CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-217

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review Memo

Date	July 28, 2009
From	Thomas A. Marciniak, M.D.
Subject	Cross-Discipline Team Leader Review
NDA/BLA # Supp #	NDA 22-217
Proprietary / Established (USAN) names	Valturna / valsartan/aliskiren
Dosage forms / strength	Oral tablets / 150/160 and 300/320 mg
Proposed Indication(s)	Initial therapy for hypertension
Recommended:	Approval (subject to response to CMC deficiencies)

1. Introduction to Review

Valturna is a dual combination of drugs (valsartan, an angiotensin receptor blocker, and aliskiren, a renin inhibitor) approved for the treatment of hypertension. The sponsor submitted the pivotal study for this combination with the original aliskiren NDA submission to support the use of aliskiren with valsartan. The sponsor is now seeking to market a combination product and to secure its approval for the initial therapy for hypertension.

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

The sponsor submitted the pivotal Study 2327 for this combination with the original aliskiren NDA 21-985 submission to support the use of aliskiren with valsartan after an initial study of the combination failed. My review of the study with the original submission confirmed that each component of the combination contributed to the antihypertensive effect. We agreed at a pre-NDA meeting on February 22, 2007, that this one study could support approval of the combination product.

3. CMC/Microbiology/Device

The FDA CMC reviewer, Dr. Prafull Shiromani, does not recommend approval until satisfactory responses to deficiencies noted in a letter dated March 27, 2009 are provided. He also notes that the environmental assessment and biowaiver and dissolution assessments are completed. Please see his review for details on the deficiencies noted.

COMMENT: The deficiencies Dr. Shiromani has noted appear to be typical of those noted in an initial CMC review, e.g., tightening some specifications and providing additional detail of manufacturing processes. He has reported at meetings that he believes the sponsor can address all deficiencies. My recommendation for approval depends upon Dr. Shiromani concluding that the sponsor has adequately addressed all deficiencies.

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 13-week repeat dose toxicity study in rats. Daily administration of aliskiren hemifumarate and valsartan at doses of 300:300 mg/kg/day for 13 weeks resulted in minimal vacuolation of the squamous epithelium at the limiting ridge of the non-glandular stomach in both sexes. It was also noted in a few males treated with valsartan alone at 300 mg/kg/day. A trend to reversibility was seen in recovery group animals. Animals receiving valsartan alone also exhibited increased incidence of renal tubular basophilia and minimal but statistically significant decreases in erythrocyte parameters. Most of the toxic effects noted in previous studies with either drug administered alone were not demonstrated in the present study because of sub-threshold doses. The combined administration of aliskiren hemifumarate and valsartan did not augment any existing toxicities of the individual agents nor induce any new toxicities. Toxicokinetics data showed that exposure to aliskiren was at least 3-fold higher in absence of valsartan than in combination with valsartan. In contrast, there was no effect of aliskiren on valsartan exposure.

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 dual combination. Both drugs have boxed warnings and contraindications 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 application contains four clinical pharmacology studies: a bioequivalence study (study number SPV100A), a food effect study (study number SPV100A2114), a drug interaction study conducted in healthy

subjects (study number SPV100A), and a pharmacodynamic (PD) study conducted in healthy subjects (study number SPV100A2101), The results of the bioequivalence study 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). Administration of the combination with a high fat meal decreased systemic exposure to aliskiren by > 70%. This is in agreement with the prior knowledge regarding aliskiren disposition.

5.2. Drug-drug interactions

The potential for a pharmacokinetic and PD drug interaction between aliskiren and valsartan was assessed in healthy subjects (Study VEA489A2104). At steady state, when administered together, the mean AUC_{last} and C_{max} for aliskiren decreased by about 25% and that of valsartan decreased by about 15%. The 90% confidence intervals for AUC and C_{max} ratios for both aliskiren and valsartan were not within the no effect boundaries (80 to 125%). The observed plasma renin concentrations following administration of the combination was higher than that observed with either aliskiren or valsartan alone. The observed decrease in plasma renin activity following administration of the combination was similar to that observed with aliskiren alone. Given the observed inter-subject variability in aliskiren and valsartan PK (~ 50% CV) and the observed PD effects of the combination, Dr. Menon-Andersen judges the decreased AUC and C_{max} observed in this study not to be of any clinical significance.

COMMENT: I agree that the interaction should not be clinically relevant.

5.3. Pathway of elimination

The sponsor did not perform additional metabolic pathway studies 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

The sponsor did not perform additional QT assessments for this combination of approved drugs.

5.6. Other notable issues

There are no other notable clinical pharmacology or biopharmaceutics issues

6. Clinical Microbiology

Valturna 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 sponsor based the doses selected for this dual combination on the approved dosages for the monotherapies. The highest approved dosages are included in one combination tablet and half of these dosages in the other.

COMMENT: These dosages are the ones studied in the pivotal study. The proposed marketed dosage forms should be reasonable for covering the typical usage of these drugs.

7.1.2. Studies essential for approval

In addition to the clinical pharmacology studies summarized in Section 5, the sponsor conducted one large double-blind factorial study of the dual combination vs. the monotherapies (Study 2327) and a long-term safety study (Study 2301).

7.1.3. Other studies

The sponsor had conducted an earlier large factorial study (Study 2203) that apparently failed because of a large placebo effect. The sponsor also submitted results from a study of the triple combination valsartan/aliskiren/hydrochlorothiazide (HCTZ) vs. the HCTZ dual combinations (Study 2331).

7.1.4. Primary clinical and statistical reviewers' findings and conclusions

From clinical and statistical perspectives Dr. Shen Xiao (clinical reviewer) and Dr. Ququan Liu (statistical reviewer) recommend approval. They conclude that this combination product demonstrated clinically and statistically significant reductions in both trough seated diastolic and systolic blood pressure (BP) compared to placebo and each respective monotherapy in one randomized, double-blind, placebo-controlled trial. Their primary review provides the details of the BP reductions. At the highest to-be-marketed dose (320/300 mg) at 8 weeks the additional reductions compared to valsartan 320 mg were –4.4/-2.5 and compared to aliskiren 300 mg -4.2/-3.2.

COMMENT: Both the clinical and statistical reviewers of this submission and I in my original review of this study conclude that Study 2327 was conducted well and that the sponsor's analyses of the primary endpoint were appropriate. We all agree that the

combination of aliskiren and valsartan has additional BP lowering effects compared to the monotherapies.

In addition the sponsor is seeking an indication for first line use in the treatment of hypertension. We have an established approach for approval of such an indication based on graphs of the probability of achieving BP goals relative to baseline BP. The statistical review, Dr. Liu, evaluated the consistency of the sponsor's submission with our guidance document called "points to consider in generating graphs for initial therapy with combination antihypertensive drugs." Overall she judged that the predicted probabilities of achieving blood pressure control obtained from the logistic regression modeling (without treatment-by-baseline interaction) with inclusion of all available data were adequate.

7.1.5. Pediatric use

We do not consider combination antihypertensives to be appropriate for pediatric use.

7.1.6. Discussion of notable efficacy issues

I have two efficacy issues that I think warrant additional comment: (1) control throughout the interdosing interval; and (2) efficacy in blacks.

I examined control throughout the interdosing interval in Study 2327 in the addendum dated February 26, 2007, to my review of the original NDA submission for aliskiren monotherapy. I have reproduced from that review below figures showing the change from baseline in ambulatory DBP by hour in Figure 1 and for SBP in Figure 2.

Figure 1: Reviewer's Changes from Baseline in Ambulatory DBP by Hour in Study 2327

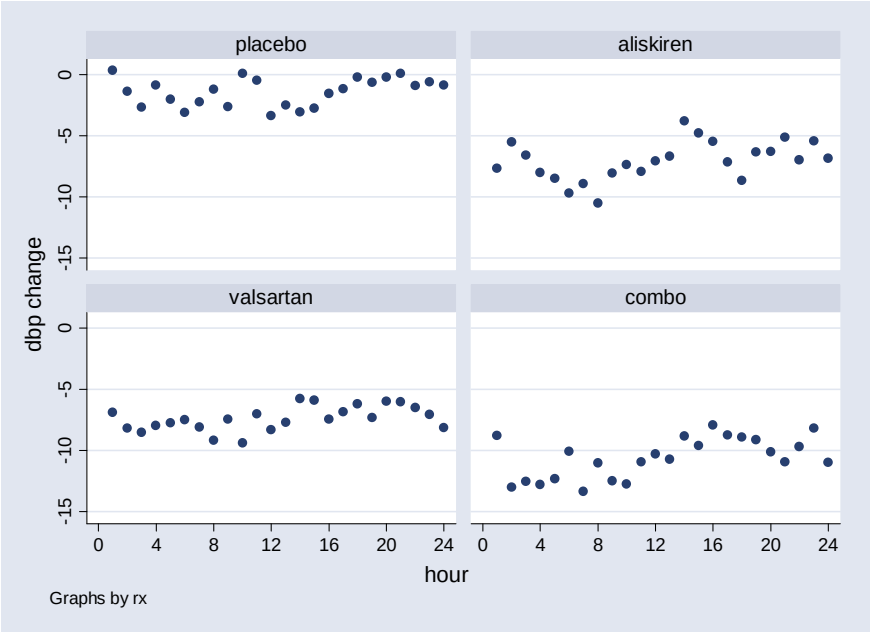
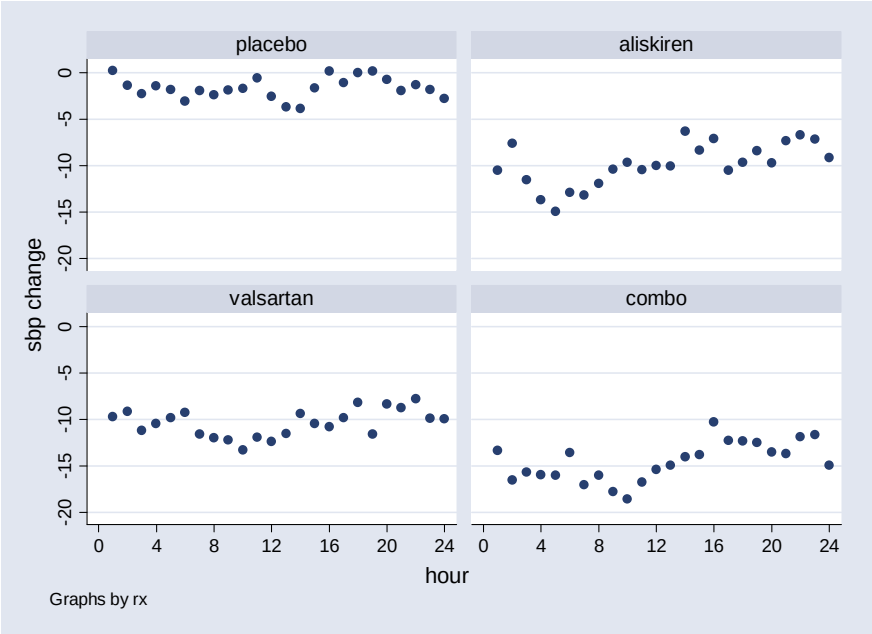


Figure 2: Reviewer's Changes from Baseline in Ambulatory SBP by Hour in Study 2327



COMMENT: The aliskiren monotherapy shows the suggestion of a more pronounced peak effect than either valsartan monotherapy or the combination. Based on this possible finding we required a postmarketing commitment for the sponsor to demonstrate that twice daily dosing was not more effective than once daily dosing. However, because the combination does not share this suggestion of a pronounced peak effect and the pattern of control looks reasonable for the combination throughout the interdosing interval, I do not recommend any additional studies regarding more frequent than daily dosing for Valturna.

Regarding race, there were two few numbers in racial groups other than blacks and whites to generate reliable estimates. I show the changes from baseline in BP by race in Table 1.

Table 1: Reviewer's Mean Placebo-Subtracted Changes from Baseline in BP by Race in Study 2327

	Half Dose at 4 weeks				Full Dose at 8 weeks			
	White		Black		White		Black	
	SBP	DBP	SBP	DBP	SBP	DBP	SBP	DBP
Aliskiren	-6.4	-2.9	-4.2	-1.9	-8.8	-5.0	-6.3	-4.0
Valsartan	-6.3	-4.3	-4.4	-3.0	-9.1	-6.0	-4.7	-4.4
Combo	-11.0	-6.5	-4.7	-3.3	-13.6	-8.7	-6.6	-6.1

COMMENT: My comments from 2007 still seem appropriate: "Both aliskiren and valsartan were substantially less effective in blacks than in whites. It is not clear that the combination is more effective than monotherapy in blacks. Only the DBP value at full dose appears to show incremental reduction, but it is the value least consistent with the other values." The label needs to mention decreased efficacy in blacks.

7.2. Safety

7.2.1. General safety considerations

Both aliskiren and valsartan are renin-angiotensin system (RAS) inhibitors. RAS inhibitors produce hyperkalemia, mild hemoglobin reduction, and (at least acutely) decreased renal function. Both drugs have shown these effects as monotherapies. Hence the safety review should place special emphasis on examining these adverse effects.

7.2.2. Safety findings

The primary clinical reviewer, Dr. Xiao, identified only hyperkalemia as the major finding worse in the combination than in the monotherapies. Otherwise he judged the adverse effects to be comparable to the monotherapies. Regarding hyperkalemia, he notes rates of hyperkalemia (serum potassium >5.5 mEq/L) of 3.4% with the combination compared to 1.2% with aliskiren monotherapy, 1.0% with valsartan monotherapy, and 2.1% with placebo in the placebo-controlled trials. He also notes that the majority of the elevations were transient and that the rate of potassiums ≥ 6.0 was not higher with the combination than with placebo. A higher rate of hyperkalemia with placebo than aliskiren or valsartan is inconsistent with the larger monotherapy trials and with the monotherapy labels.

I examined the potassiums ≥ 6.0 in the placebo group in Study 2327. I show the extreme values in Table 2 and all values for the two patients with more than one extreme value in Table 3.

Table 2: Potassiums ≥ 6.0 in the Placebo Group in Study 2327

patient	creatinine*	day	potassium
1	1.1	1	6.3
2	1.3	1	7.5
2	1.3	45	8.5
3	1.1	-21	8.9
3	1.1	28	6.9
6	0.7	1	8.9
7	0.8	1	9.1
13	0.7	28	7.7
15	1.6	1	6.1
16	0.9	42	6.1

patient	creatinine*	day	potassium
18	0.8	14	9.4
40	0.9	56	6

*baseline

Table 3: Potassiums for Placebo Patients with >1 High Potassium in Study 2327

patient 2		patient 3	
day	potassium	day	potassium
-33	4.2	-21	8.9
1	7.5	-8	4.4
15	4.7	1	4.8
30	4.5	14	4.7
45	8.5	28	6.9
59	5	40	4
		56	4.5

The high potassiums in the placebo group appear highly erratic and likely related to specimen hemolysis. However, patient 16 also had a high value (5.5) at day 56 with all values >5 and patient 40 also had a high value (5.7) at day 42.

There were no hyperkalemia AEs in either Study 2327 or in Study 2203. In the long term, uncontrolled, open-label Study 2301, hyperkalemia AEs were reported in 7 patients (1%), 2 of whom were reported to be discontinued due to the AE. About 5% of the patients had at least one serum potassium ≥ 5.5 meq/L (excluding anomalous high values) at some time during the study; about 0.8% of patients discontinued study treatment with a high serum potassium. Patients with hyperkalemia were older (median age 62 vs. 55) with slightly lower mean baseline estimated creatine clearance compared to patients without hyperkalemia; patients who discontinued with a high potassium were substantially older (median age 67) and had greater reductions in estimated creatinine clearance on-study (median -24 vs. -10 ml/min). While about 25% of the hyperkalemic episodes began in the first two months, the median time to the first potassium ≥ 5.5 was about 7 months and first episodes were reported throughout the study.

COMMENT: The sponsor proposes (b) (4) *I recommend including a summary of the Study 2301 findings in the label because those findings should be more reflective of clinical practice.*

Regarding hemoglobin reductions, the sponsor reported a slightly greater mean decrease in the short-term, placebo-controlled studies for the combination (-2.5 g/L) than for aliskiren (-0.4) or valsartan (-1.3) compared to an increase for placebo (+0.7). I noted a mean decrease of about 2% in each of the two large aliskiren/valsartan factorial studies, consistent with the sponsor's estimates. In the long term safety Study 2301 I also found about a 2.2% mean reduction if hemoglobin from baseline to last measurement. This reduction may represent an underestimate because, for the four

patients for whom the investigators reported anemia AEs, only two of them have decreases exceeding this mean reduction. The sponsor also reports that in the long term study eight patients (1.4%) had hemoglobin decreases >20%, only one remaining in the normal range.

7.2.3. Safety update

Per Dr. Xiao, the 120-day safety update did not provide any new clinical study data. Data from the sponsor's global safety database for aliskiren and valsartan as concomitant medication did not reveal any safety signals other than the ones reported in the NDA.

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.

7.2.6. Primary reviewers' comments and conclusions

Dr. Xiao overall judged the AE rates to be comparable with the combination and the monotherapies and noted only the differences in hyperkalemia rates in Study 2327. Please see my discussion of the problems with Study 2327 in Section 7.2.2. He judged the AE profile of this combination product to be acceptable for antihypertensive combination therapy.

7.2.7. Discussion of notable safety issues

I do not have any major safety concerns regarding this product. As with other RAAS inhibitors, physicians will need to monitor patients for increases in serum potassium and for decreases in renal function. In the clinical studies investigators handled these problems by monitoring, occasional changes in dosages, and rarely discontinuation.

8. Advisory Committee Meeting

We are not submitting this combination product 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. There are no financial involvements that should adversely affect the overall integrity of the studies.

11. Labeling

11.1. Proprietary name

The proprietary name Valturna is acceptable.

11.2. Physician labeling

I have a number of minor changes to recommend. 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. DSI has audited other studies for aliskiren recently and has not identified critical problems.

13. Conclusions and Recommendations

13.1. Recommended regulatory action

I recommend Valturna be approved for the treatment of hypertension in adults contingent upon satisfactory resolution of the CMC issues. This dual combination produced greater reductions in blood pressure than the monotherapies. The adverse event profile is similar to those of the monotherapies. The combination does appear to produce more hyperkalemia than the monotherapies but discontinuations for hyperkalemia were still rare and the hyperkalemia can be managed with monitoring and dosage reduction if needed.

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.

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/s/

THOMAS A MARCINIAK
07/28/2009