

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

22-314

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review Memo

Date	April 7, 2009
From	Thomas A. Marciniak, M.D.
Subject	Cross-Discipline Team Leader Review
NDA/BLA #	NDA 22-314
Supp #	
Proprietary / Established (USAN) names	Exforge HCT / valsartan/hydrochlorothiazide/amlodipine
Dosage forms / strength	Oral tablets / 320/25/10, 160/25/10, 160/25/5, 160/12.5/10, and 160/12.5/5 mg
Proposed Indication(s)	Treatment of hypertension
Recommended:	Approval

1. Introduction to Review

Exforge HCT is a triple combination of drugs approved for the treatment of hypertension. As such the major issue for its approval is whether each drug contributes to the combination's antihypertensive effect, i.e., does the triple, at its highest dosages, produce greater reductions in blood pressure than each of the three double combinations, at their highest dosages? A second issue is whether the triple combination produces any synergistic toxicities greater than the double combinations.

2. Background/Regulatory History/Previous Actions/Foreign Regulatory Actions/Status

As the primary clinical and statistical review states, the sponsor met with the Division on October 13, 2004, and discussed the development plans for this triple combination. The discussion culminated in a special protocol assessment that agreed that only one clinical trial was needed.

3. CMC/Microbiology/Device

The CMC reviewer, Dr. Lyudmila Soldatova, recommends approval of the product pending satisfactory completion of the facility inspections. Some initial review issues regarding adequacy of Drug Master Files (DMFs) and test specifications were resolved satisfactorily. Dr. Raanan Bloom reviewed the environmental assessment and recommended a Finding of No Significant Impact (FONSI).

4. Nonclinical Pharmacology/Toxicology

4.1. General nonclinical pharmacology/toxicology considerations (including pharmacologic properties of the product, both therapeutic and otherwise).

The Division pharmacology and toxicology reviewer, Dr. G. Jagadeesh, recommends approval from a nonclinical pharmacology and toxicology perspective. As he notes, the

sponsor did not perform pharmacology or ADME studies for the combination. The sponsor did a 12-week repeat dose toxicity study in rats. The toxicities found ((hyperplasia of the juxtaglomerular apparatus in the kidney, focal erosions of the stomach and decreased erythroid parameters) were similar to those with valsartan alone but slightly greater in incidence and severity than those found with the individual components. The sponsor attributes the toxicities to excessive pharmacologic effects of the components, although data directly supporting this exertion are not available.

4.2. Carcinogenicity

Additional carcinogenicity studies were not done for this combination product of approved drugs.

4.3. Reproductive toxicology

The sponsor did not do reproductive toxicology studies for the triple combination. Valsartan has a boxed warning and contraindication for use during pregnancy because of the risk of teratogenicity. This combination will share that labeling language.

4.4. Other notable issues

There are no other notable nonclinical pharmacology or toxicology issues.

5. Clinical Pharmacology/Biopharmaceutics

5.1. General clinical pharmacology/biopharmaceutics considerations, including absorption, metabolism, half-life, food effects, bioavailability, etc.

The clinical pharmacology reviewer, Dr. Divya Menon-Andersen, considers the NDA acceptable from a clinical pharmacology perspective. The sponsor submitted six clinical studies to support approval: three bioequivalence or relative bioavailability studies, one food effect study, one drug interaction study, and the active-controlled efficacy trial. These studies 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) and showed that there were no clinically significant pharmacokinetic (PK) interactions among the components and that food did not affect the PK.

5.2. Drug-drug interactions

The one drug-drug interaction study conducted for this submission was a comparison of the PK of the components when administered in the dual combinations versus the triple combination. The AUCs and C_{max} s are similar and within the regulatory acceptable limits with one exception: at steady state, the mean AUC and C_{max} of valsartan increased by 25 and 22%, respectively, when administered in the triple combination. However, Dr. Menon-Andersen concludes that, given the observed inter-subject variability in valsartan

PK (~ 50% CV), the increased AUC and C_{max} observed in this study is judged not to be of any clinical significance.

COMMENT: I agree that this variation of PK for valsartan, a safe and titrated antihypertensive, is not of concern.

5.3. Pathway of elimination

Additional metabolic pathway studies were not done for this combination of approved drugs.

5.4. Demographic interactions/special populations

There were no demographic interactions or special populations addressed in the PK studies. Please see the Clinical/Statistical section below for a summary of these types of interactions in the clinical study.

5.5. Thorough QT study or other QT assessment

Additional QT assessments were not done for this combination of approved drugs.

5.6. Other notable issues

There are no other notable clinical pharmacology or biopharmaceutics issues

6. Clinical Microbiology

Drug is an oral non-antimicrobial drug for which there are no clinical microbiology concerns.

7. Clinical/Statistical

7.1. Efficacy

7.1.1. Dose identification/selection and limitations

The doses selected for this triple combination are based on the approved dosages for the monotherapies and for the two approved dual combinations. The dosing of HCTZ is limited to a maximum of 25 mg as is the current practice for HCTZ monotherapy and as approved for other HCTZ combinations.

7.1.2. Studies essential for approval

In addition to the PK studies summarized in Section 5, the sponsor conducted one large double-blind factorial study of the triple combination vs. the dual combinations, Study A2302.

7.1.3. Other studies

The sponsor also conducted a long-term open label safety study of amlodipine/valsartan with optional addition of HCTZ and provided safety data from six other trials of the dual combinations with optional addition of the third component.

7.1.4. Primary clinical and statistical reviewers' findings and conclusions

From clinical and statistical perspectives Dr. Salma Lemtouni (efficacy reviewer), Dr. Shona Pendse (safety reviewer), and Dr. Ququan Liu (statistical reviewer) recommend approval. They conclude that 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. They do note that African Americans, the elderly, and individuals having concomitant cardiac conditions were under-represented in the pivotal study so that there may be populations for which the risk-benefit is not as favorable as that observed in the pivotal study.

The primary reviewers base their conclusions predominantly upon the results of the pivotal study A2302. This was a typical 8-week antihypertensive study using seated blood pressure (BP) as the primary endpoint. It did have some variations from the typical study:

- Entry BPs could be higher (145-199/110-119 or 180-199/100-109).
- The control arms were the dual combinations rather than placebo.
- The study was large—2271 patients randomized 1:1:1:1 to four arms.
- Because there were three control arms and the goal was to show superiority of the triple combo to each dual combo for either DBP or SBP or both, the Hochberg step-up procedure was used to control the type I error at 0.05. Please see the primary review for the details.

The changes from baseline in trough seated BP in Study A2302 are summarized in Table 1.

Table 1: Changes from Baseline in Seated BP in Study A2302

	LSM change from baseline	LSM difference in change (SE)	p-value	Hochberg adjusted p-value
Diastolic BP				
Val/HCTZ/Aml 320/25/10	-24.74			<0.0001*
Val/HCTZ 320/25	-19.69	-5.05 (0.539)	<0.0001	
Val/Aml 320/10	-21.49	-3.25 (0.537)	<0.0001+	
HCTZ/Aml 25/10	-19.46	-5.28 (0.539)	<0.0001	

Systolic BP				
Val/HCTZ/Aml 320/25/10	-39.68			<0.0001*
Val/HCTZ 320/25	-32.04	-7.64 (0.848)	<0.0001	
Val/Aml 320/10	-33.50	-6.18 (0.846)	<0.0001+	
HCTZ/Aml 25/10	-31.48	-8.20 (0.848)	<0.0001	
Least square means and standard errors, confidence intervals, and p-values were provided by the ANCOVA model containing treatment and region as factors and centered baseline value as covariate.				
The Hochberg adjusted p-values are based on the maximum p-value for the three comparisons in MSDBP and the maximum p-value for the three comparisons in MSSBP.				
+ Maximum p-values of the three comparisons.				

The additional reductions in BP with the triple combination compared to the dual combinations as shown in Table 1 appear to be reasonable. While I have not reproduced them here, the curves for all four arms from an ABPM substudy (shown in the primary review) are reasonably parallel throughout the 24-hour interdosing interval, with the triple showing the greatest reductions.

COMMENT: Greater reduction in BP for the triple combination compared to the dual combinations appears to be well established by Study A2302.

The primary reviewers performed appropriate subgroup analyses. There are some interesting findings from them:

- BP reductions did not appear to differ by gender.
- The additional reductions in adding HCTZ were lower in the elderly (≥ 65) than in younger patients (< 65): -3.4/2.9 vs. -6.6/3.3. Adding valsartan or amlodipine did not show differential effects by age. However, the numbers of elderly patients in the study are low so that a firm conclusion can not be drawn.
- Blacks showed lower efficacy of adding valsartan than whites: -4/1.6 vs. -9.4/6.4.

COMMENT: The label needs to note lower efficacy in blacks.

7.1.5. Pediatric use

This triple combination is not appropriate for pediatric use. The differing natures of pediatric hypertension from adult hypertension and the likelihood of a long, life-time use argue for careful selection and titration of antihypertensives in children.

7.1.6. Discussion of notable efficacy issues

There are no notable efficacy issues.

7.2. Safety

7.2.1. General safety considerations

The safety of the approved components of this triple combination is well-established. Two issues worth considering are whether the triple combo produces more hypotension and whether it ameliorates the edema seen particularly with amlodipine monotherapy.

7.2.2. Safety findings

The most frequently observed adverse events in the triple therapy subjects of the pivotal study were dizziness and edema. Regarding dizziness and hypotension, there were 9 discontinuations in the triple therapy group, 11 in the valsartan/HCTZ group, 3 in the valsartan/amlodipine group, and 1 in the HCTZ/amlodipine group. The primary review pooled dizziness, dizziness exertional, and dizziness postural and found the frequency of the pooled event of dizziness to be 9.1% in the triple therapy group, 8.2% in the valsartan/HCTZ group, 4.3% in the HCTZ/amlodipine group, and 2.7% in the valsartan/amlodipine group. However, orthostatic hypotension, as defined by a decrease of ≥ 20 in SBP or ≥ 10 in DBP when a subject moved from a sitting to a standing position, was measured at all visits. By these criteria orthostatic hypotension was very similar in all groups (about 10%).

Regarding edema, the primary reviewer pooled edema, generalized edema, gravitational edema, peripheral edema, and pitting edema. She found the frequency of edema to be 7.0% in the triple therapy group, 11.9% and 13.4% in the HCTZ/amlodipine and valsartan/amlodipine groups respectively, and 1.4% in the valsartan/HCTZ group.

COMMENT: I don't think any of these differences are critical, but they should be included in labeling. We will discuss with the sponsor what AE frequencies to include during the label negotiations.

7.2.3. Safety update

The 120-day safety update, dated October 17, 2008, include safety data from a small bioequivalence study and a 229 patient open-label study of valsartan/amlodipine plus optional HCTZ, then atenolol, vs. standard therapy. The AEs in these studies did not suggest any additional problems.

7.2.4. Immunogenicity

Immunogenicity is not a significant concern for the components of this combination.

7.2.5. Special safety concerns

The one well-known special safety concern is the potential for teratogenicity with ACE inhibitor or angiotensin receptor blocker use. There were two discontinuations due to pregnancy in the pivotal study, both in the triple therapy group. One resulted in the delivery of a healthy newborn and the other was terminated.

7.2.6. Primary reviewers' comments and conclusions

The primary safety reviewer Dr. Pendse concluded that there do not appear to be any strong safety signals with the triple therapy regimen and, given that Exforge HCT is not a novel entity and all of its individual components have been used for a significant time, both alone and in combination, the side effects of these therapies are fairly well known to health care practitioners. She judged the safety profile for Exforge HCT to be acceptable. She commented that the draft of the label provided by the sponsor does need to be amended to include greater emphasis on dizziness as a notable adverse effect seen in the triple therapy subjects, as opposed to highlighting only the frequencies of hypotension and orthostatic hypotension.

7.2.7. Discussion of notable safety issues

There are no notable safety issues.

8. Advisory Committee Meeting

We are not submitting this supplemental submission to an advisory committee.

9. Other Relevant Regulatory Issues

There are no other relevant regulatory issues.

10. Financial Disclosure

The primary clinical and statistical review describes the financial disclosures. Only one site reported a financial interest, a payment exceeding \$25,000 for honoraria and travel expenses. Hence financial interests do not appear to have affected the performance of the pivotal study.

11. Labeling

11.1. Proprietary name

The proprietary name Exforge HCT is acceptable.

11.2. Physician labeling

The primary safety reviewer is recommending including some variations in AE frequencies noted above. We will discuss these changes with the sponsor during label negotiations.

11.3. Carton and immediate container labeling

The primary reviewers did not note any problems with carton or immediate container labeling.

11.4. Patient labeling/medication guide

A medication guide is not required.

12. DSI Audits

DSI audits were not done. The results were robust by regional analyses, including comparable effects at the many U.S. sites.

13. Conclusions and Recommendations

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.

13.2. Safety concerns to be followed postmarketing

I have no safety concerns that need to be followed postmarketing.

13.3. Risk Minimization Plan

I do not recommend a risk minimization plan. There are no unusual or excessive risks for this product.

13.4. Postmarketing studies

I do not recommend any postmarketing studies. There are no concerning unanswered questions regarding this product.

13.5. Comments to be conveyed to the applicant

The proposed labeling changes will be discussed with the sponsor during label negotiations.

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Thomas Marciniak
4/7/2009 01:54:18 PM
MEDICAL OFFICER