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APPLICATION NUMBER:
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CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review Memo

Date	August 9, 2010
From	Thomas A. Marciniak, M.D.
Subject	Cross-Discipline Team Leader Review
NDA/BLA #	NDA 22-545
Supp #	
Proprietary / Established (USAN) names	Tekamlo™/ aliskiren/amlodipine
Dosage forms / strength	Oral tablets / 150/5, 150/10, 300/5, and 300/10 mg
Proposed Indication(s)	Treatment of hypertension; initial therapy for hypertension
Recommended:	Approval

1. Introduction to Review

Tekamlo is a dual combination of drugs (aliskiren, a renin inhibitor, and amlodipine, a calcium channel blocker) approved for the treatment of hypertension. Amlodipine has exhausted its exclusivity and is now eligible for generic distribution. Because the drugs are from different classes with different mechanisms of action, we would expect their blood pressure lowering effects to be additive. Hence the aliskiren sponsor is seeking to market a combination product of the two drugs and to secure approval of the combination for the initial therapy for hypertension.

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

The primary clinical review includes a pertinent summary of the US regulatory history. My short summary is that the sponsor discussed their pivotal study with us and the study and its analysis are consistent with our recommendations. This combination is not currently approved elsewhere in the world.

3. CMC/Microbiology/Device

The FDA CMC reviewer, Dr. Lyudmila Soldatova, recommends approval from a CMC standpoint. She is recommending 24 and 18 month expiration periods for various packagings of the combination based on the submitted data. (b) (4)

She notes that the Office of Compliance has assigned an overall Acceptable rating for all drug substance and drug product manufacturing facilities.

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 amlodipine besylate separately and together at doses of 30/1, 90/3, and 300/10 mg/kg/day for 13 weeks resulted primarily in findings of hypertrophy and vacuolation of the zona glomerulosa of the adrenals. Toxicology studies with amlodipine alone have reported similar findings. There were also three deaths attributed to drug, two males in the high dose combination and one male in the aliskiren alone group. These deaths were attributed to aspiration of the dosing solution, which was administered by gavage. This toxicology study of the combination did not identify any new toxicities not reported for the monotherapy toxicology studies.

The plasma concentrations of aliskiren measured at the highest combination dose used in the current study were below those anticipated clinically (0.4 to 0.6 times based on AUC values), indicating the absence of a safety margin for humans. However, there was no observed toxicity for aliskiren in this study. There are safety margins for the observed adrenal toxicity, which Dr. Jagadeesh estimates as 40 and 3.

COMMENT: Dr. Jagadeesh also notes that these marketed products have been used frequently concurrently in humans. I agree with him that the preclinical findings, considered in light of the clinical experience, do not suggest a safety signal for the combination.

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, recommends approval from a clinical pharmacology perspective. She notes that, in addition to the clinical

efficacy and safety studies, the application contains four clinical pharmacology studies: one relative bioavailability study, two bioequivalence studies, and one food effect study. Her key findings are the following:

- Tekamlo is bioequivalent to the free combination of aliskiren and amlodipine.
- Systemic exposure to aliskiren was reduced by ~ 70% when Tekamlo 300/10 mg was administered with food. This observation is consistent with prior findings for aliskiren¹. Systemic exposure to amlodipine following administration of Tekamlo 300/10 mg was not affected by food.

5.2. Drug-drug interactions

The review has this labeling recommendation: “Aliskiren exposure is increased slightly (up to 29%) when co-administered with amlodipine, but amlodipine exposure remains unchanged when co-administered with aliskiren. The slight exposure change of aliskiren in the presence of amlodipine is not clinically relevant.”

COMMENT: The “up to 29%” is not accurate. The mean aliskiren AUC was 29% higher with coadministration of aliskiren and amlodipine than with aliskiren alone. I agree that the interaction should not be clinically relevant but we will amend the label to report accurately the results of the study performed.

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

Tekamlo 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 aliskiren monotherapy and the commonly used dosages for amlodipine monotherapy. The sponsor omitted testing the approved amlodipine 2.5 mg dosage recommended for small, fragile, or elderly individuals or patients with hepatic insufficiency.

COMMENT: For fragile patients individualizing monotherapies would appear to be more appropriate clinically. Hence I consider the dosages studied and proposed to be marketed for this combination to be acceptable.

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, 8-week factorial study of the dual combination vs. the monotherapies (Study 2305) and a long-term safety study of the combination (Study 2301). Because the pair-wise comparisons of the combinations with amlodipine 10 mg were not statistically significantly better than amlodipine 10 mg monotherapy, the sponsor also conducted another study (Study 2304) with the 10 mg combinations.

7.1.3. Other studies

The sponsor also performed an 8-week study in blacks and additional 6-8 week studies in patients inadequately controlled on monotherapies for the European regulatory authorities. ^{(b) (4)}

7.1.4. Primary clinical and statistical reviewers' findings and conclusions

From clinical and statistical perspectives Dr. Shen Xiao (clinical reviewer) and Dr. Valeria Freidlin (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 and a second randomized, double-blind, active-controlled trial of the amlodipine 10 mg dosages. Dr. Freidlin reports no statistical issues in this NDA and agrees with the statistical methods used by the sponsor. At the highest dosage (300/10) the reduction in trough cuff BP was only 2.2/2.6 compared to amlodipine 10 mg in Study 2305. In Study 2304 the reductions at the highest dosage were more significant, 6.2/3.8. The

reductions in BP were evident at 1 week after initiating therapy but, particularly when considering that the placebo effect was virtually maximal at 1 week, the reductions were only about half maximal and were only close to maximal at 2 weeks—see Figures 1 and 2 in the Statistical Review for the BP reductions by week in Study 2305. The primary reviews provide more details of the BP reductions.

In addition the sponsor is seeking an indication for first line use in the treatment of hypertension. Dr. Freidlin confirmed the results of the sponsor's logistic regression model with treatment and region as factors and baseline BP as a covariate. For DBP statistically significantly greater number of patients reached DBP response (msDBP <90 mmHg, or a > 10 mmHg reduction from baseline) at endpoint in the 300/10 group than in the amlodipine 10 mg group ($p < 0.0001$). Numerically more patients in the 150/10 mg group reached DBP response as compared to amlodipine 10 mg monotherapy but the difference was not statistically significant. For SBP both comparisons were statistically significant.

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

There are two other notable efficacy issues:

- Aliskiren has a pronounced food effect. A high fat meal reduces mean AUC and C_{max} by 71% and 85% respectively. This variability in absorption did not translate into a more variable BP than with other active controls in the monotherapy trials in which drug was administered without a prespecified relationship to meals. Aliskiren monotherapy is currently labeled that patients should establish a routine pattern for taking it with regard to meals.

Aliskiren AUC and C_{max} were reduced by 80% and 90% respectively when aliskiren was administered as Tekamlo compared to Tekturna. The combination clinical trials, like the monotherapy trials, did not specify the relationship to meals for study drug administration. Despite this failure, the variability (e.g., the standard errors) of the BP measurements for the combination is virtually identical to those for amlodipine alone.

COMMENT: Because we did not require more restrictive labeling than taking aliskiren monotherapy with a constant relationship to meals, I do not see the need for more restrictive labeling for the combination. The addition of amlodipine should help with smoothing any variability due to the food effect—if any exists. Some colleagues have argued that not controlling for a food effect may have produced an unfair trial, i.e., the aliskiren monotherapy may not have been taken fasting for maximal effect. I do not agree with this argument because the critical

challenge for the combination was beating amlodipine 10 mg and because the combination also may not have been administered fasting.

- Aliskiren monotherapy produces lower BP reductions in blacks than whites. In Study 2305, in which blacks constituted about 20% of the study populations and which included between 34 and 39 blacks per arm, the 300/10 combination results (11/9 mean placebo-subtracted reduction) were worse than amlodipine 10 mg alone (17/10) while the 150/10 combination (17/11) was similar to amlodipine 10 mg alone. The 300/5 combination (10/8) also did not beat amlodipine 5 mg alone (14/6) for SBP. Regarding the combinations with aliskiren 150 mg, the combinations with 10 mg were similar to amlodipine 10 mg alone while the combinations with 5 mg beat the monotherapies. Study US01 exclusively in blacks and with more severe hypertension did show that the high dose combination beats amlodipine 10 mg by a mean reduction of 5.2/3.3.

COMMENT: While Study US01 is somewhat reassuring, I am still concerned that the other study of two suggests no benefit in blacks for the combination compared to amlodipine 10 mg alone. The 300/10 combination appears to be not useful for blacks with mild-to-moderate hypertension because the BP effect is no different than amlodipine 10 mg alone and the adverse effects, such as edema for amlodipine and hyperkalemia for aliskiren, are not ameliorated.

7.2. Safety

7.2.1. General safety considerations

We have no expectations regarding negative interactions for safety for these two drugs. In fact, we have some suggestions that RAAS inhibitors may reduce the edema associated with amlodipine.

7.2.2. Safety findings

The primary clinical reviewer, Dr. Xiao, found that, in general, the adverse event profile was similar across the aliskiren/amlodipine combination and component monotherapy arms. He notes that peripheral edema, seen with increased frequency with amlodipine monotherapy and with the combination, was the most common adverse event (with amlodipine 10 mg alone and in combination) and was also the most common reason for AE-related patient withdrawals. The edema rates in Study 2305 are confusing: Both the amlodipine 10 mg monotherapy and the 300/10 combination had the highest rates, about 14%, while the 150/10 combination was lower 8% and the combinations with amlodipine 5 mg were only slightly higher than placebo or aliskiren alone. None of the edema AEs were serious; withdrawals for edema were uncommon, with 5 in the amlodipine 10 mg arm, 2 in the 150/5 arm, and 1 each in the 150/5 and 300/10 arms. In the long term safety study, edema was as frequent with the amlodipine/aliskiren combination as it was with the amlodipine/HCTZ combinations (both about 11%) and much more frequent than with aliskiren monotherapy (about

1%). Women reported edema more frequently than men regardless of arm. In blacks in Study 2305 the edema rate was high (14%) only in the 300/10 combination arm, with most other amlodipine-containing arms reporting 2.4-2.9% and no edema reported in the arms without amlodipine and in the 150/5 combination arm. In blacks in Study US01 edema rates for amlodipine and for the combination were also similar (9% vs. 8% respectively) but this study only tested the aliskiren 300 mg and amlodipine 10 mg dosages (except for an initial week at half these dosages.)

COMMENT: There appears to be some consistency that aliskiren 300 mg does not reduce the rates of edema associated with amlodipine 10 mg use. In the original NDA submission aliskiren was only associated with peripheral edema at dosages of 600 mg. There have been post-marketing reports of edema associated with aliskiren use and we changed the label to mention those reports.

As Dr. Xiao notes, no dose-dependent AEs were observed in the combination studies other than peripheral edema. Hypotension was uncommon. Other common adverse events identified in aliskiren or amlodipine monotherapy, including dizziness, headache, cough, and diarrhea, occurred at a similar incidence in the combination, placebo, and monotherapy treatment arms in the short-term studies. The incidence of hyperkalemia (defined as a serum potassium level >5.5 mmol/L at any post baseline visit) during aliskiren/amlodipine combination treatment was similar to that seen with aliskiren monotherapy.

7.2.3. Safety update

Dr. Xiao, the primary clinical reviewer, incorporated the data from the 120-day safety update into his overall review of safety. One major addition from this update was the study report for Study US01 in blacks with stage 2 hypertension.

7.2.4. Immunogenicity

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

7.2.5. Special safety concerns

The sponsor provided a risk management plan for the aliskiren/amlodipine fixed combination. This plan will be the same as that planned for aliskiren monotherapy and will focus on risks including hyperkalemia, diarrhea, rash, angioedema, decreases in hemoglobin and hematocrit, hypotension, renal dysfunction, cough, moderate and severe renal impairment, renal vascular hypertension, and cardiovascular morbidity and mortality. The risk management activities will include the regular pharmacovigilance activities and risk minimization activities as shown in the aliskiren monotherapy.

COMMENT: I agree that risk management for this combination does not need to differ significantly from that for aliskiren monotherapy. The one additional adverse effect of

minor concern is the peripheral edema induced by amlodipine. At the 10 mg dosage of amlodipine aliskiren 300 mg does not appear to ameliorate it.

7.2.6. Primary reviewers' comments and conclusions

Dr. Xiao overall considers the adverse event (AE) profile to be acceptable for an antihypertensive. He does not note any particular safety concerns or have any recommendations regarding risk management beyond what the sponsor proposed and he does not have any recommendations for post-marketing studies.

7.2.7. Discussion of notable safety issues

I do not have any major safety concerns regarding this product. The sponsor has already addressed my minor concerns as described in Section 7.2.5 above.

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 review describes the financial disclosures. One investigator reported receiving speaker honoraria in excess of \$25,000 but otherwise there are no financial involvements that should adversely affect the overall integrity of the studies.

11. Labeling

11.1. Proprietary name

The proprietary name Tekamlo 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

We did not request DSI audits of the clinical efficacy studies because many aliskiren hypertensive studies have been audited in the past without evidence for significant problems. The clinical pharmacology reviewer requested DSI audits of the sites for the bioequivalence Study 2102. The DSI reviewer considered one subjects data to be unacceptable because of pre-dose amlodipine concentrations and requested the clinical pharmacology reviewer to assess the data for four other subjects but concluded the remainder of the data were acceptable.

13. Conclusions and Recommendations

13.1. Recommended regulatory action

I recommend Tekamlo be approved for the treatment of hypertension in adults. This dual combination produced greater reductions in blood pressure than the monotherapies. The adverse event profile is similar to those of the monotherapies.

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.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22545	ORIG-1	NOVARTIS PHARMACEUTICA LS CORP	ALISKIREN/AMLODPINE(SPA 100A)FIXED COMBO

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

/s/

THOMAS A MARCINIAK
08/09/2010