

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**22-401**

**CROSS DISCIPLINE TEAM LEADER REVIEW**

## Cross-Discipline Team Leader Review Memo

<b>Date</b>	September 14, 2009
<b>From</b>	Thomas A. Marciniak, M.D.
<b>Subject</b>	Cross-Discipline Team Leader Review
<b>NDA/BLA #</b>	NDA 22-401
<b>Supp #</b>	
<b>Proprietary / Established (USAN) names</b>	Twynsta / telmisartan/amlodipine
<b>Dosage forms / strength</b>	Oral tablets / 40/5, 40/10, 80/5, 80/10 mg
<b>Proposed Indication(s)</b>	Initial therapy for hypertension
<b>Recommended:</b>	Approval for initial therapy for hypertension subject to acceptable manufacturing site inspections and supplemental quality reviews

### 1. Introduction to Review

Twynsta is a dual combination of drugs (telmisartan, an angiotensin receptor blocker, and amlodipine, a calcium channel blocker) approved for the treatment of hypertension. Amlodipine has exhausted its exclusivity and is now eligible for generic distribution. The telmisartan 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 sponsor discussed plans for this combination at a pre-IND meeting on July 22, 2005. The Division recommended studying the highest dose T80/A10 and left open the lowest dose to study. The sponsor also discussed first-line use with the Division at a meeting on April 9, 2008. The Division noted that, because the lowest dose of amlodipine was not used, there may be limitations placed on the population considered for initial therapy.

### 3. CMC/Microbiology/Device

The FDA CMC reviewer, Dr. David J. Claffey, Recommend that this application be approved from a CMC perspective on receipt of acceptable recommendations from the Office of Compliance (manufacturing sites), the environmental assessment reviewer, and the ONDQA biopharmaceutics reviewer. Dr. Claffey had expressed concerns about possible mutagenic impurities and about the instability of the tablets in 50% relative humidity or greater environments. The sponsor addressed the former concern by reporting that the current synthetic process does not produce the mutagenic impurities and the latter concern by withdrawing [REDACTED] (b) (4) and proposing marketing the tablets only in aluminum blister packs.

#### **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. Gowra Jagadeesh, recommends approval from a nonclinical pharmacology and toxicology perspective. The sponsor did not perform any additional pharmacology or toxicology studies for the combination but is relying upon its studies done for telmisartan, NDA 20-850, and our findings of safety and efficacy for amlodipine, NDA 19-787. Dr. Jagadeesh considers this acceptable.

##### **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. Telmisartan has a 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. Islam Younis, considers the NDA acceptable from a clinical pharmacology perspective, provided that the audit reports from the Division of Scientific Investigations (DSI) are satisfactory. DSI recommends accepting the bioanalytical data for review from site (b) (4) without onsite inspection because that site was inspected twice since early 2008 and considered the staff highly qualified and keen on improving procedures where necessary. Audits of other sites are pending.

The sponsor performed two studies to evaluate the bioequivalence of the highest and lowest fixed dose combination tablets with respect to the individual tablets: 1235.3 for the 40/5 tablet and 1235.4 for the 80/10 tablet. There was no statistically significant difference in C<sub>max</sub> and AUC between the combination tablets and the individual tablets.

The sponsor also performed a food effect study with the 80/10 tablet. Dr. Younis notes that the proposed labeling does not include information for the effect that food has on

telmisartan's Cmax (60% decrease). He recommends including this information in the label.

#### 5.2. Drug-drug interactions

Dr. Younis comments that there is no *in vitro* basis to suspect drug-drug interactions between amlodipine and telmisartan. The sponsor performed two studies to evaluate any potential interactions: 1235.2 for the effect of amlodipine on telmisartan and 502.125 for the effect of telmisartan on amlodipine, both at steady state for the individual components. These studies did not demonstrate any interaction between the two drugs.

#### 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

Twynsta 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 and half of the highest approved dosages are included in four combination tablets.

*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 double-blind, placebo-controlled factorial study 1235.1 of the dual combinations vs. the monotherapies and a long-term safety study. The factorial study was large: 16 arms (4 x 4 factorial for telmisartan 20, 40, and 80 mg and amlodipine 2.5, 5, and 10 mg plus placebo), 1461 adult patients with hypertension (DBP 95-119) randomized. Randomization was unequal, with the arms of primary interest (the planned to-be-marketed dosages) with more patients. The primary endpoint was change from baseline in seated cuff trough DBP at eight weeks. Ambulatory blood pressure monitoring (ABPM) was also done at baseline and end in half the patients.

#### 7.1.3. Other studies

The sponsor also used data from the ONTARGET study to support safety findings. ONTARGET was a large (25,620) cardiovascular (CV) outcomes trial of telmisartan, ramipril, or the combination in high CV risk patients. Many patients also received amlodipine as a concomitant medication (non-randomized).

#### 7.1.4. Primary clinical and statistical reviewers' findings and conclusions

From clinical and statistical perspectives Dr. Melanie Blank (clinical reviewer) and Dr. Ququan Liu (statistical reviewer) recommend approval for the treatment of hypertension. 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.

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 study also seems to support the combination therapy for use as an initial therapy indication in patients with higher blood pressure baselines.

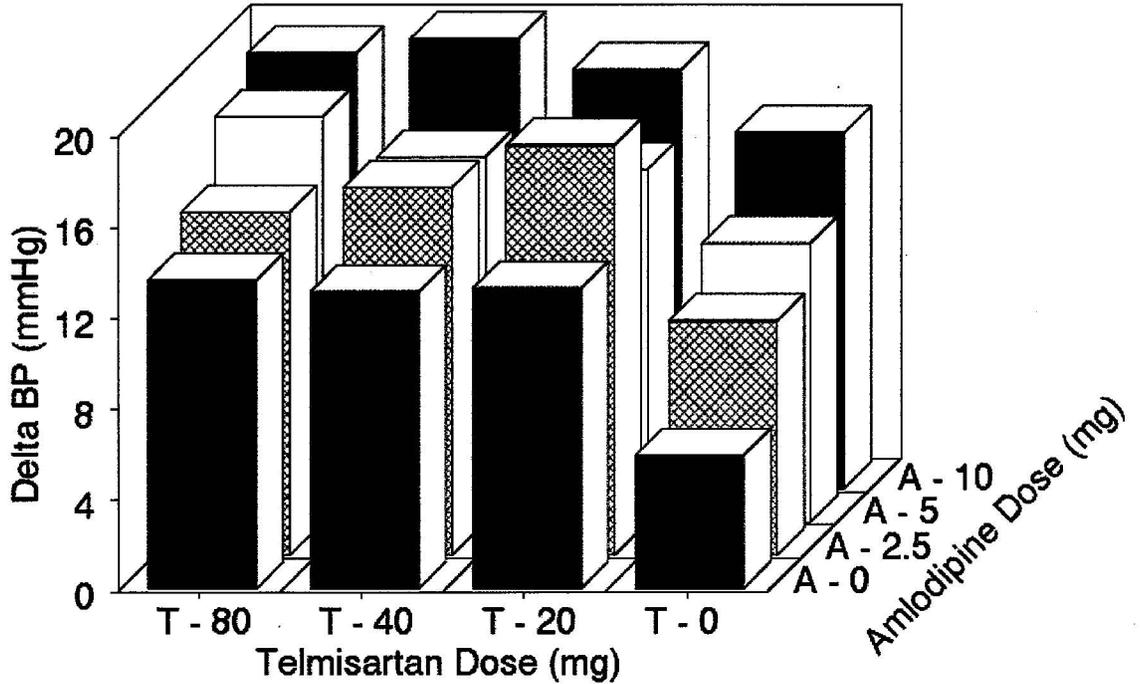
#### 7.1.5. Pediatric use

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

#### 7.1.6. Discussion of notable efficacy issues

Telmisartan has a relatively flat dose-response curve. As documented in the label, the dosages of 40 and 80 mg produce similar reductions in BP. In the pivotal trial 1235.1, telmisartan dosages of 40 and 80 mg produced similar reductions and even 20 mg was little different, as shown in Figure 1 (Figure 8 from the primary clinical and statistical review.)

**Figure 1: Delta Sitting Diastolic Mean BP, Baseline to Final (mmHg) from FAS-TC**

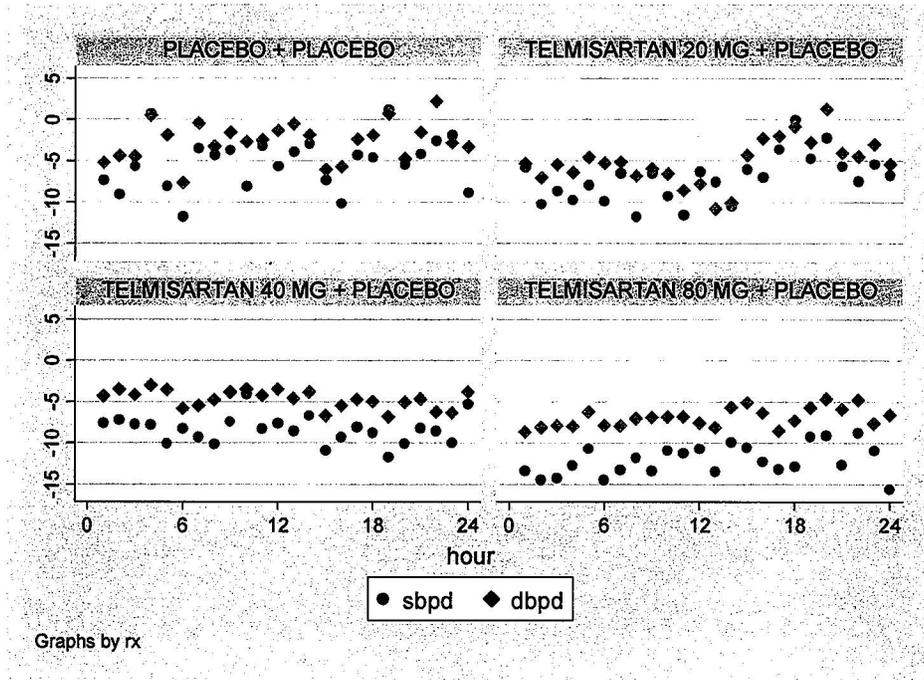


These results raise the question of whether the telmisartan 80 mg dosage should be marketed—and one could even make a similar argument for not marketing the 40 mg dosage. Hence I scrutinized the ABPM results to determine whether they confirmed or refuted the seated cuff trough findings. I show in Table 1 the mean 24-hour BP reductions and in Figure 2 through Figure 7 the mean BP reductions from baseline by hour for the various groups in Study 1235.1.

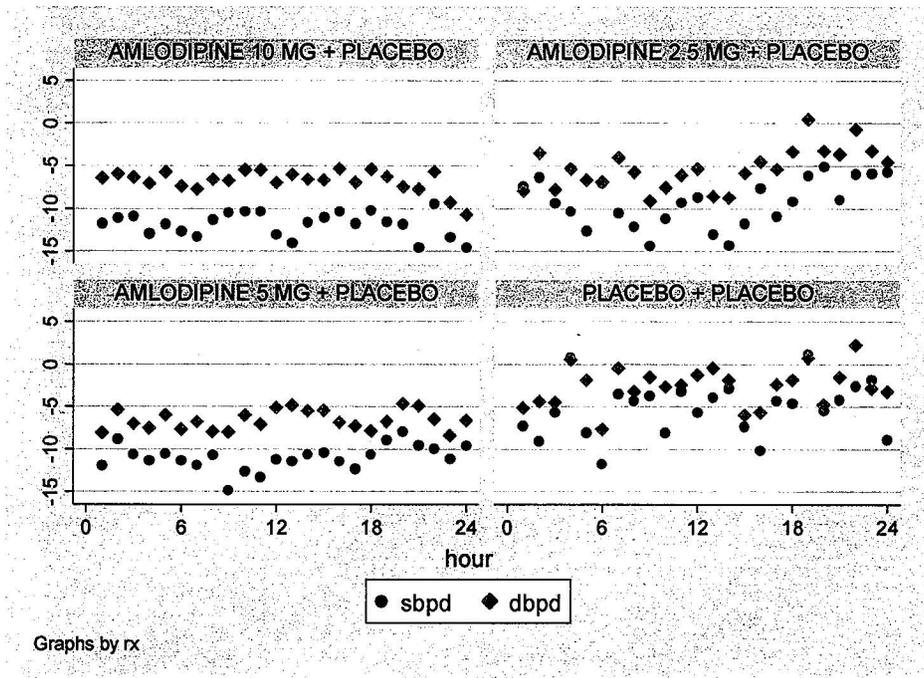
**Table 1: Mean 24-Hour BP Reductions from Baseline in Study 1235.1**

amlodipine	telmisartan	SBP	DBP
0	0	-5.2	-2.6
2.5	0	-9.3	-5.3
5	0	-11.0	-6.6
10	0	-11.9	-6.8
0	20	-7.1	-5.2
0	40	-8.4	-4.7
0	80	-12.1	-7.0
2.5	20	-13.0	-6.5
5	20	-17.8	-11.8
10	20	-14.1	-9.4
2.5	40	-12.5	-9.5
5	40	-16.4	-10.5
10	40	-21.1	-13.4
2.5	80	-16.2	-9.8
5	80	-19.1	-11.9
10	80	-22.5	-14.0

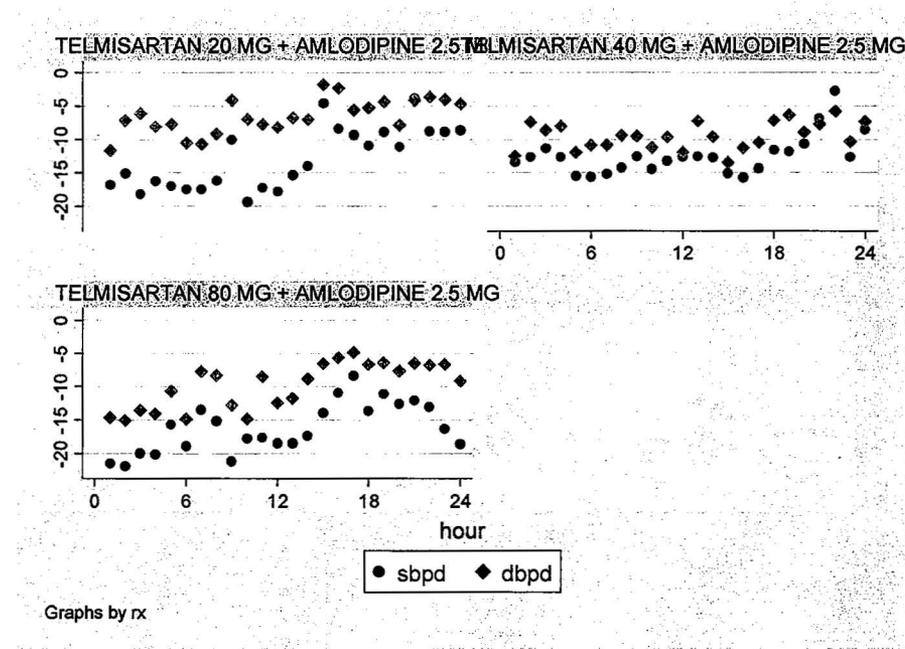
**Figure 2: Mean BP Reductions from Baseline for the Placebo and Telmisartan Monotherapy Groups in Study 1235.1**



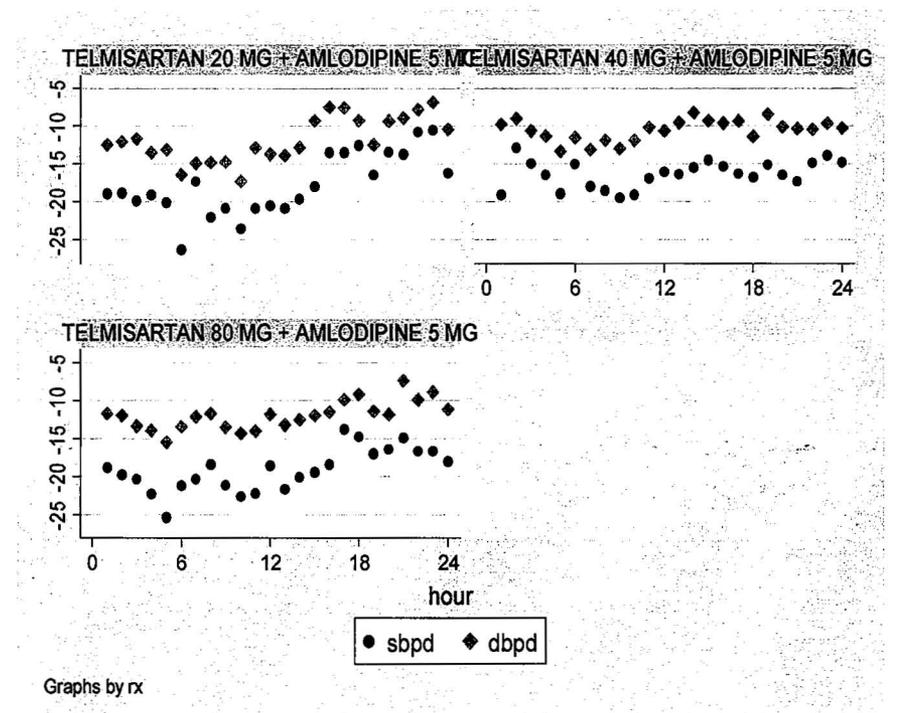
**Figure 3: Mean BP Reductions from Baseline for the Placebo and Amlodipine Monotherapy Groups in Study 1235.1**



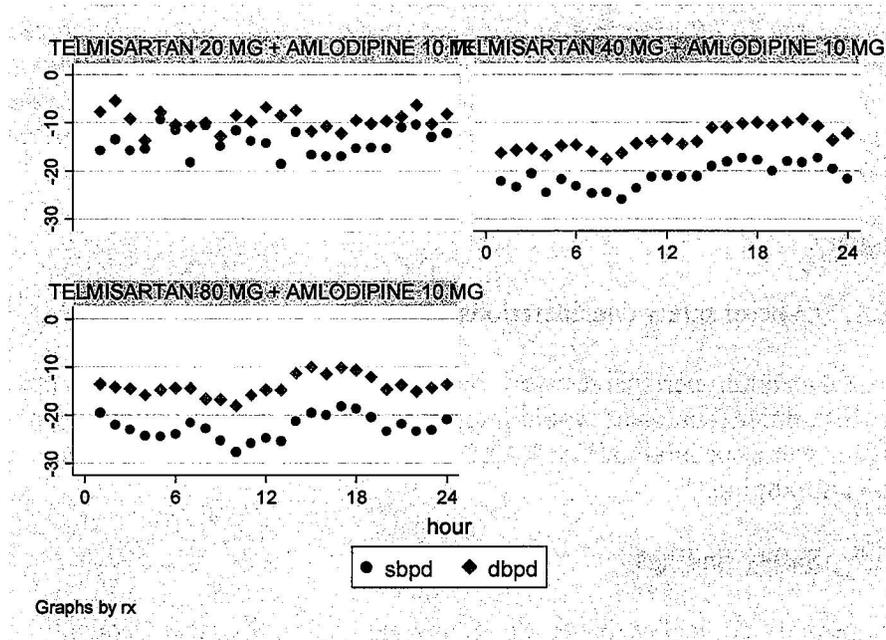
**Figure 4: Mean BP Reductions from Baseline for the Telmisartan 20-80 mg/Amlodipine 2.5 mg Groups in Study 1235.1**



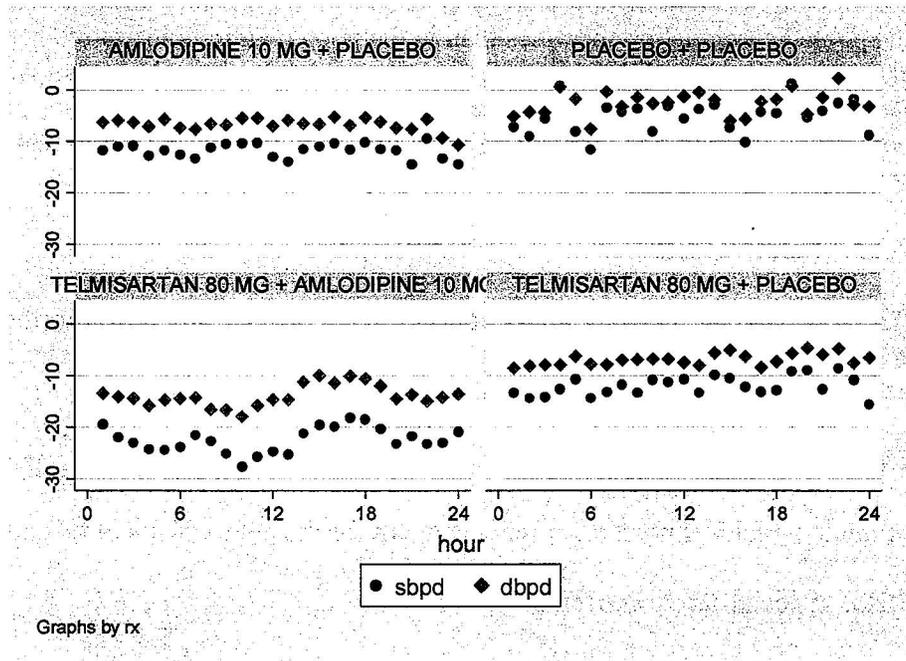
**Figure 5: Mean BP Reductions from Baseline for the Telmisartan 20-80 mg/Amlodipine 5 mg Groups in Study 1235.1**



**Figure 6: Mean BP Reductions from Baseline for the Telmisartan 20-80 mg/Amlodipine 10 mg Groups in Study 1235.1**



**Figure 7: Mean BP Reductions from Baseline for Telmisartan 80 mg/Amlodipine 10 mg and Corresponding Monotherapy Groups in Study 1235.1**



*COMMENT: The ABPM data generally show a dose-response for both amlodipine and telmisartan alone and in combination for the dosages studied. The one exception is the 10/20 combination, the results for which appear anomalous. At the high end of the dosages the 10/80 combination does not appear to offer much advantage to the 10/40 combination, but the 24-hour mean BP reductions for the 10/80 combination are slightly greater than for the 10/40 combination. The low dosages, 2.5 and 20, appear to be less effective. The ABPM data provide adequate justification for the proposed to-be-marketed combinations.*

## 7.2. Safety

### 7.2.1. General safety considerations

These two antihypertensives work by different mechanisms. I would not anticipate that the different mechanisms would interact to produce greater toxicity. On the contrary, there is some speculation that RAAS inhibitors may decrease the edema associated with amlodipine.

### 7.2.2. Safety findings

The primary clinical reviewer, Dr. Blank, noted that the most frequently reported adverse events in the pooled combination therapies in the pivotal factorial trial were peripheral edema (4.8%), headache (4.7%), dizziness (3.0%), and back pain (2.2%). There was no great difference in incidence of these common AEs between the combination and monotherapy treatment cells except for dizziness which was twice as common in the combination therapy cells and for peripheral edema which was lower in the pooled combination therapies than in the pooled amlodipine monotherapies. She also observed that in ONTARGET, the outcome trial using telmisartan with non-randomized amlodipine use in some patients, the mortality rate was lower with use of both drugs compared to telmisartan use alone, although the SAE rate was higher with combined use.

### 7.2.3. Safety update

Per Dr. Blank, the 120-day safety update did not provide any new information to raise any new safety concerns. She does note that amlodipine 10 mg was associated with peripheral edema with or without telmisartan while amlodipine 5 mg was not.

### 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 angiotensin receptor blocker use.

#### 7.2.6. Primary reviewers' comments and conclusions

Dr. Blank overall concluded that there were no compelling safety issues. In fact, she noted that the dose-limiting side effect of peripheral edema caused by amlodipine 10 mg was substantially less with the co-administration of telmisartan.

#### 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 Twynsta 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 audit the sites for the pivotal clinical study 1235-1 because both drugs are approved and there are a large number of sites, none of which accounted for a significant proportion of the patients. Audits for the clinical pharmacology studies are pending.

## **13. Conclusions and Recommendations**

### **13.1. Recommended regulatory action**

I recommend Twynsta 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-22401	ORIG-1	BOEHRINGER INGELHEIM PHARMACEUTICA LS INC	TELMISARTAN/AMLODIPINE FIXED DOSE COM TB

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THOMAS A MARCINIAK  
09/17/2009