

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

22-401

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**

EXCLUSIVITY SUMMARY

NDA # 22-401

SUPPL #

HFD # 110

Trade Name Twynsta Tablets

Generic Name telmisartan/amlodipine

Applicant Name Boehringer Ingelheim Pharmaceuticals, Inc.

Approval Date, If Known 10/16/09

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES NO

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3, SE4, SE5, SE6, SE7, SE8

505(b)(2)

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES NO

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES NO

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

Applicant did not specify.

e) Has pediatric exclusivity been granted for this Active Moiety?

YES NO

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES NO

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# 19-787 Norvasc (amlodipine besylate) Tablets

NDA# 20-850 Micardis (telmisartan) Tablets

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)

IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES NO

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES NO

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES NO

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES NO

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES NO

If yes, explain:

- (c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Studies 1235.1, 1235.3, 1235.4

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

- a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES NO

Investigation #2 YES NO

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

- b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES NO

Investigation #2 YES NO

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Studies 1235.1, 1235.3, 1235.4

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1
IND # 71,882 YES ! NO
! Explain:

Investigation #2
IND # YES ! NO
! Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1
YES ! NO
Explain: ! Explain:

Investigation #2

!
!

YES

! NO

Explain:

! Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES NO

If yes, explain:

Name of person completing form: Quynh Nguyen, Pharm.D.
Title: Regulatory Health Project Manager, Division of Cardiovascular and Renal Products
Date: 10/16/09

Name of Office/Division Director signing form: Norman Stockbridge, M.D., Ph.D.
Title: Director, Division of Cardiovascular and Renal Products

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05

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

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

/s/

QUYNH M NGUYEN
10/16/2009

NORMAN L STOCKBRIDGE
10/16/2009

PEDIATRIC PAGE
(Complete for all filed original applications and efficacy supplements)

NDA/BLA#: 22-401 Supplement Number: _____ NDA Supplement Type (e.g. SE5): _____

Division Name: Cardiovascular and Renal Products PDUFA Goal Date: 10/18/09 Stamp Date: 12/18/2008

Proprietary Name: Twynsta

Established/Generic Name: telmisartan/amlodipine

Dosage Form: Tablet

Applicant/Sponsor: Boehringer Ingelheim Pharmaceuticals, Inc.

Indication(s) previously approved (please complete this question for supplements and Type 6 NDAs only):

- (1) _____
(2) _____
(3) _____
(4) _____

Pediatric use for each pediatric subpopulation must be addressed for each indication covered by current application under review. A Pediatric Page must be completed for each indication.

Number of indications for this pending application(s): 2
(Attach a completed Pediatric Page for each indication in current application.)

Indication: Twynsta Tablets are indicated for the treatment of hypertension. They may be used in patients whose blood pressure is not adequately controlled on antihypertensive monotherapy.

Q1: Is this application in response to a PREA PMR? Yes Continue
No Please proceed to Question 2.

If Yes, NDA/BLA#: _____ Supplement #: _____ PMR #: _____

Does the division agree that this is a complete response to the PMR?

- Yes. Please proceed to Section D.
 No. Please proceed to Question 2 and complete the Pediatric Page, as applicable.

Q2: Does this application provide for (If yes, please check all categories that apply and proceed to the next question):

(a) NEW active ingredient(s) (includes new combination); indication(s); dosage form; dosing regimen; or route of administration?*

(b) No. PREA does not apply. **Skip to signature block.**

* **Note for CDER: SE5, SE6, and SE7 submissions may also trigger PREA.**

Q3: Does this indication have orphan designation?

- Yes. PREA does not apply. **Skip to signature block.**
 No. Please proceed to the next question.

Q4: Is there a full waiver for all pediatric age groups for this indication (check one)?

- Yes: (Complete Section A.)
- No: Please check all that apply:
- Partial Waiver for selected pediatric subpopulations (Complete Sections B)
 - Deferred for some or all pediatric subpopulations (Complete Sections C)
 - Completed for some or all pediatric subpopulations (Complete Sections D)
 - Appropriately Labeled for some or all pediatric subpopulations (Complete Sections E)
 - Extrapolation in One or More Pediatric Age Groups (Complete Section F)
- (Please note that Section F may be used alone or in addition to Sections C, D, and/or E.)

Section A: Fully Waived Studies (for all pediatric age groups)

Reason(s) for full waiver: (**check, and attach a brief justification for the reason(s) selected**)

- Necessary studies would be impossible or highly impracticable because:
- Disease/condition does not exist in children
 - Too few children with disease/condition to study
 - Other (e.g., patients geographically dispersed): _____
- Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients AND is not likely to be used in a substantial number of pediatric patients.
- Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- Justification attached.

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please complete another Pediatric Page for each indication. Otherwise, this Pediatric Page is complete and should be signed.

Section B: Partially Waived Studies (for selected pediatric subpopulations)

Check subpopulation(s) and reason for which studies are being partially waived (fill in applicable criteria below):

Note: If Neonate includes premature infants, list minimum and maximum age in "gestational age" (in weeks).

		Reason (see below for further detail):					
		minimum	maximum	Not feasible [#]	Not meaningful therapeutic benefit [*]	Ineffective or unsafe [†]	Formulation failed ^Δ
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

Reason(s) for partial waiver (**check reason** corresponding to the category checked above, and **attach a brief justification**):

Not feasible:

- Necessary studies would be impossible or highly impracticable because:
 - Disease/condition does not exist in children
 - Too few children with disease/condition to study
 - Other (e.g., patients geographically dispersed): _____

* Not meaningful therapeutic benefit:

- Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in this/these pediatric subpopulation(s) AND is not likely to be used in a substantial number of pediatric patients in this/these pediatric subpopulation(s).

† Ineffective or unsafe:

- Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (Note: if studies are partially waived on this ground, this information must be included in the labeling.)
- Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (Note: if studies are partially waived on this ground, this information must be included in the labeling.)
- Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (Note: if studies are partially waived on this ground, this information must be included in the labeling.)

Δ Formulation failed:

- Applicant can demonstrate that reasonable attempts to produce a pediatric formulation necessary for this/these pediatric subpopulation(s) have failed. (Note: A partial waiver on this ground may only cover the pediatric subpopulation(s) requiring that formulation. An applicant seeking a partial waiver on this ground must submit documentation detailing why a pediatric formulation cannot be developed. This submission will be posted on FDA's website if waiver is granted.)

Justification attached.

For those pediatric subpopulations for which studies have not been waived, there must be (1) corresponding study plans that have been deferred (if so, proceed to Sections C and complete the PeRC Pediatric Plan Template); (2) submitted studies that have been completed (if so, proceed to Section D and complete the PeRC Pediatric Assessment form); (3) additional studies in other age groups that are not needed because the drug is appropriately labeled in one or more pediatric subpopulations (if so, proceed to Section E); and/or (4)

additional studies in other age groups that are not needed because efficacy is being extrapolated (if so, proceed to Section F). Note that more than one of these options may apply for this indication to cover all of the pediatric subpopulations.

Section C: Deferred Studies (for selected pediatric subpopulations).

Check pediatric subpopulation(s) for which pediatric studies are being deferred (and fill in applicable reason below):

Deferrals (for each or all age groups):				Reason for Deferral			Applicant Certification †
				Population	minimum	maximum	Ready for Approval in Adults
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	All Pediatric Populations	0 yr. 0 mo.	16 yr. 11 mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Date studies are due (mm/dd/yy): _____							

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

* Other Reason: _____

† Note: Studies may only be deferred if an applicant submits a certification of grounds for deferring the studies, a description of the planned or ongoing studies, evidence that the studies are being conducted or will be conducted with due diligence and at the earliest possible time, and a timeline for the completion of the studies. If studies are deferred, on an annual basis applicant must submit information detailing the progress made in conducting the studies or, if no progress has been made, evidence and documentation that such studies will be conducted with due diligence and at the earliest possible time. This requirement should be communicated to the applicant in an appropriate manner (e.g., in an approval letter that specifies a required study as a post-marketing commitment.)

If all of the pediatric subpopulations have been covered through partial waivers and deferrals, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section D: Completed Studies (for some or all pediatric subpopulations).

Pediatric subpopulation(s) in which studies have been completed (check below):

Population		minimum	maximum	PeRC Pediatric Assessment form attached?	
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

Note: If there are no further pediatric subpopulations to cover based on partial waivers, deferrals and/or completed studies, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section E: Drug Appropriately Labeled (for some or all pediatric subpopulations):

Additional pediatric studies are not necessary in the following pediatric subpopulation(s) because product is appropriately labeled for the indication being reviewed:

Population		minimum	maximum
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

If all pediatric subpopulations have been covered based on partial waivers, deferrals, completed studies, and/or existing appropriate labeling, this Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section F: Extrapolation from Other Adult and/or Pediatric Studies (for deferred and/or completed studies)

Note: Pediatric efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations if (and only if) (1) the course of the disease/condition AND (2) the effects of the product are sufficiently similar between the reference population and the pediatric subpopulation for which information will be extrapolated. Extrapolation of efficacy from studies in adults and/or other children usually requires supplementation with other information obtained from the target pediatric subpopulation, such as

IF THERE ARE QUESTIONS, PLEASE CONTACT THE CDER PMHS VIA EMAIL (cderpmhs@fda.hhs.gov) OR AT 301-796-0700.

pharmacokinetic and safety studies. Under the statute, safety cannot be extrapolated.

Pediatric studies are not necessary in the following pediatric subpopulation(s) because efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations:					
Population		minimum	maximum	Extrapolated from:	
				Adult Studies?	Other Pediatric Studies?
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	<input type="checkbox"/>	<input type="checkbox"/>

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

Note: If extrapolating data from either adult or pediatric studies, a description of the scientific data supporting the extrapolation must be included in any pertinent reviews for the application.

If there are additional indications, please complete the attachment for each one of those indications. Otherwise, this Pediatric Page is complete and should be signed and entered into DFS or DARRTS as appropriate after clearance by PeRC.

This page was completed by:

{See appended electronic signature page}

Regulatory Project Manager

(Revised: 6/2008)

NOTE: If you have no other indications for this application, you may delete the attachments from this document.

Attachment A

(This attachment is to be completed for those applications with multiple indications only.)

Indication #2: Tywnsta may also be used as initial therapy in patients who are likely to need multiple drugs to achieve their blood pressure goals.

Q1: Does this indication have orphan designation?

- Yes. PREA does not apply. **Skip to signature block.**
- No. Please proceed to the next question.

Q2: Is there a full waiver for all pediatric age groups for this indication (check one)?

- Yes: (Complete Section A.)
 - No: Please check all that apply:
 - Partial Waiver for selected pediatric subpopulations (Complete Sections B)
 - Deferred for some or all pediatric subpopulations (Complete Sections C)
 - Completed for some or all pediatric subpopulations (Complete Sections D)
 - Appropriately Labeled for some or all pediatric subpopulations (Complete Sections E)
 - Extrapolation in One or More Pediatric Age Groups (Complete Section F)
- (Please note that Section F may be used alone or in addition to Sections C, D, and/or E.)

Section A: Fully Waived Studies (for all pediatric age groups)

Reason(s) for full waiver: (**check, and attach a brief justification for the reason(s) selected**)

- Necessary studies would be impossible or highly impracticable because:
 - Disease/condition does not exist in children
 - Too few children with disease/condition to study
 - Other (e.g., patients geographically dispersed): _____
- Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients AND is not likely to be used in a substantial number of pediatric patients.
- Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)

Justification attached.

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please complete another Pediatric Page for each indication. Otherwise, this Pediatric Page is complete and should be signed.

Section B: Partially Waived Studies (for selected pediatric subpopulations)

Check subpopulation(s) and reason for which studies are being partially waived (fill in applicable criteria below):

Note: If Neonate includes premature infants, list minimum and maximum age in "gestational age" (in weeks).

			Reason (see below for further detail):				
	minimum	maximum	Not feasible [#]	Not meaningful therapeutic benefit [*]	Ineffective or unsafe [†]	Formulation failed ^Δ	
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

Reason(s) for partial waiver (**check reason** corresponding to the category checked above, and **attach a brief justification**):

Not feasible:

Necessary studies would be impossible or highly impracticable because:

- Disease/condition does not exist in children
- Too few children with disease/condition to study
- Other (e.g., patients geographically dispersed): _____

* Not meaningful therapeutic benefit:

Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in this/these pediatric subpopulation(s) AND is not likely to be used in a substantial number of pediatric patients in this/these pediatric subpopulation(s).

† Ineffective or unsafe:

- Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (Note: if studies are partially waived on this ground, this information must be included in the labeling.)
- Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (Note: if studies are partially waived on this ground, this information must be included in the labeling.)
- Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (Note: if studies are partially waived on this ground, this information must be included in the labeling.)

Δ Formulation failed:

Applicant can demonstrate that reasonable attempts to produce a pediatric formulation necessary for this/these pediatric subpopulation(s) have failed. (Note: A partial waiver on this ground may only cover the pediatric subpopulation(s) requiring that formulation. An applicant seeking a partial waiver on this ground must submit documentation detailing why a pediatric formulation cannot be developed. This submission will be posted on FDA's website if waiver is granted.)

Justification attached:

For those pediatric subpopulations for which studies have not been waived, there must be (1) corresponding study plans that have been deferred (if so, proceed to Section C and complete the PeRC Pediatric Plan Template); (2) submitted studies that have been completed (if so, proceed to Section D and complete the PeRC Pediatric Assessment form); (3) additional studies in other age groups that are not needed because the

drug is appropriately labeled in one or more pediatric subpopulations (if so, proceed to Section E); and/or (4) additional studies in other age groups that are not needed because efficacy is being extrapolated (if so, proceed to Section F).. Note that more than one of these options may apply for this indication to cover all of the pediatric subpopulations.

Section C: Deferred Studies (for some or all pediatric subpopulations).

Check pediatric subpopulation(s) for which pediatric studies are being deferred (and fill in applicable reason below):

Deferrals (for each or all age groups):				Reason for Deferral			Applicant Certification †
Population		minimum	maximum	Ready for Approval in Adults	Need Additional Adult Safety or Efficacy Data	Other Appropriate Reason (specify below)*	Received
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	All Pediatric Populations	0 yr. 0 mo.	16 yr. 11 mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Date studies are due (mm/dd/yy): _____							

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

* Other Reason: _____

† Note: Studies may only be deferred if an applicant submits a certification of grounds for deferring the studies, a description of the planned or ongoing studies, evidence that the studies are being conducted or will be conducted with due diligence and at the earliest possible time, and a timeline for the completion of the studies. If studies are deferred, on an annual basis applicant must submit information detailing the progress made in conducting the studies or, if no progress has been made, evidence and documentation that such studies will be conducted with due diligence and at the earliest possible time. This requirement should be communicated to the applicant in an appropriate manner (e.g., in an approval letter that specifies a required study as a post-marketing commitment.)

If all of the pediatric subpopulations have been covered through partial waivers and deferrals, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section D: Completed Studies (for some or all pediatric subpopulations).

Pediatric subpopulation(s) in which studies have been completed (check below):					
Population		minimum	maximum	PeRC Pediatric Assessment form attached?	
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

Note: If there are no further pediatric subpopulations to cover based on partial waivers, deferrals and/or completed studies, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section E: Drug Appropriately Labeled (for some or all pediatric subpopulations):

Additional pediatric studies are not necessary in the following pediatric subpopulation(s) because product is appropriately labeled for the indication being reviewed:			
Population		minimum	maximum
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

If all pediatric subpopulations have been covered based on partial waivers, deferrals, completed studies, and/or existing appropriate labeling, this Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section F: Extrapolation from Other Adult and/or Pediatric Studies (for deferred and/or completed studies)

Note: Pediatric efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations if (and only if) (1) the course of the disease/condition AND (2) the effects of the product are sufficiently similar between the reference population and the pediatric subpopulation for which information will be extrapolated. Extrapolation of efficacy from studies in adults and/or other children usually requires supplementation with other information obtained from the target pediatric subpopulation, such as pharmacokinetic and safety studies. Under the statute, safety cannot be extrapolated.

Pediatric studies are not necessary in the following pediatric subpopulation(s) because efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations:					
Population		minimum	maximum	Extrapolated from:	
				Adult Studies?	Other Pediatric Studies?
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	<input type="checkbox"/>	<input type="checkbox"/>

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

Note: If extrapolating data from either adult or pediatric studies, a description of the scientific data supporting the extrapolation must be included in any pertinent reviews for the application.

If there are additional indications, please copy the fields above and complete pediatric information as directed. If there are no other indications, this Pediatric Page is complete and should be entered into DFS or DARRTS as appropriate after clearance by PeRC.

This page was completed by:

{See appended electronic signature page}

Regulatory Project Manager

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE PEDIATRIC AND MATERNAL HEALTH STAFF at 301-796-0700

(Revised: 6/2008)

Pediatric Research and Equity Act Waivers

IND/NDA/BLA #: 22-401

Supplement Type: ____

Supplement Number: ____

Product name and active ingredient/dosage form: Twynsta (telmisartan/amlodipine) Tablets

Sponsor: Boehringer Ingelheim Pharmaceuticals, Inc.

Indications(s): (1) Twynsta Tablets are indicated for the treatment of hypertension. They may be used in patients whose blood pressure is not adequately controlled on antihypertensive monotherapy. (2) Twynsta may also be used as initial therapy in patients who are likely to need multiple drugs to achieve their blood pressure goals.

(NOTE: If the drug is approved for or Sponsor is seeking approval for more than one indication, address the following for each indication. The following applies for both indications.)

1. Pediatric age group(s) to be waived. Birth to 16 years old
2. Reason(s) for waiving pediatric assessment requirements (choose all that apply **and provide justification**):
 - c. 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: Twynsta 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).

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

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

/s/

QUYNH M NGUYEN
10/13/2009

DEBARMENT CERTIFICATION

Certification Requirement Section 306(k)(l) of the Act 21 U.S.C. 355a(k)

Boehringer Ingelheim Pharmaceuticals, Inc. hereby certifies that it did not and will not use in any capacity the services of any person debarred under Section 306 of the Federal Food, Drug and Cosmetic Act in connection with this application.

Signature: Christopher D. Corsico

Name of Applicant: Christopher Corsico, M.D.
Vice President, Drug Regulatory Affairs
Boehringer Ingelheim Pharmaceuticals, Inc.

Date: 4 December 2008

Mailing Address: Boehringer Ingelheim Pharmaceuticals Inc.
900 Ridgebury Road
P.O. Box 368
Ridgefield, CT 06877-0368

NDA/BLA REGULATORY FILING REVIEW
(Including Memo of Filing Meeting)

Application Information		
NDA # 22-401 BLA#	NDA Supplement #: BLA STN #	Efficacy Supplement Type:
Proprietary Name: Twynsta Established/Proper Name: telmisartan/amlodipine Dosage Form: Tablet Strengths: 40/5, 40/10, 80/5, 80/10 mg		
Applicant: Boehringer Ingelheim Pharmaceuticals, Inc. Agent for Applicant (if applicable):		
Date of Application: 12/18/08 Date of Receipt: 12/18/08 Date clock started after UN:		
PDUFA Goal Date: 10/18/09		Action Goal Date (if different):
Filing Date: 2/16/09 Date of Filing Meeting: 2/5/09		
Chemical Classification: (1,2,3 etc.) (original NDAs only) 4		
Proposed Indication(s): (1) Treatment of hypertension. May be used in patients whose blood pressure is not adequately controlled on antihypertensive monotherapy. (2) Twynsta may also be used as initial therapy in patients who are likely to need multiple drugs to achieve their blood pressure goals.		
Type of Original NDA: AND (if applicable) Type of NDA Supplement:		<input type="checkbox"/> 505(b)(1) <input checked="" type="checkbox"/> 505(b)(2) <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)
Refer to Appendix A for further information.		
Review Classification: <i>If the application includes a complete response to pediatric WR, review classification is Priority.</i> <i>If a tropical disease Priority review voucher was submitted, review classification defaults to Priority.</i>		<input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority <input type="checkbox"/> Tropical disease Priority review voucher submitted
Resubmission after withdrawal? <input type="checkbox"/> Resubmission after refuse to file? <input type="checkbox"/>		
Part 3 Combination Product? <input type="checkbox"/>	<input type="checkbox"/> Drug/Biologic <input type="checkbox"/> Drug/Device <input type="checkbox"/> Biologic/Device	
<input type="checkbox"/> Fast Track <input type="checkbox"/> Rolling Review <input type="checkbox"/> Orphan Designation <input type="checkbox"/> Rx-to-OTC switch, Full <input type="checkbox"/> Rx-to-OTC switch, Partial <input type="checkbox"/> Direct-to-OTC	<input type="checkbox"/> PMC response <input type="checkbox"/> PMR response: <input type="checkbox"/> FDAAA [505(o)] <input type="checkbox"/> PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] <input type="checkbox"/> Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41)	

Other:	<input type="checkbox"/> Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)
Collaborative Review Division (if OTC product):	
List referenced IND Number(s): 71,882	
PDUFA and Action Goal dates correct in tracking system? <i>If not, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.</i>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
Are the proprietary, established/proper, and applicant names correct in tracking system? <i>If not, ask the document room staff to make the corrections. Also, ask the document room staff to add the established name to the supporting IND(s) if not already entered into tracking system.</i>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
Are all classification codes/flags (e.g. orphan, OTC drug, pediatric data) entered into tracking system? <i>If not, ask the document room staff to make the appropriate entries.</i>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
Application Integrity Policy	
Is the application affected by the Application Integrity Policy (AIP)? <i>Check the AIP list at: http://www.fda.gov/ora/compliance_ref/aiplist.html</i> If yes, explain: If yes, has OC/DMPQ been notified of the submission? Comments:	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO
User Fees	
Form 3397 (User Fee Cover Sheet) submitted	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
User Fee Status Comments: User Fee ID Number PD3008825	<input checked="" type="checkbox"/> Paid <input type="checkbox"/> Exempt (orphan, government) <input type="checkbox"/> Waived (e.g., small business, public health) <input type="checkbox"/> Not required
<i>Note: 505(b)(2) applications are no longer exempt from user fees pursuant to the passage of FDAAA. It is expected that all 505(b) applications, whether 505(b)(1) or 505(b)(2), will require user fees unless otherwise waived or exempted (e.g., business waiver, orphan exemption).</i>	
Exclusivity	

<p>Does another product have orphan exclusivity for the same indication? <i>Check the Electronic Orange Book at: http://www.fda.gov/cder/ob/default.htm</i></p> <p>If yes, is the product considered to be the same product according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]?</p> <p><i>If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007)</i></p> <p>Comments:</p>	<p><input type="checkbox"/> YES <input checked="" type="checkbox"/> NO</p> <p><input type="checkbox"/> YES <input type="checkbox"/> NO</p>
<p>Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? (<i>NDAs/NDA efficacy supplements only</i>)</p> <p><i>Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i></p> <p>Comments:</p>	<p><input checked="" type="checkbox"/> YES # years requested: <input type="checkbox"/> NO</p>
<p>If the proposed product is a single enantiomer of a racemic drug previously approved for a different therapeutic use (<i>NDAs only</i>):</p> <p>Did the applicant (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b) request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)?</p> <p><i>If yes, contact Mary Ann Holovac, Director of Drug Information, OGD/DLPS/LRB.</i></p>	<p><input checked="" type="checkbox"/> Not applicable</p> <p><input type="checkbox"/> YES <input type="checkbox"/> NO</p>
505(b)(2) (NDAs/NDA Efficacy Supplements only)	
<p>1. Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?</p> <p>2. Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action less than that of the reference listed drug (RLD)? (see 21 CFR 314.54(b)(1)).</p> <p>3. Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug (see 21 CFR 314.54(b)(2))?</p>	<p><input type="checkbox"/> Not applicable</p> <p><input type="checkbox"/> YES <input checked="" type="checkbox"/> NO</p> <p><input type="checkbox"/> YES <input checked="" type="checkbox"/> NO</p> <p><input type="checkbox"/> YES <input checked="" type="checkbox"/> NO</p>

Note: If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9).

<p>4. Is there unexpired exclusivity on the active moiety (e.g., 5-year, 3-year, orphan or pediatric exclusivity)? Check the Electronic Orange Book at: http://www.fda.gov/cder/ob/default.htm</p> <p>If yes, please list below:</p>	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
--	--

Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration

If there is unexpired, 5-year exclusivity remaining on the active moiety for the proposed drug product, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 108(b)(2). Unexpired, 3-year exclusivity will only block the approval, not the submission of a 505(b)(2) application.

Format and Content

<p>Do not check mixed submission if the only electronic component is the content of labeling (COL).</p> <p>Comments: Waiver granted to allow BI to submit the NDA electronically, but not in an eCTD format.</p>	<input type="checkbox"/> All paper (except for COL) <input checked="" type="checkbox"/> All electronic <input type="checkbox"/> Mixed (paper/electronic) <input type="checkbox"/> CTD <input checked="" type="checkbox"/> Non-CTD <input type="checkbox"/> Mixed (CTD/non-CTD)
--	---

<p>If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?</p>	
--	--

<p>If electronic submission: <u>paper</u> forms and certifications signed (non-CTD) or <u>electronic</u> forms and certifications signed (scanned or digital signature)(CTD)?</p> <p><i>Forms include: 356h, patent information (3542a), financial disclosure (3454/3455), user fee cover sheet (3542a), and clinical trials (3674); Certifications include: debarment certification, patent certification(s), field copy certification, and pediatric certification.</i></p> <p>Comments:</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
---	--

<p>If electronic submission, does it follow the eCTD guidance? (http://www.fda.gov/cder/guidance/7087rev.pdf)</p> <p>If not, explain (e.g., waiver granted): Waiver granted to allow BI to submit the NDA electronically, but not in an eCTD format. In general, the documents and data files have been formatted as suggested in the eCTD Guidance.</p>	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
--	--

<p>Form 356h: Is a signed form 356h included?</p> <p><i>If foreign applicant, both the applicant and the U.S. agent must sign the form.</i></p> <p>Are all establishments and their registration numbers listed on the form?</p> <p>Comments: Listed in attachment.</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<p>Index: Does the submission contain an accurate comprehensive index?</p> <p>Comments:</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<p>Is the submission complete as required under 21 CFR 314.50 (NDAs/NDA efficacy supplements) or under 21 CFR 601.2 (BLAs/BLA efficacy supplements) including:</p> <p><input checked="" type="checkbox"/> legible <input checked="" type="checkbox"/> English (or translated into English) <input checked="" type="checkbox"/> pagination <input checked="" type="checkbox"/> navigable hyperlinks (electronic submissions only)</p> <p>If no, explain:</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<p>Controlled substance/Product with abuse potential:</p> <p>Abuse Liability Assessment, including a proposal for scheduling, submitted?</p> <p>Consult sent to the Controlled Substance Staff?</p> <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO
<p>BLAs/BLA efficacy supplements only:</p> <p>Companion application received if a shared or divided manufacturing arrangement?</p> <p>If yes, BLA #</p>	<input type="checkbox"/> YES <input type="checkbox"/> NO
Patent Information (NDAs/NDA efficacy supplements only)	
<p>Patent information submitted on form FDA 3542a?</p> <p>Comments:</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
Debarment Certification	
<p>Correctly worded Debarment Certification with authorized signature?</p> <p><i>If foreign applicant, both the applicant and the U.S. Agent must sign the certification.</i></p>	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO

<p><i>Note: Debarment Certification should use wording in FD&C Act section 306(k)(l) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as, "To the best of my knowledge..."</i></p> <p>Comments: Incorrectly worded debarment certification; sponsor will be asked to re-submit.</p>	
Field Copy Certification (NDAs/NDA efficacy supplements only)	
<p>Field Copy Certification: that it is a true copy of the CMC technical section (<i>applies to paper submissions only</i>)</p> <p><i>If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.</i></p>	<p><input checked="" type="checkbox"/> Not Applicable (<i>electronic submission or no CMC technical section</i>)</p> <p><input type="checkbox"/> YES</p> <p><input type="checkbox"/> NO</p>
Financial Disclosure	
<p>Financial Disclosure forms included with authorized signature?</p> <p><i>Forms 3454 and/or 3455 must be included and must be signed by the APPLICANT, not an Agent.</i></p> <p><i>Note: Financial disclosure is required for bioequivalence studies that are the basis for approval.</i></p> <p>Comments:</p>	<p><input checked="" type="checkbox"/> YES</p> <p><input type="checkbox"/> NO</p>
Pediatrics	
<p>PREA</p> <p><i>Note: NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.</i></p> <p>Are the required pediatric assessment studies or a full waiver of pediatric studies included?</p> <p>If no, is a request for full waiver of pediatric studies OR a request for partial waiver/deferral and a pediatric plan included?</p> <ul style="list-style-type: none"> • <i>If no, request in 74-day letter.</i> • If yes, does the application contain the certification(s) required under 21 CFR 314.55(b)(1), (c)(2), (c)(3)/21 CFR 601.27(b)(1), (c)(2), (c)(3) <p>Comments: Full pediatric waiver requested.</p>	<p><input type="checkbox"/> Not Applicable</p> <p><input checked="" type="checkbox"/> YES</p> <p><input type="checkbox"/> NO</p> <p><input type="checkbox"/> YES</p> <p><input type="checkbox"/> NO</p> <p><input type="checkbox"/> YES</p> <p><input type="checkbox"/> NO</p>

<u>BPCA (NDAs/NDA efficacy supplements only):</u>	
Is this submission a complete response to a pediatric Written Request? <i>If yes, contact PMHS (pediatric exclusivity determination by the Pediatric Exclusivity Board is needed).</i>	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
Comments:	
Prescription Labeling	
Check all types of labeling submitted. Comments:	<input type="checkbox"/> Not applicable <input checked="" type="checkbox"/> Package Insert (PI) <input checked="" type="checkbox"/> Patient Package Insert (PPI) <input type="checkbox"/> Instructions for Use <input type="checkbox"/> MedGuide <input checked="" type="checkbox"/> Carton labels <input checked="" type="checkbox"/> Immediate container labels <input type="checkbox"/> Diluent <input type="checkbox"/> Other (specify)
Is electronic Content of Labeling submitted in SPL format? <i>If no, request in 74-day letter.</i>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
Comments:	
Package insert (PI) submitted in PLR format? If no , was a waiver or deferral requested before the application was received or in the submission? If before , what is the status of the request? <i>If no, request in 74-day letter.</i>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO
Comments:	
All labeling (PI, PPI, MedGuide, carton and immediate container labels) consulted to DDMAC?	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
Comments:	
MedGuide or PPI (plus PI) consulted to OSE/DRISK? (<i>send WORD version if available</i>)	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
Comments:	
REMS consulted to OSE/DRISK?	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
Comments:	
Carton and immediate container labels, PI, PPI, and proprietary name (if any) sent to OSE/DMEDP?	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
Comments:	

OTC Labeling	
<p>Check all types of labeling submitted.</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input type="checkbox"/> Outer carton label <input type="checkbox"/> Immediate container label <input type="checkbox"/> Blister card <input type="checkbox"/> Blister backing label <input type="checkbox"/> Consumer Information Leaflet (CIL) <input type="checkbox"/> Physician sample <input type="checkbox"/> Consumer sample <input type="checkbox"/> Other (specify)
<p>Is electronic content of labeling submitted?</p> <p><i>If no, request in 74-day letter.</i></p> <p>Comments:</p>	<input type="checkbox"/> YES <input type="checkbox"/> NO
<p>Are annotated specifications submitted for all stock keeping units (SKUs)?</p> <p><i>If no, request in 74-day letter.</i></p> <p>Comments:</p>	<input type="checkbox"/> YES <input type="checkbox"/> NO
<p>If representative labeling is submitted, are all represented SKUs defined?</p> <p><i>If no, request in 74-day letter.</i></p> <p>Comments:</p>	<input type="checkbox"/> YES <input type="checkbox"/> NO
<p>Proprietary name, all labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEDP?</p> <p>Comments:</p>	<input type="checkbox"/> YES <input type="checkbox"/> NO
Meeting Minutes/SPA Agreements	
<p>End-of Phase 2 meeting(s)?</p> <p><i>If yes, distribute minutes before filing meeting.</i></p> <p>Comments:</p>	<input type="checkbox"/> YES Date(s): <input checked="" type="checkbox"/> NO
<p>Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)?</p> <p><i>If yes, distribute minutes before filing meeting.</i></p> <p>Comments: Pre-NDA meeting scheduled for 6/10/08 was cancelled after sponsor received Preliminary Responses.</p>	<input checked="" type="checkbox"/> YES Date(s): 6/10/08 (Pre-NDA Preliminary Responses); 4/9/08 (Guidance Meeting) <input type="checkbox"/> NO
<p>Any Special Protocol Assessment (SPA) agreements?</p> <p><i>If yes, distribute letter and/or relevant minutes before filing meeting.</i></p> <p>Comments:</p>	<input type="checkbox"/> YES Date(s): <input checked="" type="checkbox"/> NO

ATTACHMENT

MEMO OF FILING MEETING

DATE: 2/5/09

NDA/BLA #: 22-401

PROPRIETARY/ESTABLISHED NAMES: Twynsta (telmisartan/amlodipine besylate) Tablets

APPLICANT: Boehringer Ingelheim Pharmaceuticals, Inc.

BACKGROUND: This original NDA provides for the use of Twynsta (telmisartan/amlodipine besylate) Tablets for the treatment of hypertension, including as initial therapy in patients likely to need multiple drugs to achieve their blood pressure goals. The NDA was submitted pursuant to section 505(b)(2) and contains full study reports of the safety and efficacy of the combination drug product. The sponsor is proposing the following 4 dosage strengths: 40/5, 40/10, 80/5, 80/10 mg.

Reference is made to the non-clinical data of Norvasc (amlodipine) and Micardis (telmisartan) as approved in their respective labels. No additional non-clinical safety data in support of the fixed dose combination was provided, as agreed to during the Pre-NDA Meeting Preliminary Responses dated June 3, 2008.

In support of approval, the submission includes quality, clinical pharmacology, and clinical/statistical data. The clinical development program included one pivotal Phase 3 study and other supportive studies, 2 bioequivalence studies, 2 drug-drug interaction studies, and a food effect study.

The pivotal trial (Study 1235.1) was an 8-week, 4x4, placebo-controlled factorial design study, which included 3 strengths each of telmisartan and amlodipine. The study randomized and treated a total of 1461 patients with Stage 1 and Stage 2 hypertension. According to the sponsor, results showed clinically and statistically significant reductions in seated trough cuff DPB and SBP for the fixed dose combination compared to the monotherapy components and placebo.

Draft labeling for the carton and container, PI, and Patient PI was submitted in SPL and PLR format.

The sponsor is requesting a full waiver from the pediatric requirement.

The NDA is fully electronic in the EDR.

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Quynh Nguyen	Y
	CPMS/TL:	Edward Fromm	Y
Cross-Discipline Team Leader (CDTL)	Tom Marciniak		Y

Clinical	Reviewer:	Melanie Blank	N
	TL:	Thomas Marciniak	Y
Social Scientist Review (<i>for OTC products</i>)	Reviewer:		
	TL:		
Labeling Review (<i>for OTC products</i>)	Reviewer:		
	TL:		
OSE	Reviewer:		
	TL:		
Clinical Microbiology (<i>for antimicrobial products</i>)	Reviewer:		
	TL:		

Clinical Pharmacology	Reviewer:	Islam Younis	Y
	TL: acting	Elena Mishina	N
Biostatistics	Reviewer:	Ququan (Cherry) Liu	Y
	TL:	James Hung	N
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Gowra Jagadeesh	N
	TL:	Charles Resnick	Y
Statistics, carcinogenicity	Reviewer:		
	TL:		
Product Quality (CMC)	Reviewer:	David Claffey	Y
	TL:	Kasturi Srinivasachar	Y
Facility (for BLAs/BLA supplements)	Reviewer:		
	TL:		
Microbiology, sterility (for NDAs/NDA efficacy supplements)	Reviewer:		
	TL:		
Bioresearch Monitoring (DSI)	Reviewer:		
	TL:		
Other reviewers			

OTHER ATTENDEES: Norman Stockbridge, Sean Bradley, Phillip Gati

505(b)(2) filing issues? If yes, list issues:	<input type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
Per reviewers, are all parts in English or English translation? If no, explain:	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO

<p>Electronic Submission comments</p> <p>List comments:</p>	<input type="checkbox"/> Not Applicable
<p>CLINICAL</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> • Clinical study site(s) inspections(s) needed? <p>If no, explain: Per Dr. Blank's 3/5/09 email, DSI clinical inspections are not needed.</p>	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
<ul style="list-style-type: none"> • Advisory Committee Meeting needed? <p>Comments:</p> <p><i>If no, for an original NME or BLA application, include the reason. For example:</i></p> <ul style="list-style-type: none"> ○ <i>this drug/biologic is not the first in its class</i> ○ <i>the clinical study design was acceptable</i> ○ <i>the application did not raise significant safety or efficacy issues</i> ○ <i>the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease</i> 	<input type="checkbox"/> YES Date if known: <input checked="" type="checkbox"/> NO <input type="checkbox"/> To be determined Reason:
<ul style="list-style-type: none"> • If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<p>CLINICAL MICROBIOLOGY</p> <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>CLINICAL PHARMACOLOGY</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter

<ul style="list-style-type: none"> Clinical pharmacology study site(s) inspections(s) needed? 	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
BIOSTATISTICS Comments:	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input checked="" type="checkbox"/> Review issues for 74-day letter
NONCLINICAL (PHARMACOLOGY/TOXICOLOGY) Comments:	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
PRODUCT QUALITY (CMC) Comments:	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> Categorical exclusion for environmental assessment (EA) requested? <p>If no, was a complete EA submitted?</p> <p>If EA submitted, consulted to EA officer (OPS)?</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input checked="" type="checkbox"/> NO <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> Establishment(s) ready for inspection? <ul style="list-style-type: none"> Establishment Evaluation Request (EER/TBP-EER) submitted to DMPQ? <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> Sterile product? <p>If yes, was Microbiology Team consulted for validation of sterilization? (NDAs/NDA supplements only)</p>	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO
FACILITY (BLAs only)	<input checked="" type="checkbox"/> Not Applicable

Comments:	<input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
REGULATORY PROJECT MANAGEMENT	
Signatory Authority: Division	
GRMP Timeline Milestones: Team meetings to be scheduled (1/month, as needed). Mid-cycle Meeting scheduled for 12/2/08.	
Comments:	
REGULATORY CONCLUSIONS/DEFICIENCIES	
<input type="checkbox"/>	The application is unsuitable for filing. Explain why:
<input checked="" type="checkbox"/>	The application, on its face, appears to be suitable for filing. <input type="checkbox"/> No review issues have been identified for the 74-day letter. <input checked="" type="checkbox"/> Review issues have been identified for the 74-day letter. List (optional): <input checked="" type="checkbox"/> Standard Review <input type="checkbox"/> Priority Review
ACTIONS ITEMS	
<input checked="" type="checkbox"/>	Ensure that the review and chemical classification codes, as well as any other pertinent classification codes (e.g., orphan, OTC) are correctly entered into tracking system.
<input type="checkbox"/>	If RTF action, notify everybody who already received a consult request, OSE PM., and Product Quality PM. Cancel EER/TBP-EER.
<input type="checkbox"/>	If filed and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
<input type="checkbox"/>	If BLA or priority review NDA, send 60-day letter.
<input checked="" type="checkbox"/>	Send review issues/no review issues by day 74
<input type="checkbox"/>	Other

Appendix A (NDA and NDA Supplements only)

NOTE: The term "original application" or "original NDA" as used in this appendix denotes the NDA submitted. It does not refer to the reference drug product or "reference listed drug."

An original application is likely to be a 505(b)(2) application if:

- (1) it relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application,
- (2) it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval, or
- (3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

- (1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies),
- (2) No additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application, and.
- (3) All other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely for

approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

- (1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2),
- (2) The applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement, or
- (3) The applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your OND ADRA or OND IO.

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

/s/

QUYNH M NGUYEN
10/13/2009

505(b)(2) ASSESSMENT

Application Information		
NDA # 22-401	NDA Supplement #: S-	Efficacy Supplement Type SE-
Proprietary Name: Twynsta Established/Proper Name: telmisartan/amlodipine Dosage Form: Tablets Strengths: 40/5 mg, 40/10 mg, 80/5 mg, 80/10 mg		
Applicant: Boehringer Ingelheim Pharmaceuticals, Inc.		
Date of Receipt: December 18, 2008		
PDUFA Goal Date: October 18, 2009		Action Goal Date (if different):
Proposed Indication(s): Treatment of hypertension in patients not adequately controlled on antihypertensive monotherapy and as initial therapy in patients likely to need multiple drugs to achieve their blood pressure goals.		

GENERAL INFORMATION

- 1) Is this application for a recombinant or biologically-derived product and/or protein or peptide product *OR* is the applicant relying on a recombinant or biologically-derived product and/or protein or peptide product to support approval of the proposed product?

YES NO

If "YES" contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.



**INFORMATION PROVIDED VIA RELIANCE
(LISTED DRUG OR LITERATURE)**

- 2) List the information essential to the approval of the proposed drug that is provided by reliance on our previous finding of safety and efficacy for a listed drug or by reliance on published literature. *(If not clearly identified by the applicant, this information can usually be derived from annotated labeling.)*

Source of information* (e.g., published literature, name of referenced product)	Information provided (e.g., pharmacokinetic data, or specific sections of labeling)
Norvasc (amlodipine besylate) Tablet (NDA 19-787)	Labeling sections for amlodipine component
Exforge (amlodipine/valsartan) tablets (NDA 21-990)	Labeling sections for amlodipine component**
Azor (amlodipine /olmesartan) tablets (NDA 22-100)	Labeling sections for amlodipine component**

*each source of information should be listed on separate rows

** references in the annotated labeling to these two products is due to PLR labeling format requirements rather than the content of labeling

- 3) Reliance on information regarding another product (whether a previously approved product or from published literature) must be scientifically appropriate. An applicant needs to provide a scientific “bridge” to demonstrate the relationship of the referenced and proposed products. Describe how the applicant bridged the proposed product to the referenced product(s). (Example: BA/BE studies)
2 BE studies

RELIANCE ON PUBLISHED LITERATURE

- 4) (a) Regardless of whether the applicant has explicitly stated a reliance on published literature to support their application, is reliance on published literature necessary to support the approval of the proposed drug product (i.e., the application *cannot* be approved without the published literature)?

YES NO

If “NO,” proceed to question #5.

- (b) Does any of the published literature necessary to support approval identify a specific (e.g., brand name) *listed* drug product?

YES NO

If “NO”, proceed to question #5.

If “YES”, list the listed drug(s) identified by name and answer question #4(c).

- (c) Are the drug product(s) listed in (b) identified by the applicant as the listed drug(s)?

YES NO

RELIANCE ON LISTED DRUG(S)

Reliance on published literature which identifies a specific approved (listed) drug constitutes reliance on that listed drug. Please answer questions #5-9 accordingly.

- 5) Regardless of whether the applicant has explicitly referenced the listed drug(s), does the application **rely** on the finding of safety and effectiveness for one or more listed drugs (approved drugs) to support the approval of the proposed drug product (i.e., the application cannot be approved without this reliance)?

YES NO

If "NO," proceed to question #10.

- 6) Name of listed drug(s) relied upon, and the NDA/ANDA #(s). Please indicate if the applicant explicitly identified the product as being relied upon (see note below):

Name of Drug	NDA/ANDA #	Did applicant specify reliance on the product? (Y/N)
Norvasc (amlodipine besylate) Tablets	19-787	Y

Applicants should specify reliance on the 356h, in the cover letter, and/or with their patent certification/statement. If you believe there is reliance on a listed product that has not been explicitly identified as such by the applicant, please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

- 7) If this is a (b)(2) supplement to an original (b)(2) application, does the supplement rely upon the same listed drug(s) as the original (b)(2) application?

N/A YES NO

If this application is a (b)(2) supplement to an original (b)(1) application or not a supplemental application, answer "N/A".

If "NO", please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

- 8) Were any of the listed drug(s) relied upon for this application:

- a) Approved in a 505(b)(2) application?

YES NO

If "YES", please list which drug(s).

Name of drug(s) approved in a 505(b)(2) application:

- b) Approved by the DESI process?

YES NO

If "YES", please list which drug(s).

Name of drug(s) approved via the DESI process:

- c) Described in a monograph?

YES NO

If "YES", please list which drug(s).

Name of drug(s) described in a monograph:

d) Discontinued from marketing?

YES NO

If "YES", please list which drug(s) and answer question d) i. below.
If "NO", proceed to question #9.

Name of drug(s) discontinued from marketing:

i) Were the products discontinued for reasons related to safety or effectiveness?

YES NO

(Information regarding whether a drug has been discontinued from marketing for reasons of safety or effectiveness may be available in the Orange Book. Refer to section 1.11 for an explanation, and section 6.1 for the list of discontinued drugs. If a determination of the reason for discontinuation has not been published in the Federal Register (and noted in the Orange Book), you will need to research the archive file and/or consult with the review team. Do not rely solely on any statements made by the sponsor.)

9) Describe the change from the listed drug(s) relied upon to support this (b)(2) application (for example, "This application provides for a new indication, otitis media" or "This application provides for a change in dosage form, from capsule to solution").

This application provides for a new combination of telmisartan and amlodipine.

The purpose of the following two questions is to determine if there is an approved drug product that is equivalent or very similar to the product proposed for approval that should be referenced as a listed drug in the pending application.

The assessment of pharmaceutical equivalence for a recombinant or biologically-derived product and/or protein or peptide product is complex. If you answered YES to question #1, proceed to question #12; if you answered NO to question #1, proceed to question #10 below.

10) (a) Is there a pharmaceutical equivalent(s) to the product proposed in the 505(b)(2) application that is already approved (via an NDA or ANDA)?

(Pharmaceutical equivalents are drug products in identical dosage forms that: (1) contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; (2) do not necessarily contain the same inactive ingredients; and (3) meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates. (21 CFR 320.1(c)).

Note that for proposed combinations of one or more previously approved drugs, a pharmaceutical equivalent must also be a combination of the same drugs.

YES NO

If "NO" to (a) proceed to question #11.

If "YES" to (a), answer (b) and (c) then proceed to question #12.

(b) Is the pharmaceutical equivalent approved for the same indication for which the 505(b)(2) application is seeking approval?

YES NO

(c) Is the listed drug(s) referenced by the application a pharmaceutical equivalent?

YES NO

If "YES" to (c) and there are no additional pharmaceutical equivalents listed, proceed to question #12.

If "NO" or if there are additional pharmaceutical equivalents that are not referenced by the application, list the NDA pharmaceutical equivalent(s); you do not have to individually list all of the products approved as ANDAs, but please note below if approved generics are listed in the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

Pharmaceutical equivalent(s):

11) (a) Is there a pharmaceutical alternative(s) already approved (via an NDA or ANDA)?

(Pharmaceutical alternatives are drug products that contain the identical therapeutic moiety, or its precursor, but not necessarily in the same amount or dosage form or as the same salt or ester. Each such drug product individually meets either the identical or its own respective compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times and/or dissolution rates. (21 CFR 320.1(d)) Different dosage forms and strengths within a product line by a single manufacturer are thus pharmaceutical alternatives, as are extended-release products when compared with immediate- or standard-release formulations of the same active ingredient.)

Note that for proposed combinations of one or more previously approved drugs, a pharmaceutical alternative must also be a combination of the same drugs.

YES NO

If "NO", proceed to question #12.

(b) Is the pharmaceutical alternative approved for the same indication for which the 505(b)(2) application is seeking approval?

YES NO

(c) Is the approved pharmaceutical alternative(s) referenced as the listed drug(s)?

YES NO

If "YES" and there are no additional pharmaceutical alternatives listed, proceed to question #12.

If "NO" or if there are additional pharmaceutical alternatives that are not referenced by the application, list the NDA pharmaceutical alternative(s); you do not have to individually list all of the products approved as ANDAs, but please note below if approved generics are listed in the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

Pharmaceutical alternative(s):

PATENT CERTIFICATION/STATEMENTS

- 12) List the patent numbers of all unexpired patents listed in the Orange Book for the listed drug(s) for which our finding of safety and effectiveness is relied upon to support approval of the (b)(2) product.

Listed drug/Patent number(s):

No patents listed *proceed to question #14*

- 13) Did the applicant address (with an appropriate certification or statement) all of the unexpired patents listed in the Orange Book for the listed drug(s) relied upon to support approval of the (b)(2) product?

YES NO

If "NO", list which patents (and which listed drugs) were not addressed by the applicant.

Listed drug/Patent number(s):

- 14) Which of the following patent certifications does the application contain? *(Check all that apply and identify the patents to which each type of certification was made, as appropriate.)*

- No patent certifications are required (e.g., because application is based solely on published literature that does not cite a specific innovator product)
- 21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA. (Paragraph I certification)
- 21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired. (Paragraph II certification)

Patent number(s):

- 21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire. (Paragraph III certification)

Patent number(s):

Expiry date(s):

- 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted. (Paragraph IV certification). *If Paragraph IV certification was submitted, proceed to question #15.*
- 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the NDA holder/patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above). *If the applicant has a licensing agreement with the NDA holder/patent owner, proceed to question #15.*

21 CFR 314.50(i)(1)(ii): No relevant patents.

21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent as described in the corresponding use code in the Orange Book. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications. (Section viii statement)

Patent number(s):

Method(s) of Use/Code(s):

15) Complete the following checklist **ONLY** for applications containing Paragraph IV certification and/or applications in which the applicant and patent holder have a licensing agreement:

(a) Patent number(s):

(b) Did the applicant submit a signed certification stating that the NDA holder and patent owner(s) were notified that this b(2) application was filed [21 CFR 314.52(b)]?

YES NO

If "NO", please contact the applicant and request the signed certification.

(c) Did the applicant submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)]? This is generally provided in the form of a registered mail receipt.

YES NO

If "NO", please contact the applicant and request the documentation.

(d) What is/are the date(s) on the registered mail receipt(s) (i.e., the date(s) the NDA holder and patent owner(s) received notification):

Date(s):

(e) Has the applicant been sued for patent infringement within 45-days of receipt of the notification listed above?

Note that you may need to call the applicant (after 45 days of receipt of the notification) to verify this information UNLESS the applicant provided a written statement from the notified patent owner(s) that it consents to an immediate effective date of approval.

YES NO Patent owner(s) consent(s) to an immediate effective date of approval

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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/s/

QUYNH M NGUYEN
10/13/2009

FIELD COPY CERTIFICATION

Certification Statement

21 CFR 314.70(a)

The applicant certifies on behalf of Boehringer Ingelheim Pharmaceuticals, Inc., that a “true copy” of the Chemistry, Manufacturing and Controls portion of NDA 22-401 submitted to the FDA Division of Cardio-Renal Drug Products is submitted to the Office of Regional Operations, Division of Emergency and Investigational Operations in Rockville, Maryland on the same date. As requested by the applicant’s home district office, the “true copy” is supplied electronically on DVD in the same format as submitted to the FDA Division of Cardio-Renal Drug Products. A copy of the Submission Cover Letter only has been sent the Boston District Office in Stoneham, Massachusetts.

Signature:


Jayne Turner
Manager
Drug Regulatory Affairs
Boehringer Ingelheim Pharmaceuticals, Inc

Mailing Address:

Boehringer Ingelheim Pharmaceuticals, Inc.
900 Ridgebury Road
P.O. Box 368
Ridgefield, CT 06877-0368

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

/s/

JOYCE K DE LEON
10/21/2009

(H) 2 pages withheld immediately following this page as b
(6) privacy

Form Approved: OMB No. 0910 - 0297 Expiration Date: January 31, 2010 See instructions for OMB Statement, below.					
DEPARTMENT OF HEALTH AND HUMAN SERVICES FOOD AND DRUG ADMINISTRATION	PRESCRIPTION DRUG USER FEE COVERSHEET				
A completed form must be signed and accompany each new drug or biologic product application and each new supplement. See exceptions on the reverse side. If payment is sent by U.S. mail or courier, please include a copy of this completed form with payment. Payment instructions and fee rates can be found on CDER's website: http://www.fda.gov/cder/pdufa/default.htm					
1. APPLICANT'S NAME AND ADDRESS BOEHRINGER INGELHEIM PHARMACEUTICALS INC Jill Szep 900 RIDGEBURY RD BOX 368 RIDGEFIELD CT 06877 US	4. BLA SUBMISSION TRACKING NUMBER (STN) / NDA NUMBER NDA 22-401				
2. TELEPHONE NUMBER 203-7787941	5. DOES THIS APPLICATION REQUIRE CLINICAL DATA FOR APPROVAL? <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO IF YOUR RESPONSE IS "NO" AND THIS IS FOR A SUPPLEMENT, STOP HERE AND SIGN THIS FORM. IF RESPONSE IS "YES", CHECK THE APPROPRIATE RESPONSE BELOW: <input checked="" type="checkbox"/> THE REQUIRED CLINICAL DATA ARE CONTAINED IN THE APPLICATION <input type="checkbox"/> THE REQUIRED CLINICAL DATA ARE SUBMITTED BY REFERENCE TO:				
3. PRODUCT NAME TWYNSTA (telmisartan / amlodipine besylate)	6. USER FEE I.D. NUMBER PD3008825				
7. IS THIS APPLICATION COVERED BY ANY OF THE FOLLOWING USER FEE EXCLUSIONS? IF SO, CHECK THE APPLICABLE EXCLUSION. <input type="checkbox"/> A LARGE VOLUME PARENTERAL DRUG PRODUCT APPROVED UNDER SECTION 505 OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT BEFORE 9/1/92 (Self Explanatory) <input type="checkbox"/> A 505(b)(2) APPLICATION THAT DOES NOT REQUIRE A FEE <input type="checkbox"/> THE APPLICATION QUALIFIES FOR THE ORPHAN EXCEPTION UNDER SECTION 736(a)(1)(E) of the Federal Food, Drug, and Cosmetic Act <input type="checkbox"/> THE APPLICATION IS SUBMITTED BY A STATE OR FEDERAL GOVERNMENT ENTITY FOR A DRUG THAT IS NOT DISTRIBUTED COMMERCIALY					
8. HAS A WAIVER OF AN APPLICATION FEE BEEN GRANTED FOR THIS APPLICATION? <input type="checkbox"/> YES <input checked="" type="checkbox"/> NO					
OMB Statement: Public reporting burden for this collection of information is estimated to average 30 minutes per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to: <table style="width:100%; border: none;"> <tr> <td style="width: 33%;"> Department of Health and Human Services Food and Drug Administration CBER, HFM-99 1401 Rockville Pike Rockville, MD 20852-1448 </td> <td style="width: 33%;"> Food and Drug Administration CDER, HFD-94 12420 Parklawn Drive, Room 3046 Rockville, MD 20852 </td> <td style="width: 33%;"> An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number. </td> </tr> </table>			Department of Health and Human Services Food and Drug Administration CBER, HFM-99 1401 Rockville Pike Rockville, MD 20852-1448	Food and Drug Administration CDER, HFD-94 12420 Parklawn Drive, Room 3046 Rockville, MD 20852	An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.
Department of Health and Human Services Food and Drug Administration CBER, HFM-99 1401 Rockville Pike Rockville, MD 20852-1448	Food and Drug Administration CDER, HFD-94 12420 Parklawn Drive, Room 3046 Rockville, MD 20852	An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.			
SIGNATURE OF AUTHORIZED COMPANY REPRESENTATIVE 	TITLE Sean S. Associate Director	DATE 11/11/2008			
9. USER FEE PAYMENT AMOUNT FOR THIS APPLICATION \$1,247,200.00					
Form FDA 3397 (03/07)					



NDA 22-401

INFORMATION REQUEST

Boehringer Ingelheim Pharmaceuticals, Inc
Attention: Jayne Turner, Manager, CMC Regulatory Affairs
900 Ridgebury Rd, PO Box 368
Ridgefield, CT 06877

Dear Ms. Turner:

Please refer to your December 18, 2008 new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Twynsta (Telmisartan/amlodipine besylate) tablets.

We are reviewing the Chemistry, Manufacturing and Controls section of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

1. For telmisartan, the proposed dissolution methodology (900 mL phosphate buffer pH 7.5 using paddle with 75 rpm) is acceptable, but the specifications should be tightened as follows: From $Q = (b)$ in 30 min to $Q = (b)$ in 15 min.
2. For amlodipine, the proposed dissolution methodology (500 mL 0.01 N HCl pH 2 using paddle with 75 rpm) and specifications ($Q = (b)$ in 30 min) are not acceptable, since >95% dissolved in 10 min. Therefore, the following dissolution methodology and specifications should be implemented:

Apparatus: Paddle (USP Apparatus II) with 75 rpm
Medium: 900 mL phosphate buffer (pH 6.8) at 37°C
Specifications: $Q = (b)$ in 15 min

If you have any questions, call Don Henry, Regulatory Project Manager, at (301) 796-4227.

Sincerely,

{See appended electronic signature page}

Ramesh Sood, Ph.D.
Branch Chief
Division of Pre-Marketing Assessment I
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

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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/s/

RAMESH K SOOD
09/04/2009



NDA 22-401

INFORMATION REQUEST LETTER

Boehringer Ingelheim Pharmaceuticals, Inc
Attention: Monika Richter, Sr. Associate Director, Drug Regulatory Affairs
900 Ridgebury Rd, PO Box 368
Ridgefield, CT 06877

Dear Ms. Richter:

Please refer to your December 18, 2008 new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Twynsta (Telmisartan/amlodipine besylate) tablets.

We are reviewing the Chemistry, Manufacturing and Controls section of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

1. For clarification purposes, provide chemical structures of the specified telmisartan derived drug substance impurities to this application.
2. Provide details of the control of possible telmisartan derived impurity (b) (4). As this reagent is likely to undergo (b) (4), provide details of the levels of its (b) (4) derivative in the drug substance. As these potential impurities are (b) (4) and therefore suspect mutagens, their levels should be controlled so that patients are exposed to levels of NMT (b) (4), unless data can be provided to show that they have no mutagenic potential.
3. Provide data to support your contention that telmisartan "drug substance is fully amorphous and in (b) (4) in the drug product. How is the degree of (b) (4) content controlled at release and during stability studies?
4. What is the hold-time for the telmisartan (b) (4)? Provide stability data to support this hold-time.
5. Provide sample tablets for each strength in the proposed blister packaging configuration.
6. Due to the difficulty in observing trends in tablet hardness we request that you provide updated (24 month) drug product stability data. In addition, we request that you provide an integrated summary of these data.
7. Provide data to support your statement that "in the drug product amlodipine besilate exists exclusively as the anhydrate".
8. Provide data on the steps that you have taken to avoid delamination of the tablets. What in-process controls are in place to avoid this situation (e.g. controls in excipient quality, limits on pre-compression force of the first layer, lubricant quantity).
9. Provide details of the tablet hardness test including details of the specific orientation of the tablet during testing and its impact on the results.

10. Provide an explanation and justification for the tablet hardness acceptance criterion: "Ensure that the tablet breaks lengthwise during testing."
11. We recommend the addition to the drug product specification of an upper tablet hardness limit based on data to date, as increased hardness may result in changes in tablet friability, brittleness and delamination potential.
12. Describe how the bulk tablets will be stored (e.g. container type, use of desiccant / maximum holding time).
13. Provide a statistical analysis for any possible trends in tablet hardness results from the stability studies.
14. Your studies indicate that tablets with (b) (4) had no significant changes in chemical degradation. How long were these tablets stored (b) (4) Provide data that would indicate that tablets with (b) (4) near the proposed (b) limit at release would meet the proposed drug product specification through the expiry period.
15. Provide data from your developmental drug product desiccant studies and describe how you determined that the proposed amounts of desiccant (b) (4) will provide adequate protection against degradation of tablets (with the maximum proposed (b) (4) through the expiry period.
16. Provide an explanation for the lack of mass balance in the drug product photostability studies, as an increase in Impurity (b) (4) results in a decrease in assay of (b)
17. Your studies indicate that the tablets softened and the (b) (4) specified limit after storage for one week outside of the container at 25°C/60%RH. At what point during this one week storage do the tablets fail to meet drug product specification (e.g. two hours, 2 days)?
18. We recommend that a friability test be implemented for the tablet release and stability testing. Provide data on the friability of the tablets at or near the end of the proposed expiry period.
19. We recommend the addition of a test to control for tablet delamination (e.g. extended friability test).

If you have any questions, call Don Henry, Regulatory Project Manager, at 301-796-4227.

Sincerely,

{See appended electronic signature page}

Ramesh Sood, Ph.D.
Branch Chief
Division of Pre-Marketing Assessment I
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

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/s/

Kasturi Srinivasachar
6/25/2009 09:49:06 AM

Nguyen, Quynh M

From: Nguyen, Quynh M
Sent: Tuesday, June 23, 2009 11:51 AM
To: 'monika.richter@boehringer-ingelheim.com'
Subject: RE: NDA 22-401/Twynsta - Carton and container labeling comments

Dear Monika,

I checked on your question and the order was not meant to be intentional, so you can keep it as "(Telmisartan and Amlodipine)."

Thanks,
Quynh

From: monika.richter@boehringer-ingelheim.com [mailto:monika.richter@boehringer-ingelheim.com]
Sent: Tuesday, June 23, 2009 9:58 AM
To: Nguyen, Quynh M
Subject: RE: NDA 22-401/Twynsta - Carton and container labeling comments

Dear Quynh,

Thank you for the feedback on the carton and container labeling. I would like to ask one follow up question: Under General Comments 2., the name is stated Twynsta (Amlodipine and Telmisartan) tablets. Is the order of the active ingredients intentional, as we have used it the other way around (Telmisartan and Amlodipine) consistently through the documentation.

Thanks in advance
Monika

-----Original Message-----

From: Nguyen, Quynh M [mailto:Quynh.Nguyen@fda.hhs.gov]
Sent: Tuesday, June 23, 2009 9:08 AM
To: Richter,Monika DRA BIP-US-R
Subject: NDA 22-401/Twynsta - Carton and container labeling comments

Dear Monika,

I received your voicemail message from yesterday and the CMC Information Request letter has not been issued yet, so it is still pending at this time.

Also, I have attached comments from DMEPA on the carton and container labeling (please see the attached file).

Thanks,
Quynh

*Quynh M. Nguyen, Pharm.D., RAC
Regulatory Health Project Manager
FDA/CDER/OND/ODE1/DCRP*

*Tel: (301) 796-0510
Fax: (301) 796-9838
quynh.nguyen@fda.hhs.gov*

DMEPA comments on the carton and container labeling – NDA 22-401/Twynsta

A. General Comments

1. Ensure that the established name is 1/2 the size of the proprietary name taking into account all pertinent factors, including typography, layout, contrast, and other printing features in accordance with 21 CFR 201.10(g)(2).
2. The dosage form of Twynsta (tablets) should be adjacent to the established name on all labels and labeling as follows:

Twynsta
(Amlodipine and Telmisartan) Tablets

B. Blister Label

1. Revise the blister labels to provide for more adequate visual differentiation between strengths. As currently presented, the blister labels look identical and make it very difficult to readily identify the different product strengths. Differentiate the product strengths on the blister labels by using contrasting color, boxing, or some other means.
2. The Applicant's name and graphic are large and takes up unnecessary space. Decrease the size of the Applicant's name and graphic, as it is more prominent than the most important information on the label such as the proprietary name, established name, strength, and instructions for removing the tablet from the blister.
3. The blister package is considered the immediate container for each tablet and therefore is required to have a bar code which contains the applicable National Drug Code (NDC) number. Include the product bar code on each tablet blister label as required by 21 CFR 201.25(c)(1).

C. Carton Labeling

As currently presented, the 40 mg/10 mg and 80 mg/5 mg carton labeling look almost identical when compared side-by-side. We acknowledge the use of different color blocking with the different strengths, however, the overall trade dress blue/gray colors still makes the labels look similar. Change the color in the color blocks (i.e., grey for 40 mg/10 mg and blue for 80 mg/5 mg) of the two strengths to colors that do not overlap and are different than the colors in the trade dress.



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

FILING COMMUNICATION

NDA 22-401

Boehringer Ingelheim Pharmaceuticals, Inc.
Attention: Ms. Monika Richter
900 Ridgebury Road
P.O. Box 368
Ridgefield, CT 06877

Dear Ms. Richter:

Please refer to your new drug application (NDA) dated December 18, 2008 submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Tywnsta (telmisartan/amlodipine) 40/5, 40/10, 80/5, and 80/10 mg Tablets.

We also refer to your submissions dated February 5, 6, and 17, 2009.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is **Standard**. Therefore, the user fee goal date is October 18, 2009.

During our filing review of your application, we identified the following potential review issues:

1. For the initial therapy indication, please refer to the attached document entitled "**Points to Consider in Generating Graphs for Initial Therapy with Combination Antihypertensive Drugs**" and provide all details to show how the graphs were generated.

We are providing the above comments to give you preliminary notice of potential review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review. Issues may be added, deleted, expanded upon, or modified as we review the application.

Please respond only to the above requests for additional information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We acknowledge receipt of your request for a full waiver of pediatric studies for this application. Once we have reviewed your request, we will notify you if the full waiver request is denied and a pediatric drug development plan is required.

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, mid-cycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing commitment requests by September 27, 2009.

If you have any questions, please call:

Quynh Nguyen, Pharm.D., RAC
Regulatory Health Project Manager
(301) 796-0510

Sincerely,

{See appended electronic signature page}

Norman Stockbridge, M.D., Ph.D.
Director
Division of Cardiovascular and Renal Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Attachment: **“Points to Consider in Generating Graphs for Initial Therapy with Combination Antihypertensive Drugs”** document

Points to Consider in Generating Graphs for Initial Therapy with Combination Antihypertensive Drugs

This document is intended to provide general guidance for use of graphs in drug labeling for initial therapy with combination antihypertensive drugs. The four graphs are to illustrate the advantage of a combination drug over its component drugs in reaching blood pressure goals of 140 and 130 mm Hg systolic and 90 and 80 mm Hg diastolic.

The graph contains regression curves for the probability of reaching a blood pressure target after treatment as a function of baseline blood pressure for the treatment groups. The curves are often based on logistic regression modeling. Some other statistical models such as probit regression may be considered. For model fitting, the following statistical considerations need attention:

1. The regression curves should fit the data reasonably well with no disproportionate leverage exerted from extreme values or potential outliers. Extensive model diagnostics are required for assessment of goodness-of-fit or a lack of fit of the fitted model. To determine overall and local fit of each regression curve, the diagnostics should include comparison of the regression curve with a LOESS non-parametric curve, comparison of the regression curve with histogram, tests (e.g., Hosmer-Lemeshow test) for fit, analysis of potential influential values. Diagnostics plots need to be generated and should include those of residuals (e.g., chi-square residual, deviance residual) versus estimated probability of achieving the blood pressure goal, difference in beta parameter value versus estimated probability, etc. If a few extreme values are suspected to cause a lack of fit, the fit may be improved by trimming these data points for further assessment. However, how many and which data points should be removed is a subjective judgment. The process of removing a few subjects for further assessment of model fit is a part of influence diagnostics. The final graphs in the drug label should include all data if possible.
2. In general, the model parameters of each treatment group should be estimated only from the data of this treatment group. In some rare situation, a simpler model such as use of a common slope for all treatment groups might improve the precision of the curves. However, applying such a simpler model to all treatment groups in regression analysis relies on strong assumptions and thus it may induce model and selection biases. Comparisons among models via statistical model selection criteria (such as AIC) need to be made, in addition to the necessary model diagnostics described above.
3. Pooling studies is discouraged because it relies on many strong and unverifiable assumptions, such as the studies pooled employ an identical design and target the same patient population, etc. When the assumptions do not hold, the curves generated from the pooled studies can be very misleading.
4. One or two studies should be chosen for display in the case that there are multiple studies conducted and pooling studies is not viable. As a general principle, the pivotal trial with the largest sample size per treatment group should be first considered. If there are multiple dose combinations, the highest dose combination is first considered with its monotherapy doses.
5. Please provide an assessment of the representation of very elderly and other fragile patients among the subjects in the factorial studies, and their adverse event profile with and tolerability to randomization to the combination.

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/s/

Norman Stockbridge
2/25/2009 04:44:06 PM



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-401

NDA ACKNOWLEDGMENT

Boehringer Ingelheim Pharmaceuticals, Inc.
Attention: Monika Richter
Senior Associate Director
Drug Regulatory Affairs
900 Ridgebury Road, P.O. Box 368
Ridgefield, CT 06877

Dear Ms. Richter:

We have received your new drug application (NDA) submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA) for the following:

Name of Drug Product: Twynsta[®] (telmisartan/amlodipine) Tablets

Date of Application: December 18, 2008

Date of Receipt: December 18, 2008

Our Reference Number: NDA 22-401

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on February 16, 2009 in accordance with 21 CFR 314.101(a).

The NDA number provided above should be cited at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Cardiovascular and Renal Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size. Non-

standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, please see <http://www.fda.gov/cder/ddms/binders.htm>.

If you have any questions, please contact:

Ms. Quynh Nguyen, Pharm.D., RAC
Regulatory Health Project Manager
(301) 796-0510

Sincerely,

{See appended electronic signature page}

Edward Fromm, RPh., RAC
Chief, Project Management Staff
Division of Cardiovascular and Renal Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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/s/

Edward Fromm
1/9/2009 02:50:11 PM

**DIVISION OF CARDIOVASCULAR AND RENAL PRODUCTS
FOOD AND DRUG ADMINISTRATION**

WHITE OAK COMPLEX
10903 NEW HAMPSHIRE AVE
BLDG. 22
SILVER SPRING, MD 20993



US Mail address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Cardiovascular and Renal Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

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FDA/CDER/DCaRP 5901-B Ammendale Rd. Beltsville, MD 20705-1266

Transmitted via email to: Monika.Richter@boehringer-ingenelheim.com

Attention: Ms. Monika Richter

Sponsor: Boehringer Ingelheim Pharmaceuticals, Inc.

Phone: (203) 791-6540

Subject: Type C Guidance Teleconference Minutes

Date: June 5, 2008

Pages, including this sheet: 8

From: Quynh Nguyen, Pharm.D.
Phone: 301-796-0510
Fax: 301-796-9838
E-mail: quynh.nguyen@fda.hhs.gov

Please note that you are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

Guidance Meeting via Teleconference with Sponsor

Application: IND 71,882
Sponsor: Boehringer Ingelheim Pharmaceuticals, Inc.
Drug: Telmisartan/Amlodipine Fixed Dose Combination (FDC)
Type of Meeting: Guidance
Classification: C
Meeting Date: April 9, 2008
Briefing Package Received: February 28, 2008
Confirmation Date: February 11, 2008
Meeting Request Received: January 18, 2008
Meeting Chair: Norman Stockbridge, M.D., Ph.D.
Recorder: Quynh Nguyen, Pharm.D.

List of Attendees:

Food and Drug Administration

Norman Stockbridge, M.D., Ph.D.	Director, Division of Cardiovascular and Renal Products (DCRP)
Ellis Unger, M.D.	Deputy Director, DCRP
Abraham Karkowsky, M.D., Ph.D.	Medical Team Leader, DCRP
Jialu Zhang, Ph.D.	Acting Team Leader, Division of Biometrics I
Ququan (Cherry) Liu, Ph.D.	Statistician, Division of Biometrics I
Quynh Nguyen, Pharm.D.	Regulatory Health Project Manager, DCRP

Boehringer Ingelheim Pharmaceuticals, Inc.

Chris Corsico, M.D.	VP Drug Regulatory Affairs (US)
Jeff Friedman, M.D.	Therapeutic Area Head Cardiovascular (US)
Dr. Rainer Kleemann	International Project Leader (Germany)
Dr. Ludwin Ley	Team Member Medical Affairs (Germany)
Dr. Thomas Meinicke	Team Member Medicine (Germany)
Heidi Reidies	Executive Director, Drug Regulatory Affairs (US)
Monika Richter	Senior Associate Director, Drug Regulatory Affairs(US)
Dr. Helmut Schumacher	Project Statistician (Germany)
Dr. Hubert Ströbele	Medical Subteam Member (Germany)
Eva Walter	Team Member Drug Regulatory Affairs (Germany)

BACKGROUND

Telmisartan and amlodipine are each approved for the treatment of hypertension. Boehringer Ingelheim Pharmaceuticals is developing a fixed dose combination (FDC) product of telmisartan and amlodipine. The sponsor requested this meeting to discuss the clinical data package required to support the use of the telmisartan/amlodipine FDC as initial therapy in hypertensive patients. The Division's Preliminary

Responses were sent to the sponsor on April 3, 2008. The sponsor provided a response to the Division's Preliminary Responses on April 8, 2008 (see attachment). The purpose of the teleconference was to discuss the responses for Questions 1 and 2 as noted below.

DISCUSSION

1. The 8-week 4x4 placebo-controlled factorial design Trial 1235.1, which included three strengths each of telmisartan (20mg, 40mg and 80mg) and amlodipine (2.5mg, 5mg and 10mg), was performed in more than 1400 mild to severe hypertensive patients. As discussed with the Division at a pre-IND meeting on 22 July 2005, the results of this study are intended to form the basis for registration of a telmisartan/amlodipine FDC product.

Results in the overall patient population showed an additive effect of telmisartan and amlodipine. Statistically and clinically significant reductions from baseline in seated DBP and seated SBP in the key treatment cells of T40/A5, T40/A10, T80/A5 and T80/A10 in comparison to the monocomponents and placebo were demonstrated. Based on regulatory precedence and our previous interactions with the Division, Boehringer Ingelheim is of the opinion that this controlled study supplemented with long term safety data on the combined use of telmisartan and amlodipine / dihydropyridine CCBs in other clinical trials will be adequate to support registration of this fixed dose combination for treatment of hypertension in patients not adequately controlled by monotherapy. This will be discussed in more detail at the pre-NDA meeting at a later date. The currently proposed commercial doses are T40/A5, T40/A10, T80/A5, and T80/A10.

In addition, BI is of the opinion that the data from this study also support the use of the telmisartan/amlodipine FDC as initial therapy in patients likely to need multiple drugs to achieve blood pressure goals. This has been demonstrated in further prespecified analyses in a subset of moderate to severe hypertensive patients for all as well as the key treatment cells. The results of these analyses and supporting safety data are presented in Section 9 Clinical data summary and Appendix 1.

a. Pending review of the data, does FDA concur that the efficacy data from Trial 1235.1 are adequate to support the use of the telmisartan/amlodipine FDC as initial therapy in patients likely to need multiple drugs to achieve their blood pressure goals?

b. Pending review of the data, does FDA concur that the proposed safety data from Trial 1235.1 with longer term safety data from other sources are adequate to support the use the telmisartan/amlodipine FDC as initial therapy in patients likely to need multiple drugs to achieve their blood pressure goals?

FDA Preliminary Response

We agree. However, based on the populations that were studied and based on the fact that the lowest dose of amlodipine will not be available, it is likely that there will be limitations placed on the population that should be considered for initial therapy.

Discussion during Meeting

The Division clarified that limitations could be placed on following patient populations: the elderly, diabetics, and patients with renal or hepatic failure. The sponsor was encouraged to address any differences seen in the study with respect to these subgroups and any other subgroups where they saw a difference.

2. BI is planning to conduct Study 1235.20 to further investigate the use of the telmisartan/amlodipine FDC as initial therapy in severe hypertensive patients (defined as seated DBP ≥ 110 mmHg at the randomization visit) who are likely to need multiple drugs to achieve their blood pressure goals. An outline of the study is provided in Appendix 2.

Does FDA have any comments on the provided study outline?

Preliminary Response

The key issue here is how much of a benefit does the combination have over the highest dose of each monotherapy. The planned study, however, does not assess the combination therapy versus the other monotherapy at its highest dose (Telmisartan 80 mg). In addition, in at least a substantial sub-population, orthostatic measurements at peak drug effect should assess any excessive blood pressure effects.

Discussion during Meeting

The sponsor stated that since the factorial study 1235.1 already demonstrated the benefit of the combination versus the respective highest doses of the monotherapies, they were unsure whether the addition of a telmisartan 80 mg third arm would provide additional information. The Division replied that having this third arm would give a fuller picture of why patients should be started on the FDC instead of telmisartan alone. It would be more valuable to show there was a contribution against both the monotherapy components rather than amlodipine alone.

Since the data on severely hypertensive patients in the 1235.1 factorial trial were quite limited, the Division was concerned whether or not these data should be described in the labeling. The sponsor should also consider how well they can defend the safe use of the FDC in patients with elevated blood pressure when the patient population is "frail." The sponsor agreed that there was very limited data in patients ≥ 75 years old based on their subgroup analyses.

There was discussion regarding the implications on labeling with respect to severely hypertensive patients. The Division stated that it was unclear at this point, but it was possible that the sponsor could receive suboptimal labeling initially and upon completion of postmarketing studies, receive more favorable labeling.

The sponsor asked whether ABPM or orthostatic measurements should be done in patients ≥ 65 years old to which the Division replied that orthostatic monitoring would be acceptable.

3. If FDA does not concur that results of the factorial design Study 1235.1 with longer term safety data from other sources are considered adequate to support the use of the telmisartan/amlodipine FDC product as initial therapy in patients who are likely to need multiple drugs to achieve blood pressure goals, then BI proposes to provide FDA with the results of Study 1235.1 combined with results from Study 1235.20 to support this claim.

Does FDA agree that this clinical package is adequate to demonstrate proof of efficacy and safety to support the proposed "initial therapy" claim?

Preliminary Response

We agree.

Additional Preliminary Responses

On page 10 of the meeting package, Table 9.2 lists an adjusted mean of -3.0 mmHg for the T80/A10 strength versus the monotherapy. However, Figure 9.7 on page 18 seems to show a much bigger difference (much more than 3.0 mmHg). Please explain.

Please provide a histogram of the baseline distribution of systolic and diastolic blood pressures for each cell (monotherapy or combination).

Discussion during Meeting

Regarding the data in Table 9.2 and Figure 9.7, the sponsor explained in their response that the difference is due to the fact that Table 9.2 includes adjusted mean reduction of DBP across the full range of baseline DBP (measured as mmHg), whereas Figure 9.7 displays the probability of achieving DBP control (depicted as % of patients being controlled) in relation to the baseline DBP.

The sponsor provided the histograms displaying the baseline blood pressure in all treatment groups of 1235.1 in their response. The Division stated that there was concern with certain outliers affecting the curve significantly. For example, in the histogram entitled "Probability of Achieving DBP < 90 mmHg," there were a low number of patients with DBP \geq 110 mmHg in each of the T80 and T80A10 arms. The Division suggested that the sponsor consider exploring a subset of the data that excludes these patients in the model fitting and send the results including the graphs to the Division for further review.

CONCLUSION

Agreement was reached on the sponsor's proposed clinical data package required to support the use of the telmisartan/amlodipine FDC as initial therapy in hypertensive patients.

Minutes preparation: Quynh Nguyen, Pharm.D.

Concurrence, Chair: *{See appended electronic signature page}*
Norman Stockbridge, M.D., Ph.D.

Rd:

N Stockbridge 6/5/08
A Karkowsky 6/4/08
J Zhang 6/4/08
Q Liu 6/4/08



Norman Stockbridge, M.D., Ph.D., Director
Division of Cardiovascular and Renal Products
Food and Drug Administration
Center for Drug Evaluation and Research
5901-B Ammendale Road
Beltsville, MD 20705

Boehringer Ingelheim
Pharmaceuticals, Inc.

Re: IND 71,882/ Serial No. 0019
Telmisartan/Amlodipine Fixed Dose Combination

April 8, 2008

General Correspondence – Type C meeting on 09 April 08

Dear Dr. Stockbridge,

We would like to confirm that the preliminary answers from FDA were received on April 3rd, 2008 and would like to thank the Division for the early feedback prior to our scheduled teleconference. Based on the answers received, we would like to obtain further clarification on the responses provided to Questions 1 and 2:

- *FDA response to Question 1:* It is pointed out that it is likely that limitations will be placed in the label for the populations eligible for initial therapy. We understand that this would particularly apply to patients with hepatic insufficiency, but may also include other subpopulations depending on the results of respective subgroup analyses of Trial 1235.1 (e.g. elderly patients equal or above the age of 75 years). In these patients a starting dose of 2.5 mg amlodipine once daily based on the recommendations in the current prescribing information may be required.

Request for clarification: We request further clarification, if limitations for other patient populations, regarding the “initial therapy” claim, can be envisioned for the label based on the results of the 1235.1 study as described in the briefing package.

- *FDA response to Question 2:* It is outlined that the key issue is to evaluate the benefit of the combination versus the respective monotherapies. As Trial 1235.20 does not assess the combination versus the highest dose of telmisartan, recommendation is provided to add a 3rd arm (telmisartan 80 mg) to the study. Furthermore, orthostatic measurements at peak drug effect are proposed to assess any excessive blood pressure effects.

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Request for clarification:

- Based on clinical developments of fixed dose combinations previously approved for initial therapy, study 1235.20 was designed with two arms in severe hypertensives. As the factorial design trial 1235.1 already demonstrated the benefit of the combination versus the respective highest doses of the monotherapies, we would therefore appreciate further clarification on the recommendation to add a third arm.
- The question of peak drug effects and orthostatic effects has been already included in the objectives of the factorial design study 1235.1. In compliance with advice of the FDA in the pre-IND meeting Ambulatory Blood Pressure Monitoring was performed in a subgroup of patients (N=562 overall, N=403 patients in the subgroup of stage 2 hypertension analyzed in the full analysis set). Results of these analyses did not reveal any safety issue, with regard to peak drug effect of the combination, as well as with regard to orthostatic effects, both in the overall population and in the subgroup of stage 2 hypertension. Further clarification is therefore required on the request to include assessment of peak drug effect and orthostatic measurements.
- We would like to get FDA feedback what potential implications for labeling, if any, potentially positive results of the study might have.

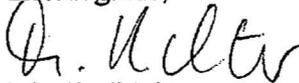
Additional preliminary responses provided by FDA:

Further clarification was requested regarding the data for T80/A10 and A10 in Table 9.2 on page 12 in comparison to Figure 9.7 on page 18. Please be informed that the difference is due to the fact that Table 9.2 includes adjusted mean reduction of DBP across the full range of baseline DBP (measured as mmHg), whereas Figure 9.7 displays the probability of achieving DBP control (depicted as % of patients being controlled) in relation to the baseline DBP.

Please find attached histograms displaying the baseline blood pressure in all treatment groups of 1235.1 as requested. We also provide for the treatment groups of T80/A10, T80 and A10 the mean DBP reduction by baseline DBP subgroups (in steps of 5 mmHg), as well as percentages of patients achieving DBP control (DBP <90 mmHg) at study termination. The graphical presentations show that mean reductions of 13 - 19 mmHg DBP were observed with monotherapy in the subgroups with baseline DBP of 105 mmHg or higher. However, these reductions were insufficient for a high percentage of patients to achieve DBP control. This confirms the results of the logistic regression investigating the relationship between probability of achieving DBP control and baseline DBP for different treatments.

We are looking forward to our discussions in the teleconference on Wednesday.

Best regards,



Monika Richter
Senior Associate Director, Drug Regulatory Affairs

Desk copy: Quynh Nguyen

Attachment: Histograms

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Linked Applications

Sponsor Name

Drug Name

IND 71882

BOEHRINGER
INGELHEIM

TELMISARTAN / AMLODIPINE

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

/s/

NORMAN L STOCKBRIDGE
06/05/2008

**DIVISION OF CARDIOVASCULAR AND RENAL PRODUCTS
FOOD AND DRUG ADMINISTRATION**

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Transmitted via email to: Monika.Richter@boehringer-ingenelheim.com

Attention: Ms. Monika Richter

Sponsor: Boehringer Ingelheim Pharmaceuticals,
Inc.

Phone: (203) 791-6540

Subject: **Pre-NDA Meeting
Preliminary Responses**

Date: June 3, 2008

Pages, including this sheet: 13

From: Quynh Nguyen, Pharm.D.

Phone: 301-796-0510

Fax: 301-796-9838

E-mail: quynh.nguyen@fda.hhs.gov

Please let me know you received this. Thanks!

IND 71,882
Telmisartan/Amlodipine FDC
Boehringer Ingelheim Pharmaceuticals, Inc.
Pre-NDA Meeting
Preliminary Responses

*This material consists of our preliminary responses to your questions and any additional comments in preparation for the discussion at the meeting scheduled for **June 10, 2008 from 1:00 to 2:30 PM** between **Boehringer Ingelheim Pharmaceuticals, Inc.** and the Division of Cardiovascular and Renal Products. We believe that these responses will address all of your questions, and do not feel that a meeting is necessary; however, if there are points that you do not understand or with which you disagree, please advise us, and we will consider your request to hold the meeting.*

DISCUSSION

Module 1 – Labeling / Regulatory

- 1) BI proposes that draft (b) (4) labels will be submitted for only one strength and configuration in the initial NDA. Final labeling for all proposed strengths and configurations supported by the application will be submitted shortly before approval.

Is this proposal acceptable to the FDA?

Preliminary Response

Yes, but please specify the timeframe for when you plan to submit the final labeling for all proposed strengths and configurations.

- 2) A request for a waiver of the requirement to conduct studies in a pediatric population for the proposed indication will be included in the NDA.

Does the FDA concur that a waiver for the requirement to perform pediatric studies is appropriate?

Preliminary Response

We agree that you should include your request for a waiver in the NDA submission for the Agency's consideration. The decision to waive pediatric studies, however, is made in conjunction with the Pediatric Review Committee (PeRC).

- 3) The NDA will be organized in the ICH Common Technical Document format. An overall Table of Contents (TOC) is provided in Appendix 1.

Does the FDA have any comments on the structure and content of the NDA as outlined in the TOC?

Preliminary Response

We have no further comments.

Module 2 – Summary Documents

- 4) The NDA for the telmisartan / amlodipine fixed dose combination will be based on a single adequate and well controlled trial (1235.1) for demonstration of efficacy. BI is of the opinion that the Summary of Clinical Efficacy (SCE) addresses all content requirements as per 21 CFR 314.50(d)(5)(v) including

meeting the requirements for the Integrated Summary of Effectiveness (ISE). Supplementary tables and listings to the SCE will be placed in Module 5.3.5.3. A mock SCE is provided in Appendix 2.

Does the FDA concur that the proposed SCE format adequately addresses the content requirements for an ISE?

Preliminary Response

We concur.

Does the FDA agree with the proposal to locate supplementary tables and listings in Module 5.3.5.3?

Preliminary Response

We agree.

- 5) BI is of the opinion that the Summary of Clinical Safety (SCS) addresses all content requirements as per 21 CFR 314.50(d)(5)(vi), including meeting the requirements for the Integrated Summary of Safety (ISS). Additional tables and listings will be placed in Module 5.3.5.3. A mock SCS is provided in Appendix 3.

Does the FDA concur that the proposed SCS format adequately addresses the content requirements for an ISS?

Preliminary Response

We concur.

Does the FDA agree with the proposal to locate supplementary tables and listings in Module 5.3.5.3?

Preliminary Response

We agree.

- 6) In the NDA, it is planned to reference to the nonclinical data of Norvasc[®] (amlodipine) and Micardis[®] (telmisartan) as approved by FDA in their respective labels. As it is not planned to provide additional nonclinical safety data in support of the combination of telmisartan and amlodipine, no nonclinical overview or nonclinical summary will be provided in Module 2.

Does the FDA concur that Modules 2.4 and 2.6 can be excluded from the NDA?

Preliminary Response

We concur. Please include a statement in the NDA stating that the modules are being excluded as explained above.

Module 3 - Chemistry, manufacturing, and controls information

- 7) Proposed Table of Contents of Module 3: The chemistry, manufacturing, and controls information will be organized in the ICH Common Technical Document (CTD) format in Module 3: Quality. The NDA will fully cross-reference NDA 20-850 for the telmisartan drug substance information (3.2.S) and therefore, there will be no section for the telmisartan drug substance. The NDA will cross-reference NDA 20-850 for the information on the telmisartan (b) (4) used in the manufacture of the telmisartan layer. The NDA will cross-reference a third party DMF for the amlodipine drug substance information (3.2.S) with the exception of sections 3.2.S.2.1., Manufacturer and 3.2.S.4.1., Specification. There will be one section for the drug product for the fixed dose combination of telmisartan and amlodipine (3.2.P) that will include dosage strengths.

There will be three Control of Excipients sections (3.2.P.4) presented, one for compendial excipients (USP/NF), one for the non-compendial colorant mixture and one for all excipients, which only includes confirmation that none of the excipients are of human or animal origin.

(b) Container Closure System sections (3.2.P.7) will be presented, one for blister (b) (4)

Throughout Module 3, sections where no information is filed will be omitted from the submission per ICH Guidance for Industry M4: The CTD - General Questions and Answers, December 2004. The titles of these sections are written in italicized type in the proposed Module 3 Table of Contents that is provided in Section 10.

Does the FDA have any comments to this proposal or to the proposed Module 3 Table of Contents?

Preliminary Response

The proposal to cross-reference NDA 20-080 for the telmisartan drug substance information is acceptable; however, you should provide the current specification and Certificates of Analysis for the drug substance telmisartan in the NDA. The proposal to cross-reference a third party DMF (b) for the amlodipine besylate drug substance is acceptable; however, Certificates of Analysis for the drug substance amlodipine should be provided in the NDA.

The reference to the USP/NF monographs for the compendial excipients is acceptable; however, representative Certificates of Analysis for all excipients should be provided in the NDA.

- 8) Executed Batch Records: BI intends to submit executed batch records (EBR) for the two bioequivalence (BE) batches. These batches were also used in primary stability studies. In addition, for each of the other two commercial strengths not studied in BE trials, BI intends to provide an EBR for a primary stability batch. A table summarizing this proposal is provided below.

Telmisartan/Amlodipine Bilayer Tablet Strengths (mg)	Batch Use		Proposed Number of EBR's
	Bioequivalence Trial	Primary Stability Study	
40/5	√	√	1
40/10	-	√	1
80/5	-	√	1
80/10	√	√	1

Does FDA concur with the number of executed batch records proposed for submission?

Preliminary Response

We concur.

Please include a complete list of all manufacturing, packaging and testing facilities for both the drug substance and drug product as an attachment to Form 356h.

Module 4 – Nonclinical Documentation

- 9) In the NDA, it is planned to reference Module 4 to the nonclinical data of Norvasc® (amlodipine) and Micardis® (telmisartan) as approved by FDA in their respective labels. It is not planned to provide additional nonclinical safety data in support of the combination of telmisartan and amlodipine.

Does the FDA concur that Module 4 can be excluded from the NDA?

Preliminary Response

We concur. Please include a statement in the NDA stating that the module is being excluded as explained above.

Module 5 - Clinical Documentation

- 10) To support the indication for treatment of hypertension in patients whose blood pressure is not adequately controlled by monotherapy, BI is proposing to provide efficacy data from an 8-week 4x4 placebo-controlled factorial design study (1235.1) which included 3 strengths each of telmisartan (20 mg, 40 mg and 80 mg) and amlodipine (2.5 mg, 5 mg and 10 mg). This study randomized and treated a total of 1461 patients with Stage 1 or 2 hypertension (DBP \geq 95 mmHg and \leq 119 mmHg at the randomisation visit). Patients randomised to treatment cells containing amlodipine 10 mg received a dose of amlodipine 5 mg for the initial 2 weeks before a forced titration to the final dose level.

Results in the overall patient population showed statistically and clinically significant additional reductions in changes from baseline for seated trough cuff DBP and SBP for telmisartan and amlodipine combinations of T40/A5, T40/A10, T80/A5 and T80/A10 in comparison to the respective mono-components and placebo.

Additivity in blood pressure reduction in the combination treatments was concluded from the absence of significant telmisartan-by-amlodipine interaction (excluding placebo patients from the analysis). The magnitude of blood pressure reductions increased with increasing doses of telmisartan and increasing doses of amlodipine (irrespective of the concomitant dose of amlodipine or telmisartan respectively). The primary trial results were confirmed by the analysis of an ambulatory blood pressure measurement (ABPM) substudy for mean changes from baseline in 24 hour mean blood pressure.

Based on regulatory precedence and our previous interactions with the Division (pre-IND meeting on 22 July 2005, Appendix 4), BI is of the opinion that this controlled study will be an adequate basis of efficacy to support registration of telmisartan/amlodipine fixed dose combination tablets for treatment of hypertension in patients not adequately controlled by monotherapy. For a summary of the results, please refer to the synopsis provided in Appendix 5.

Pending review of the data, does the FDA concur that the results of Trial 1235.1 are adequate to demonstrate proof of efficacy of the telmisartan/amlodipine fixed dose combination tablets for treatment of hypertension in patients not adequately controlled by monotherapy?

Preliminary Response

We concur.

Furthermore, please be informed that based on the FDA feedback in a Type C meeting held on April 9, 2008, BI is also planning to pursue an initial therapy indication for this telmisartan/amlodipine fixed dose combination.

11) The following clinical studies are proposed to be included in the NDA to profile the biopharmaceutics of the telmisartan/amlodipine FDC:

- Two bioequivalence Studies 1235.3 and 1235.4 to confirm bioequivalence of the single entity tablets in the doses of telmisartan 40 mg / amlodipine 5 mg and telmisartan 80 mg / amlodipine 10 mg with the respective fixed dose combination tablets. Please note that the FDA previously **provided comments to BI's concept to confirm bioequivalence** between the clinical trial supplies and the future commercial FDC tablets in a general correspondence dated 10 Aug 2007 (Appendix 6).
- Two drug-drug interaction Studies 1235.2 and 502.126 to demonstrate the absence of pharmacokinetic interactions between telmisartan and amlodipine.
- A food interaction Study 1235.12 to investigate the impact of concomitant food intake on the bioavailability of the telmisartan/amlodipine fixed dose combination.

A tabular overview of these studies is provided in Appendix 7. Furthermore, available study results are provided as study synopses for the completed Studies 1235.2 and 502.126 in Appendix 8.

Pending review of the data, does FDA concur that the proposed clinical biopharmaceutical package, supplemented by the known pharmacokinetic profiles of each of the active components as described in their respective approved US labeling, is adequate to support approval of the telmisartan/amlodipine fixed dose combination tablets?

Preliminary Response

We concur.

12) The clinical safety data package will include 1461 patients from the pivotal factorial design Trial 1235.1 who were treated with placebo, telmisartan, amlodipine or the combination of telmisartan and amlodipine in different strengths for up to 8 weeks. A total of 789 patients were treated with telmisartan and amlodipine concomitantly.

The safety data package will be supplemented with further clinical trial data from controlled Trials 502.236, 502.396 and 502.397 with telmisartan in hypertensive patients with diabetic nephropathy (subsets of patients with or without (open label) amlodipine prescribed as concomitant therapy). In these studies, a total number of approximately 380 patients were exposed to telmisartan and concomitant amlodipine therapy, approximately 280 patients exposed for at least 6 months and approximately 90 patients exposed for at least one year.

Patients with concomitant use of amlodipine and telmisartan							
Study	No of Pat.	No of pat. with concomit. use ≥ 182 days	No of pat. with concomit. use ≥ 365 days	Mean exposure duration [days]	Patient Years ¹	Minimum exposure duration [days]	Maximum exposure duration [days]
Controlled trials							
1235.1	789	0	0	54.7	118.1	1	83
<i>Supportive telmisartan studies with uncontrolled concomitant use of amlodipine in hypertensive pts</i>							
502.236	38	34	28	959.2	99.8	11	1923
502.396	171	119	30	257.3	120.5	1	394
502.397	177	127	38	261.2	126.6	1	434
<i>Supportive telmisartan studies with uncontrolled concomitant use of amlodipine in other patient populations</i>							
502.332	12	0	0	57.1	1.9	37	70
502.398	3	0	0	67.7	0.6	65	71
Open label trials							
<i>Supportive telmisartan studies with uncontrolled concomitant use of amlodipine</i>							
502.219	22	14	8	307.1	18.5	14	798
502.220	44	29	23	465.5	56.1	2	1228
502.221	6	4	0	193.5	3.2	67	268
502.228	2	1	1	532.0	2.9	5	1059
502.260	3	1	0	134.3	1.1	35	256
502.321	7	0	0	77.7	1.5	14	99
502.339	20	0	0	85.8	4.7	77	100
	Σ 1294	Σ 329	Σ 128	$\bar{\Sigma}$ 156.7	Σ 555.3	Min 1	Max 1923

Furthermore, the pooled safety analysis of the biopharmaceutical Phase I Studies 1235.2, 1235.3, 1235.4, 1235.12 and 502.126 in 258 healthy volunteers will be provided.

As discussed at the pre-IND meeting, the safety exposure will be further supplemented by a presentation of safety data from the ONTARGET study (502.373) for the subgroup of patients receiving telmisartan concomitantly with dihydropyridine calcium channel blockers (these patients will be further subgrouped by their history of hypertension).

¹ Patient years = Σ (days on treatment for each patient / 365.25)

For a tabular overview on the studies mentioned, please refer to Appendix 7.

Pending review of the data, does the FDA concur that the proposed safety data package is adequate to support approval of the telmisartan/amlodipine fixed dose combination for treatment of hypertension?

Preliminary Response

We concur.

13) For completeness, the following clinical studies with telmisartan which permitted concomitant use of (open label) amlodipine were reviewed to identify patients who experienced a serious adverse event and/or an adverse event leading to discontinuation while taking both telmisartan and amlodipine:

- Open-label Studies 502.219, 502.220, 502.221, 502.228, 502.260, 502.321 and 502.339 and
- Double-blind controlled Studies 502.332 and 502.398

Note that a brief description of each of these studies is provided in the tabular overview in Appendix 7.

As shown in that table below, a total of 119 patients were identified who received amlodipine while also administered telmisartan in one of these studies. Of these 119 patients, 11 reported serious adverse events and 6 discontinued due to an adverse event(s).

To support the safety assessment, BI is proposing to provide in the NDA narratives and CRFs for the 11 patients reporting serious adverse events and the six patients who discontinued due to adverse events.

Due to the limited number of patients with concomitant use of telmisartan and amlodipine (n=119) in these studies, it is not planned to include these safety data in the overall safety analyses to be presented in the Summary of Clinical Safety (SCS), nor is it planned to provide copies of these clinical trial reports.

Patients in selected telmisartan clinical studies with telmisartan and uncontrolled concomitant use of amlodipine				
Study	Total Number	Number of Patients with AEs leading to discontinuation	Number of Patients with SAEs	Number of cases (AEs leading to disc. or SAEs) judged related to telmisartan*
502.219	22	3 (13.6%)	2	0
502.220	44	2 (4.5%)	6	0
502.221	6	0 (0%)	0	0
502.228	2	1 (50.0%)	1	0
502.260	3	0 (0%)	0	0
502.321	7	0 (0%)	0	0
502.332	12	0 (0.0%)	1	0
502.339	20	0 (0.0%)	1	0
502.398	3	0 (0%)	0	0
Σ	119	6	11	0

*Relationship to amlodipine was not assessed (as amlodipine was given as concomitant therapy)

Does FDA concur with this proposal?

Preliminary Response

We concur.

- 14) In addition to the CRFs outlined in question (13), BI is proposing to submit Case Report Forms (CRFs) for subjects that died or discontinued the study due to an adverse event in the biopharmaceutical Studies 1235.2, 1235.3, 1235.4, 1235.12 and 502.126 and patients randomized to telmisartan that died or discontinued the study due to an adverse event in the Phase III supportive safety Studies 502.236, 502.396, and 502.397. The organization of the CRFs in the submission is further outlined in the electronic submission proposal included in Appendix 9.

For the pivotal factorial design Trial 1235.1, electronic data capture was used. Therefore, BI is requesting a waiver of the requirement to submit CRFs, given that the data as approved by the site is being provided as datasets.

For the ONTARGET sNDA submission for MICARDIS, it has been agreed with FDA to submit CRFs for all deaths or adverse events leading to permanent discontinuation. For ONTARGET as part of the T+A FDC NDA, it is proposed not to provide any CRFs but to provide a listing for patients who died or permanently discontinued due to an adverse event which were treated with telmisartan and dihydropyridine calcium channel blockers concomitantly at onset of the event.

a) Does FDA agree to the proposal of trials for which CRFs will be provided?

Preliminary Response

We agree.

b) Does FDA agree to grant a waiver for the submission of CRFs for Trial 1235.1 for which electronic data capture was used?

Preliminary Response

Since electronic data capture was used for the pivotal factorial design Trial 1235.1, please describe how data integrity was maintained between the study sites, central sites, and BI.

Please submit patient profiles including for those patients who died, had serious events, or who withdrew.

c) Does FDA agree not to provide any CRFs for ONTARGET with the NDA for the telmisartan / amlodipine FDC?

Preliminary Response

We agree, but we reserve the right to request that you submit within a certain timeframe the patient profiles for those patients of interest to us during the course of NDA review.

- 15) Narratives for deaths, other serious adverse events and adverse events leading to discontinuation of study medication will be provided as part of the clinical reports for the Phase III Studies 1235.1, 502.236, 502.396 and 502.397 and for the biopharmaceutical Studies 1235.2, 1235.3, 1235.4, 1235.12 and 502.126. For the supportive studies 502.332, 502.398 and 502.219, 502.220, 502.221, 502.228, 502.260, 502.321, 502.339, narratives will be included in the SCS in the respective sections (see Appendix 3, section 2.7.4.2.2).

For ONTARGET, it is proposed not to provide narratives but to cross refer to the narratives that will be submitted in the sNDA for MICARDIS. As the adverse event tables in the ONTARGET clinical trial report will not differentiate between telmisartan patients treated or not treated concomitantly with dihydropyridine calcium channel blockers, it is proposed to provide listings of patients on concomitant

therapy of telmisartan with and without dihydropyridine calcium channel blockers to facilitate finding the respective patient narratives in the clinical trial report.

Does FDA agree to this proposal?

Preliminary Response

We agree, but we reserve the right to request that you submit within a certain timeframe the patient profiles for those patients of interest to us during the course of NDA review.

- 16) Full tabulation and analysis datasets are proposed to be provided for the pivotal Study 1235.1.

For the supportive safety Studies 502.236, 502.396, and 502.397, we suggest to provide a reduced set of data, focusing on tabulation datasets for demographics, concomitant therapy, disposition, exposure, safety lab and adverse events for patients randomized to telmisartan.

For ONTARGET, full tabulation datasets and analysis datasets for demographics, baseline disease characteristics and adverse events will be provided for randomized patients on telmisartan with and without hypertension and with or without concomitant treatment with dihydropyridine calcium channel blockers.

The datasets to be provided are outlined in more detail in the electronic submission proposal included in Appendix 9.

Does the FDA have any comments related to:

- **The studies and patient groups for which tabulation and analysis datasets will be provided?**
- **The proposed structure and/or format of the tabulation and analysis datasets and to the electronic submission proposal in general?**

Preliminary Response

Please submit the SAS codes for the primary and secondary endpoint analyses in your NDA submission.

- 17) For the Phase I Studies 1235.2 1235.3, 1235.4, 1235.12 and 502.126, datasets for the pharmacokinetic data will be provided as outlined in the electronic submission proposal provided in Appendix 9.

Does the FDA concur with this proposal?

Preliminary Response

We concur.

General

- 18) The NDA will be submitted electronically as a hybrid in the format of the Common Technical Document. The folder structure is outlined in the esub proposal included in Appendix 9.

Does the FDA have any comments on this proposal?

Preliminary Response

We have no further comments.

19) The table below outlines studies in hypertensive patients with telmisartan and amlodipine that are currently ongoing or are expected to be ongoing during the review of the NDA, and projects the amount of new safety data expected to be included in the 4-month safety update to the T+A NDA, assuming a data cut-off date of 1 Dec 2008 (and an NDA submission 1Q09).

Study number	Design / Strengths	Submission with the initial NDA	No. of patients with safety data in 4 Month Safety Update (T+A patients)	Duration of exposure	Target completion date (Data base lock)
Controlled Trials					
1235.5	Double blind, active-controlled T40/A5, T80/A5, A5, A10	N/A	appr. 500 T+A patients (unblinded data)	8 weeks	December 08
1235.6	Double blind, active-controlled T40/A10, T80/A10, A10	N/A	appr. 500 T+A patients (unblinded data)	8 weeks	December 08
1235.20	Double blind, active-controlled T80/A5, T80/A10, A5, A10	N/A	N/A (blinded data)	8 weeks	Nov 09
1235.21	Double blind, active-controlled T80/A5, T80/A10, A5, A10	N/A	N/A (blinded data)	8 weeks	Nov 09
Uncontrolled Trials					
1235.7	Open label extension to trial 1235.5 T40/A5, T80/A5	N/A	appr. 850 (appr. 640 of these patients will have been treated with T+A for ≥ 6 months)	34 weeks	June 09
1235.8	Open label extension to Trial 1235.6 T40/A10, T80/A10	N/A	appr. 450 (appr. 250 of these patients will have been treated with T+A for ≥ 6 months)	34 weeks	June 09

Does FDA have any comments on the proposal for submission of safety data from ongoing trials?

Preliminary Response

We have no further comments.

20) An electronic submission (esub) proposal is provided in Appendix 9.

Does the FDA have any further comments to the esub proposal?

Preliminary Response

We have no further comments.

21) **Does the FDA have any further comments on the NDA submission strategy as outlined in the briefing document?**

Preliminary Response

We have no further comments.

If you have any questions, please call:

Quynh Nguyen, Pharm.D.
Regulatory Health Project Manager
(301) 796-0510

Sincerely,

{See appended electronic signature page}

Norman Stockbridge, M.D., Ph.D.
Director
Division of Cardiovascular and Renal Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Linked Applications

Sponsor Name

Drug Name

IND 71882

BOEHRINGER
INGELHEIM

TELMISARTAN / AMLODIPINE

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

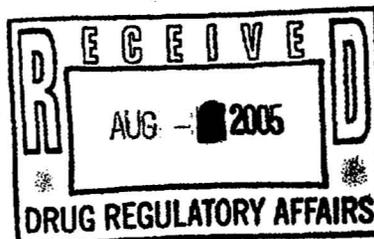
/s/

NORMAN L STOCKBRIDGE
06/03/2008

**DIVISION OF CARDIO-RENAL DRUG PRODUCTS
FOOD AND DRUG ADMINISTRATION**



US Mail address:
FDA/CDER/HFD-110
5600 Fishers Lane
Rockville, MD 20857



IND 71, 882
1

Woodmont II
1451 Rockville Pike
Rockville, MD 20852

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Transmitted to FAX Number: 203 791 6262

Attention: David Brill, Ph.D.

Company Name: Boehringer Ingelheim

Phone: 203 798 4345

Subject: Minutes of Meeting with FDA
Pre-IND 71,882

Date: 2 August 2005

Pages including this sheet: 6

From: Cheryl Ann Borden, MSN, R.N. CCRN, CCNS
LCDR, U.S. Public Health Service

Phone: 301-594-5312
Fax: 301-594-5494

PLEASE LET ME KNOW YOU RECEIVED THIS. THANKS!

IND 71, 882

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Meeting Minutes

Pre-IND Teleconference between Boehringer Ingelheim Pharmaceuticals, Inc. and the FDA

Date: 22 July 2005

Sponsor: Boehringer Ingelheim Pharmaceuticals, Inc.

Subject: Telmisartan/ Amlodipine Fixed Dose Combination
Fixed Dose Combination Tablets
IND 71,882

Type of Meeting: Pre-IND (teleconference)

FDA Participants:

Abraham Karkowsky, M.D. Ph.D., HFD-110, Acting Deputy Division Director
James Hung, Ph.D., HFD-710, Team Leader, Statistics
Charles Le, Ph.D., HFD-710, Statistician
Elena Mishina, Ph.D., HFD-860, Biopharmaceutics Reviewer
Edward Fromm, R.Ph., HFD-110, Chief, Project Management Staff
LCDR Cheryl Ann Borden MSN, R.N., HFD-110, Regulatory Health Project Manager

Sponsor Participants:

Manfred Baumeister, Ph.D., International Project Toxicologist
Helmut Schumacher, Ph.D., International Project Statistician
Jeffrey Friedman, M.D., International Therapeutic Area Head, Cardiovascular Medicine
Thomas Meinicke, M.D., Lead Clinical Research Team Member
Paul Tanswell, Ph.D., Lead Pharmacokinetics Team Member
Scott McGraw, Ph.D., Pharmaceutical Development Team Member
Mattias Klueglich, Ph.D., International Project Manager
Ralf Rischke, Ph.D., International Drug Regulatory Affairs
David Brill, Ph.D., Director, Drug Regulatory Affairs

BACKGROUND:

The sponsor requested a Pre-IND meeting to discuss a fixed dose combination product containing telmisartan and amlodipine. This product is targeted to be indicated as an antihypertensive agent in patients "whose blood pressure is not adequately controlled by telmisartan or amlodipine alone."

DISCUSSION POINTS:

The telecon was opened by the Division with brief introductions. The following schema was sent via email to the sponsor to be used as a reference point for questions 1 and 2 of the briefing package.

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telmisartan/ amlodipine
22 July 2005

(b) (4)

Review of Questions submitted to the Agency by Boehringer Ingelheim:

1. Does the FDA concur with the sponsor's proposal not to develop and commercialize amlodipine FDC? (b) (4)
2. Does the FDA concur with the sponsor's proposal not to develop and commercialize a telmisartan FDC? (b) (4)

Division response: There are two issues to the questions posed above:

- a. Dose development
- b. Commercialized dose strengths

The Division encourages exploration of the entire dose range as illustrated in the schema provided. Preferably, explore the lowest dose to the highest dose and distribute within the remaining cells. The use of unbalanced design cells with under-representation of some doses is acceptable. We acknowledge there may be some issues with the design that will need revision.

What you choose to market is at your discretion.

3. The current development plan does not include a long-term safety exposure trial for the FDC. Does FDA concur with the plan to use the long-term safety data from existing telmisartan studies (where concomitant use of telmisartan and dihydropyridine calcium antagonists were allowed) as described in section 2 of this document ?

Division response: It is acceptable to reference detailed information you have already submitted to the Division.

4. Assuming 4 Fixed Combination products are developed (T80/A10, T80/A5, T40/A10, T40/A5), does the FDA concur with the plan to demonstrate BE of the highest and lowest dose strengths,

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T80/A10 and T40/A5, and their single components? Is the proposed number of 36 subjects for these bioequivalence studies acceptable on the basis of the statistical calculations presented?

Division response: The Division would like to see the highest dose T80/A10 studied. The sponsor has to decide what would be the lowest dose to study (b) (4). They may first perform the study of the high dose and add the study of the lower dose later. Although the proposed number of 36 patients is large, the desired confidence interval (CI) for C_{max} may not be achieved due to the high variability of telmisartan C_{max}. In this case, the combination product will be declared not BE by C_{max}. The clinical significance of this would be at the discretion of the medical officer; however, since the therapeutic window of telmisartan is wide it may not be clinically important to prove BE with respect to telmisartan C_{max}.

5. Does FDA concur with the proposed interaction study investigating the effect of amlodipine on the pharmacokinetics of telmisartan in addition to the reported study showing no effect of telmisartan on the pharmacokinetics of amlodipine?

Division response: We concur.

6. Does FDA concur with the proposed clinical study investigating the effect of food on the pharmacokinetics of the highest dose strength of the telmisartan and amlodipine fixed dose combination?

Division response: This is acceptable.

7. Does FDA concur that further toxicity studies beyond that was done for the US registrations of telmisartan or amlodipine should not be required?

Division response: There are no further requirements.

8. Does FDA concur that the FDC of telmisartan and amlodipine should be labelled with a precautionary statement in hepatic impaired patients and not as a contraindication?

Division response: What is seen in the interaction study may be somewhat dose related. At this point it will probably remain with a precautionary statement, the specific wording to be determined.

9. Does FDA concur with the clinical trial design of the pivotal factorial design registration study?

Division response: The design will need revision with a primary statistical approach that provides information on the dose range and sample size/cells.

10. Does FDA concur with our proposal to support the FDC approval with a single Phase III trial?

Division response: A single Phase III trial is acceptable if the trial is successful and includes the biopharmaceutics and stability data.

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11. Does FDA have any other comments to the proposed overall development program as planned to achieve registration?

Division response: We have no further comments.

OTHER:

BI queried if the Division would require an ambulatory study (ABPM), and if representation of all cells are required.

Division response: We recommend capturing the peak effects of telmisartan either with a separate study or as a subset to the planned study. There are no particular numbers of subjects required as there have been previous studies utilizing 20-25 patients. It would be difficult to maintain blinding without representation of all cells.

SUMMARY/ RECOMMENDATIONS:

- BI to revise factorial design for review.

Signature recorder : (see appended electronic signature page)
LCDR Cheryl Ann Borden, MSN, R.N.

Concurrence, Chair: (see appended electronic signature page)
Abraham Karkowsky, M.D., PhD.

Routed: 29 July 05
Fromm: 29 July 05
Mishina: 30 July 05
Le: 1 Aug 05
Hung: 1 Aug 05
Karkowsky: 1 Aug 05
Stockbridge: 1 Aug 05

Final: 2 August 05

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/s/

Abraham Karkowsky
8/2/05 11:48:41 AM

ACTION PACKAGE CHECKLIST

ACTION PACKAGE CHECKLIST		
BLA # NDA # 22-401	BLA STN# NDA Supplement #	If NDA, Efficacy Supplement Type
Proprietary Name: Twynsta Established Name: telmisartan/amlodipine Dosage Form: Tablets		Applicant: Boehringer Ingelheim Pharmaceuticals, Inc.
RPM: Quynh Nguyen, Pharm.D., RAC		Division: DCRP Phone # 301-796-0510
<p>NDA Application Type: <input type="checkbox"/> 505(b)(1) <input checked="" type="checkbox"/> 505(b)(2)</p> <p>Efficacy Supplement: <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)</p> <p>(A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). Consult page 1 of the NDA Regulatory Filing Review for this application or Appendix A to this Action Package Checklist.)</p>		<p>505(b)(2) NDAs and 505(b)(2) NDA supplements: Listed drug(s) referred to in 505(b)(2) application (NDA #(s), Drug name(s)):</p> <p>NDA 19-787 Norvasc (amlodipine beyslate) Tablets NDA 20-850 Micardis (telmisartan) Tablets</p> <p>Provide a brief explanation of how this product is different from the listed drug. Twynsta is a combination product of telmisartan and amlodipine tablets.</p> <p><input type="checkbox"/> If no listed drug, check here and explain:</p> <p>Review and confirm the information previously provided in Appendix B to the Regulatory Filing Review. Use this Checklist to update any information (including patent certification information) that is no longer correct.</p> <p><input checked="" type="checkbox"/> Confirmed <input type="checkbox"/> Corrected Date: 10-15-09</p>
❖ User Fee Goal Date ❖ Action Goal Date (if different)		10-18-09
❖ Actions		
• Proposed action		<input checked="" type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> AE <input type="checkbox"/> NA <input type="checkbox"/> CR
• Previous actions (<i>specify type and date for each action taken</i>)		<input checked="" type="checkbox"/> None
❖ Advertising (<i>approvals only</i>) Note: If accelerated approval (21 CFR 314.510/601.41), advertising must have been submitted and reviewed (<i>indicate dates of reviews</i>)		<input checked="" type="checkbox"/> Requested in AP letter <input type="checkbox"/> Received and reviewed

❖ Application Characteristics	
Review priority: <input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority Chemical classification (new NDAs only): NDAs, BLAs and Supplements: <input type="checkbox"/> Fast Track <input type="checkbox"/> Rolling Review <input type="checkbox"/> CMA Pilot 1 <input type="checkbox"/> CMA Pilot 2 <input type="checkbox"/> Orphan drug designation NDAs: Subpart H <input type="checkbox"/> Accelerated approval (21 CFR 314.510) <input type="checkbox"/> Restricted distribution (21 CFR 314.520) Subpart I <input type="checkbox"/> Approval based on animal studies NDAs and NDA Supplements: <input type="checkbox"/> OTC drug Other: Other comments:	
❖ Application Integrity Policy (AIP)	
<ul style="list-style-type: none"> Applicant is on the AIP 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
<ul style="list-style-type: none"> This application is on the AIP <ul style="list-style-type: none"> Exception for review (<i>file Center Director's memo in Administrative Documents section</i>) OC clearance for approval (<i>file communication in Administrative Documents section</i>) 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Yes <input type="checkbox"/> Not an AP action
❖ Public communications (approvals only)	
<ul style="list-style-type: none"> Office of Executive Programs (OEP) liaison has been notified of action 	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
<ul style="list-style-type: none"> Press Office notified of action 	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
<ul style="list-style-type: none"> Indicate what types (if any) of information dissemination are anticipated 	<input checked="" type="checkbox"/> None <input type="checkbox"/> FDA Press Release <input type="checkbox"/> FDA Talk Paper <input type="checkbox"/> CDER Q&As <input type="checkbox"/> Other

notice of certification?

(Note: The date that the patent owner received the applicant's notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e)).

If "Yes," skip to question (4) below. If "No," continue with question (2).

- (2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)?

Yes No

If "Yes," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).

If "No," continue with question (3).

- (3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant?

Yes No

(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)).

If "No," the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.

- (4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)?

Yes No

If "Yes," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).

If "No," continue with question (5).

- (5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the (b)(2) applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification?

Yes No

(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced

<p>within the 45-day period).</p> <p><i>If "No," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).</i></p> <p><i>If "Yes," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007) and attach a summary of the response.</i></p>	
<p>❖ Summary Reviews (e.g., Office Director, Division Director) (<i>indicate date for each review</i>)</p>	<p>Division Director's Memo, 9-28-09</p>
<p>❖ BLA approvals only: Licensing Action Recommendation Memo (LARM) (<i>indicate date</i>)</p>	
<p>❖ Package Insert</p>	
<ul style="list-style-type: none"> • Most recent division-proposed labeling (only if generated after latest applicant submission of labeling) 	
<ul style="list-style-type: none"> • Most recent applicant-proposed labeling (only if subsequent division labeling does not show applicant version) 	<p>Included</p>
<ul style="list-style-type: none"> • Original applicant-proposed labeling • Other relevant labeling (e.g., most recent 3 in class, class labeling), if applicable 	<p>Included</p>
<p>❖ Patient Package Insert</p>	
<ul style="list-style-type: none"> • Most-recent division-proposed labeling (only if generated after latest applicant submission of labeling) 	
<ul style="list-style-type: none"> • Most recent applicant-proposed labeling (only if subsequent division labeling does not show applicant version) 	<p>Included</p>
<ul style="list-style-type: none"> • Original applicant-proposed labeling 	
<ul style="list-style-type: none"> • Other relevant labeling (e.g., most recent 3 in class, class labeling), if applicable 	<p>Included</p>
<p>❖ Medication Guide</p>	
<ul style="list-style-type: none"> • Most recent division-proposed labeling (only if generated after latest applicant submission of labeling) 	<p>N/A</p>
<ul style="list-style-type: none"> • Most recent applicant-proposed labeling (only if subsequent division labeling does not show applicant version) 	
<ul style="list-style-type: none"> • Original applicant-proposed labeling 	
<ul style="list-style-type: none"> • Other relevant labeling (e.g., most recent 3 in class, class labeling) 	
<p>❖ Labels (full color carton and immediate-container labels)</p>	
<ul style="list-style-type: none"> • Most-recent division-proposed labels (only if generated after latest applicant submission) 	
<ul style="list-style-type: none"> • Most recent applicant-proposed labeling 	
<p>❖ Labeling reviews and minutes of any labeling meetings (<i>indicate dates of reviews and meetings</i>)</p>	<p><input checked="" type="checkbox"/> DMETS 9-16-09; 5-4-09 <input checked="" type="checkbox"/> DSRCS 10-1-09 <input checked="" type="checkbox"/> DDMAC 9-28-09 <input type="checkbox"/> SEALD <input type="checkbox"/> Other reviews <input type="checkbox"/> Memos of Mtgs</p>

❖ Administrative Reviews (RPM Filing Review/Memo of Filing Meeting; ADRA) (<i>indicate date of each review</i>)	10-13-09
❖ NDA and NDA supplement approvals only: Exclusivity Summary (<i>signed by Division Director</i>)	<input checked="" type="checkbox"/> Included
❖ AIP-related documents <ul style="list-style-type: none"> Center Director's Exception for Review memo If AP: OC clearance for approval 	
❖ Pediatric Page (all actions)	<input checked="" type="checkbox"/> Included
❖ Debarment certification (original applications only): verified that qualifying language was not used in certification and that certifications from foreign applicants are cosigned by U.S. agent. (<i>Include certification.</i>)	<input checked="" type="checkbox"/> Verified, statement is acceptable
❖ Postmarketing Commitment Studies	<input type="checkbox"/> None
<ul style="list-style-type: none"> Outgoing Agency request for post-marketing commitments (<i>if located elsewhere in package, state where located</i>) 	In AP Letter
<ul style="list-style-type: none"> Incoming submission documenting commitment 	
❖ Outgoing correspondence (letters including previous action letters, emails, faxes, telecons)	Included
❖ Internal memoranda, telecons, email, etc.	
❖ Minutes of Meetings	
<ul style="list-style-type: none"> Pre-Approval Safety Conference (<i>indicate date; approvals only</i>) 	N/A
<ul style="list-style-type: none"> Pre-NDA/BLA meeting (<i>indicate date</i>) 	<input checked="" type="checkbox"/> No mtg See Preliminary Responses dated 6-3-08
<ul style="list-style-type: none"> EOP2 meeting (<i>indicate date</i>) 	<input checked="" type="checkbox"/> No mtg
<ul style="list-style-type: none"> Other (e.g., EOP2a, CMC pilot programs) 	
❖ Advisory Committee Meeting	<input checked="" type="checkbox"/> No AC meeting
<ul style="list-style-type: none"> Date of Meeting 48-hour alert or minutes, if available 	
❖ Federal Register Notices, DESI documents, NAS/NRC reports (if applicable)	
❖ CMC/Product review(s) (<i>indicate date for each review</i>)	10-14-09 (two); 10-5-09; 9-23-09; 9-1-09; 8-31-09; 2-6-09
❖ Reviews by other disciplines/divisions/Centers requested by CMC/product reviewer (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
❖ BLAs: Product subject to lot release (APs only)	<input type="checkbox"/> Yes <input type="checkbox"/> No
❖ Environmental Assessment (check one) (original and supplemental applications)	
<ul style="list-style-type: none"> <input type="checkbox"/> Categorical Exclusion (<i>indicate review date</i>)(<i>all original applications and all efficacy supplements that could increase the patient population</i>) 	
<ul style="list-style-type: none"> <input checked="" type="checkbox"/> Review & FONSI (<i>indicate date of review</i>) 	9-4-09; 3-5-09
<ul style="list-style-type: none"> <input type="checkbox"/> Review & Environmental Impact Statement (<i>indicate date of each review</i>) 	
❖ NDAs: Microbiology reviews (sterility & apyrogenicity) (<i>indicate date of each review</i>)	<input checked="" type="checkbox"/> Not a parenteral product
❖ Facilities Review/Inspection	
<ul style="list-style-type: none"> NDAs: Facilities inspections (include EER printout) 	Date completed: 10-1-09 <input checked="" type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation

❖ BLAs: Facility-Related Documents <ul style="list-style-type: none"> • Facility review (<i>indicate date(s)</i>) • Compliance Status Check (approvals only, both original and supplemental applications) (<i>indicate date completed, must be within 60 days prior to AP</i>) 	<input type="checkbox"/> Requested <input type="checkbox"/> Accepted <input type="checkbox"/> Hold
❖ NDAs: Methods Validation	<input type="checkbox"/> Completed <input type="checkbox"/> Requested <input type="checkbox"/> Not yet requested <input checked="" type="checkbox"/> Not needed
❖ Pharm/tox review(s), including referenced IND reviews (<i>indicate date for each review</i>)	3-26-09
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
❖ Statistical review(s) of carcinogenicity studies (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> No carc
❖ ECAC/CAC report/memo of meeting	
❖ Nonclinical inspection review Summary (DSI)	<input checked="" type="checkbox"/> None requested
❖ Clinical review(s) (<i>indicate date for each review</i>)	9-9-09
❖ Financial Disclosure reviews(s) or location/date if addressed in another review	9-9-09
❖ Clinical consult reviews from other review disciplines/divisions/Centers (<i>indicate date of each review</i>)	<input checked="" type="checkbox"/> None
❖ Microbiology (efficacy) reviews(s) (<i>indicate date of each review</i>)	<input checked="" type="checkbox"/> Not needed
❖ Safety Update review(s) (<i>indicate location/date if incorporated into another review</i>)	9-9-09
❖ Risk Management Plan review(s) (including those by OSE) (<i>indicate location/date if incorporated into another review</i>)	N/A
❖ Controlled Substance Staff review(s) and recommendation for scheduling (<i>indicate date of each review</i>)	<input checked="" type="checkbox"/> Not needed
❖ DSI Inspection Review Summary(ies) (<i>include copies of DSI letters to investigators</i>)	<input checked="" type="checkbox"/> None requested
• Clinical Studies	
• Bioequivalence Studies	9-11-09; 6-5-09
• Clin Pharm Studies	
❖ Statistical Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None 8-31-09
❖ Clinical Pharmacology review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None 5-8-09

Appendix A to Action Package Checklist

An NDA or NDA supplemental application is likely to be a 505(b)(2) application if:

- (1) It relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application.
- (2) **Or** it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval.
- (3) **Or** it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

- (1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies).
- (2) **And** no additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application.
- (3) **And** all other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

- (1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2).
- (2) **Or** the applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement.
- (3) **Or** the applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your ODE's Office of Regulatory Policy representative.

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/s/

QUYNH M NGUYEN
10/16/2009