiazide) Tablets. The comments below are based on the "working" draft Exforge HCT label located within the DCRP e-room, (rev working draft Exforge HCT 3-12-09, modified 3-19-09, 12:14 PM). Please refer to our March 2, 2009, review for comments regarding the proposed PPI.

We offer the following comments:

12.1 Mechanism of Action

12.2 Pharmacodynamics

Please consider eliminating the first paragraph in sections 12.1 and 12.2. The language is promotional in tone. In particular, the language appears to contradict the fact that

DDMAC notes that the same sections within the Exforge and Diovan HCT labels do not include such language.

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Section 12.2 includes the statements, "Amlodipine has indications other than hypertension which are described in its full prescribing information" and "Valsartan has indications other than hypertension which are described in its full prescribing information." We acknowledge that similar language appears in the approved product labeling for Exforge. The language is highly promotional in tone. We recommend eliminating the statements.

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/s/

Lisa Hubbard
3/31/2009 09:53:02 AM
DDMAC PROFESSIONAL REVIEWER

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications

Memorandum

****PRE-DECISIONAL AGENCY MEMO****

Date: March 02, 2009

To: Quynh M. Nguyen
Senior Regulatory Project Manager
Division of Cardiovascular and Renal Products (DCRP)

From: Zarna Patel, PharmD
Consumer Safety Officer
Division of Drug Marketing, Advertising, and Communications
(DDMAC)

Subject: Drug: Exforge HCT (amlodipine besylate, valsartan,
hydrochlorothiazide) Tablets
NDA: 22-314

DDMAC has reviewed the proposed patient package insert (PPI) for EXFORGE HCT and we offer the following comments.

Currently, the FDA does not have a guidance or standard for PPIs. We recommend referring to DSCRS, for their review of this proposed PPI for comments on formatting, order or presentation, consistency, and readability.

If you have any questions or concerns regarding my comments, please contact me.

What is EXFORGE HCT?

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 X Draft Labeling (b4)

 Draft Labeling (b5)

 Deliberative Process (b5)

- Please consider presenting the paragraph regarding low blood pressure in bullet format, similar to the presentation in the Diovan HCT PPI, to increase readability and comprehension.

Thank you. If you have any questions, please contact Zarna Patel at 301.796.3822 or Zarna.Patel@fda.hhs.gov

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/s/

Zarna Patel
3/2/2009 11:37:59 AM
DDMAC CONSUMER REVIEWER