

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

22-287

**ADMINISTRATIVE and
CORRESPONDENCE
DOCUMENTS**

EXCLUSIVITY SUMMARY

NDA # 22,287

SUPPL #

HFD # 180

Trade Name Kapidex

Generic Name Dexlansoprazole

Applicant Name Takeda Global Research and Development Center

Approval Date, If Known January 30, 2009

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)(1)

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?

3 years

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

YES NO

Pediatric exclusivity granted on July 15, 2008, to Lansoprazole NDA # 020406, 021281, 021428, 021566, 021507

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?

YES NO

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# 020406,021281, Lansoprazole
021428,021566,
021507

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#

NDA#

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:

Efficacy and Safety T-GD04-082
Efficacy and Safety T-GD05-137
Efficacy and Safety T-EE04-084
Efficacy and Safety T-EE04-085
Efficacy and Safety T-EE04-086
Efficacy and Safety T-EE05-135
Safety T-G104-088

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

Investigation #3 YES NO

Investigation #4 YES NO

Investigation #5	YES <input type="checkbox"/>	NO <input checked="" type="checkbox"/>
Investigation #6	YES <input type="checkbox"/>	NO <input checked="" type="checkbox"/>
Investigation #7	YES <input type="checkbox"/>	NO <input checked="" type="checkbox"/>

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 <input type="checkbox"/>	NO <input checked="" type="checkbox"/>
Investigation #2	YES <input type="checkbox"/>	NO <input checked="" type="checkbox"/>
Investigation #3	YES <input type="checkbox"/>	NO <input checked="" type="checkbox"/>
Investigation #4	YES <input type="checkbox"/>	NO <input checked="" type="checkbox"/>
Investigation #5	YES <input type="checkbox"/>	NO <input checked="" type="checkbox"/>
Investigation #6	YES <input type="checkbox"/>	NO <input checked="" type="checkbox"/>
Investigation #7	YES <input type="checkbox"/>	NO <input checked="" type="checkbox"/>

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"):

Efficacy and Safety T-GD04-082
 Efficacy and Safety T-GD05-137
 Efficacy and Safety T-EE04-084
 Efficacy and Safety T-EE04-085

Efficacy and Safety T-EE04-086
Efficacy and Safety T-EE05-135
Safety T-G104-088

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 # 69,927 YES ! NO
! Explain:

Investigation #2
IND # 69,927 YES ! NO
! Explain:

Investigation #3
IND # 69,927 YES ! NO
! Explain:

Investigation #4
IND # 69,927 YES ! NO
! Explain:

Investigation #5
IND # 69,927 YES ! NO
! Explain:

Investigation #6
IND # 69,927 YES ! NO
! Explain:

Investigation #7
IND # 69,927 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: Anna M. Simon
Title: Regulatory Project Manager
Date: 01-27-09

Name of Office/Division Director signing form: Donna Griebel, M.D.
Title: Division Director

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

Appears This Way On Original

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

/s/

Donna Griebel
1/30/2009 02:25:59 PM

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

NDA/BLA#: 22-287

Supplement Number: 000

NDA Supplement Type (e.g. SE5): _____

Division Name: Division of Gastroenterology Products

PDUFA Goal Date: 31 JAN 09 (major amendment extension)

Stamp Date: 12/31/2007

Proprietary Name: Kapidex (pending tradename review)

Established/Generic Name: dexlansoprazole

Dosage Form: delayed release capsules

Applicant/Sponsor: Takeda Pharmaceuticals North America

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: Maintenance and Healing of all grades of erosive esophagitis (EE)

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 checked="" type="checkbox"/>	Neonate	0 wk. __ mo.	__ wk. 1 mo.	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input checked="" type="checkbox"/>	Other	__ yr. 1 mo.	__ yr. 11 mo.	<input checked="" 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 †
				Ready for Approval in Adults	Need Additional Adult Safety or Efficacy Data	Other Appropriate Reason (specify below)*	Received
Population	minimum	maximum					
<input type="checkbox"/> Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<input checked="" type="checkbox"/> Other	12 yr. __ mo.	17 yr. __ mo.	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<input checked="" type="checkbox"/> Other	1 yr. __ mo.	11 yr. __ mo.	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input checked="" 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): (1-11 yr: 10/31/2013)(12-17 yr: 3/31/2013)							

- 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: Sponsor needs to develop an age-appropriate formulation (1 month-11 yrs.), Study design (i.e. primary efficacy endpoint) needs to be further discussed (1-11 months)

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

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.

Appears This Way On Original

Attachment A

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

Indication #2: Treating heartburn (b) (4) ; associated with non-erosive GERD**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 checked="" type="checkbox"/>	Neonate	0 wk. __ mo.	__ wk. 1 mo.	<input checked="" 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 checked="" type="checkbox"/> Other	__ yr. <u>1</u> mo.	__ yr. <u>11</u> mo.	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
<input checked="" type="checkbox"/> Other	<u>1</u> yr. __ mo.	<u>11</u> yr. __ mo.	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
<input checked="" type="checkbox"/> Other	<u>12</u> yr. __ mo.	<u>17</u> yr. __ mo.	<input checked="" 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): (1-11months: 7/31/2016); (1-11yr: 10/31/2013); (12-17 yr: 3/31/2013)							

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: Need to develop an age appropriate formulation (1 month to 11 years), Study design (i.e. primary efficacy endpoint) needs to be further discussed (1-11 months).

† 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)

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

/s/

Chantal N. Phillips
12/5/2008 02:56:37 PM

DEBARMENT CERTIFICATION

TAP Pharmaceutical Products 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.

Appears This Way On Original



**NDA 22-287
Amendment to a Pending Application**

January 12, 2009

Donna Griebel, M.D., Director
Division of Gastroenterology Products
Center for Drug Evaluation and Research
Food and Drug Administration
Central Document Room
5901-B Ammendale Road
Beltsville, MD 20705-1266

Attention: Lt. Commander Chantal Phillips, Project Manager

**RE: NDA 22-287 / Amendment No. 0030
Dexlansoprazole Delayed Release Capsules**

Dear Dr. Griebel:

The Sponsor, Takeda Pharmaceuticals North America, Inc. (TPNA) is submitting an amendment to a New Drug Application under section 505(b) of the Federal Food, Drug, and Cosmetic Act, and 21 CFR §314.60.

This amendment provides Takeda's commitment to conduct the required Phase 4 study. The commitment and key elements of the study design and timeline are located in Module 1.13.12.

This amendment is submitted in electronic Common Technical Document (eCTD) format. The documents are provided in Adobe PDF 1.3 (Adobe 4.05b) format in accordance with eCTD guidances. This submission is approximately 1 MB, and is provided on one CD-ROM. It has been checked for viruses using Symantec Endpoint Protection Version 11.0.2010.25, and is virus-free. If you should have any questions concerning the technical aspects of this submission, please contact Lois Householder at 847-582-2682. The printed contents of the index-md5.txt file are appended to this letter.



Any questions regarding this submission may be directed to my attention.

Sincerely,

A handwritten signature in black ink that reads "Nancianne Knipfer".

Nancianne Knipfer, PhD, RAC
Manager, Regulatory Affairs Strategy
Takeda Global Research and Development Center, Inc.
Tel: 847-582-2193
Fax: 847-582-2880

Enclosure: Printed contents of the index-md5.txt file

NK:vt

Appears This Way On Original

MEMORANDUM OF TELECON

DATE: December 19, 2008

APPLICATION NUMBER: NDA 22-287

BETWEEN:

Name: Nancianne Knipfer, PhD, Manager, Regulatory Affairs Strategy
Donna Helms, BS, MBA, Director Regulatory Affairs Strategy
Stuart Atkinson, MD, ChB, Vice President, Clinical Science
Claudia Perez, MD Medical Director, Clinical Science
Maria Paris, MD, Sr. Vice President, Pharmacovigilance
Aruna Dabholkar, MD, Medical Director, Pharmacovigilance
Nancy Siepman, PhD, Vice President, Analytical Sciences

Phone: International line provided by sponsor

Representing: Takeda

AND

Name:

Ruyi He, M.D., Medical Team Leader, DGP
Tamara Johnson, M.D., Medical Officer, DGP
Kristina Estes, LT, Pharm D., Regulatory Reviewer, Clinical
Pharmacology
Freda Cooner, Ph.D., Statistical Reviewer, Division of Biometrics III
Tarun Mehta, PhD., Review Chemist, Office of New Drug Quality
Assessment, Pre-Marketing Assessment Division II
Chantal Phillips, LCDR, M.S.H.S., Regulatory Project Manager, DGP
Anna Simon, MSN, CPNP, Regulatory Project Manager, DGP
Division of Gastroenterology Products, HFD-180

SUBJECT: Labeling negotiation and Post Marketing Requirement

SUMMARY:

Labeling negotiation on-going.

Sponsor agreed to submit the following information regarding Post Marketing Requirement for NDA 22-287 Dexlansoprazole Delayed Release Capsules:

1. Submit the PMR study to be conducted
2. Proposed start date
3. Enrollment date
4. Final submission date

Anna M. Simon, MSN, CPNP
Regulatory Health Project Manager
Division of Gastroenterology Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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

/s/

Anna Maria Simon
2/2/2009 12:25:03 PM
CSO

Anna Maria Simon
2/2/2009 12:25:18 PM
CSO

2 Page(s) Withheld

√ Trade Secret / Confidential (b4)

 Draft Labeling (b4)

 Draft Labeling (b5)

 Deliberative Process (b5)

Withheld Track Number: Administrative- 1

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

/s/

Anna Maria Simon
12/22/2008 09:31:49 AM
CSO

Moo-Jhong Rhee
12/22/2008 09:38:57 AM
CHEMIST
Chief, Branch III



NDA 22-287

DISCIPLINE REVIEW LETTER

Takeda Global Research and Development Center, Inc
Attention: Nancianne Knipfer, Ph.D., RAC
Manager, Regulatory Affairs Strategy
One Takeda Parkway
Deerfield, IL 60015

Dear Dr. Knipfer:

Please refer to your December 28, 2007 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for dexlansoprazole Delayed-Release Capsules.

We also refer to your submissions for labeling dated March 7, 2008 and September 26, 2008.

We have reviewed the carton and container labels for dexlansoprazole and have the following recommendations :

1. All Labels and Labeling

- 1.1. Since the colors selected for the proprietary name (green) and the established name (blue) are also colors utilized as part of the trade dress to differentiate the strengths, all of the labels and labeling appear similar. Using the same blue and green color on all the labels and labeling contributes to their similarity and diminishes the usefulness of color for product strength differentiation. Additionally, the numerical portions of all of the strengths are presented in the same black color font, which further contributes to the similarity of the labels and labeling. Revise the colors of the proprietary name and established names so they do not overlap with any of the colors used to differentiate the strengths. Additionally, distinguish the numerical portions of the strengths with the use of colors, shading, boxing, or some other means. This will also minimize the similarity of the strength and net quantity.
- 1.2. Ensure the unit of measurement (mg) appears to the immediate right of the strength, since this is the location that practitioners and patients are accustomed to finding it when reading from left to right.

2. Container Labels (30 count, 90 count, and 1000 count)

- 2.1. De-bold the net quantity and remove the colored strip from the net quantity and RX only statement. This will lessen the potential for the net quantity to be confused with the strength since the 30 quantity overlaps with the 30 mg strength. In revising the appearance of the net quantity, maximize the distance between the strength and the net quantity.
- 2.2. Relocate the NDC number to the top one-third of the principle display panel, to be in accordance with 21 CFR 207.35(b)(3)(i).

3. Professional Sample Blister Card (5 count)

- 3.1. As currently presented, the identical color (green) is used on the majority of the principle display panel for all three strengths. Revise the colors of the principle display panel so that they are undoubtedly distinguishable from one another and the colors do not overlap.
- 3.2. Include the product strength in conjunction with the proprietary name and established names on the panels which contain the blisters. Additionally, ensure this information remains present and intact when the capsules are removed from the blister.
- 3.3. Revise and include the statement: "Each capsule contains XX mg" so that patients will know that the entire blister card is not equivalent to 30 mg or 60 mg. Ensure this statement is prominently displayed.

4. Professional Sample Container Label (7 count)

- 4.1. As currently presented, the identical color (green) is used on the majority of the principle display panel for all three strengths. Revise the colors of the principle display panel so that they are undoubtedly distinguishable from one another and the colors do not overlap.
- 4.2. Relocate the statement "Professional Sample-Not for Sale" to the principle display panel, as it is presented on the sample 30 count container.
- 4.3. Relocate the NDC number to the top one-third of the principle display panel, to be in accordance with 21 CFR 207.35(b)(3)(i).

5. Professional Sample Container Label (30 count)

- 5.1. De-bold the net quantity and remove the colored strip from the net quantity and RX only statement. This will lessen the potential for the net quantity to be confused with the strength since the 30 quantity overlaps with the 30 mg strength. In revising the appearance of the net quantity, maximize the distance between the strength and the net quantity.

- 5.2. Relocate the NDC number to the top one-third of the principle display panel, to be in accordance with 21 CFR 207.35(b)(3)(i).

We are providing these comments to you before we complete our review of the entire application to give you preliminary notice of issues that we have identified. In conformance with the prescription drug user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and subject to change as we finalize our review of your application. In addition, we may identify other information that must be provided before we can approve this application. If you respond to these issues during this review cycle, depending on the timing of your response, and in conformance with the user fee reauthorization agreements, we may not be able to consider your response before we take an action on your application during this review cycle.

If you have any questions, call Chantal Phillips, Regulatory Project Manager, at 301-796-2259.

Sincerely,

{See appended electronic signature page}

Donna Griebel, M.D.
Director
Division of Gastroenterology Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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

/s/

Donna Griebel

11/5/2008 12:21:22 PM



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-287

Takeda Pharmaceuticals North America, Inc.
Attention: Nancianne Knipfer, Ph.D., RAC
Manager, Regulatory Affairs Strategy
One Takeda Parkway
Deerfield, IL 60015

Dear Dr. Knipfer:

Please refer to your December 28, 2007 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Dexlansoprazole Delayed Release Capsules.

On August 27, 2008, we received your August 26, 2008 major amendment to this application. The receipt date is within 3 months of the user fee goal date. Therefore, we are extending the goal date by three months to provide time for a full review of the submission. The extended user fee goal date is January 31, 2009.

If you have any questions, call me at 301-796-2259.

Sincerely,

{See appended electronic signature page}

Chantal Phillips, LCDR, M.S.H.S
Regulatory Project Manager
Division of Gastroenterology Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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

/s/

Chantal N. Phillips
10/15/2008 02:35:44 PM



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-287

Takeda Global Research and Development Center, Inc
Attention: Nancianne Knipfer, Ph.D., RAC
Manager, Regulatory Affairs Strategy
675 N. Field Drive
Lake Forest, IL 60045

Dear Dr. Knipfer:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for dexlansoprazole Delayed Release Capsules 30/6**(b)** mg (dexlansoprazole).

We also refer to your submissions dated February 5, 18 & 19, 2008; March 7 & 26, 2008; April 28 & 29, 2008; May 5, 22 & 30, 2008; June 24, 26 & 30; and July 15, 2008.

We are reviewing the Clinical and Chemistry sections of your submission and have the following request for information.

For the Clinical section, we request the following:

For subjects experiencing serious and non-serious adverse events for Phase 3 studies encompassed by the following High-level terms (HLTs), please provide length of exposure to proton pump inhibitors (PPI) prior to enrollment in the NDA 22-287 studies for the following:

- Limb injuries NEC
- Lower limb fractures/dislocations
- Muscle/tendon/ligament injuries
- Non-site specific injuries NEC
- Site-specific injuries NEC
- Thoracic cage fractures/dislocations
- Upper limb fractures/dislocations

Please provide this information in a tabular format to include number of subjects with prior PPI exposure and average person-time prior PPI exposure by treatment group in 1) all Phase 3 studies and 2) in Phase 3 controlled studies (minus the uncontrolled study).

For the Chemistry section, we request the following:

Please identify the suppliers of excipients and provide the CoAs for all excipients.

If you have any questions, call me at 301-796-2259.

Sincerely,

{See appended electronic signature page}

Chantal Phillips, LCDR, M.S.H.S.
Acting Chief, Project Management Staff
Division of Gastroenterology Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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

/s/

Chantal N. Phillips
8/28/2008 10:45:55 AM



Andrea Ramsay, M.D.
University Clinical Research, Inc.
1150 N. University Dr.
Pembroke Pines, FL 33024-5031

Dear Dr. Ramsay:

The purpose of this letter is to inform you of the findings of a Food and Drug Administration (FDA) inspection conducted at your site. This inspection is part of FDA's Bioresearch Monitoring Program, which evaluates the research conduct and ensures that the rights, safety, and welfare of human study subjects are protected. Between June 13 and June 19, 2008, Ms. Ileana Barreto-Pettit, representing the FDA, met with you and your staff to review your conduct of the following two clinical investigations of the investigational drug dexlansoprazole, performed for TAP Pharmaceutical Products:

1. Protocol T-GD04-083, entitled "A Phase 3 Study to Evaluate the Efficacy and Safety of TAK-390MR (60 mg QD and 90 mg QD) Compared to Placebo on Symptom Relief in Subjects with Symptomatic Non-Erosive Gastroesophageal Reflux Disease (GERD)"; and
2. Protocol T-GD05-137, entitled "A Phase 3 Study to Evaluate the Efficacy and Safety of TAK-390MR (30 mg QD and 60 mg QD) Compared to Placebo on Symptom Relief in Subjects with Symptomatic Non-Erosive Gastroesophageal Reflux Disease (GERD)"

Based on our review of the establishment inspection report, the documents submitted with that report, and your letter dated July 2, 2008, we conclude that you did not adhere to the applicable statutory requirements and FDA regulations governing the conduct of clinical investigations and the protection of human subjects. We wish to emphasize the following:

You did not ensure that the investigations were conducted according to the investigational plans [21 CFR 312.60].

- a. Both protocols specified that the electronic diaries are to be reviewed at each visit. There is no record that this requirement was followed.
- b. Protocol T-GD04-083 specified that the endoscopic pictures are to be kept in the site's source document files. Two subjects (#1834001 and #18345004) did not have endoscopy pictures at the site.

Please make appropriate corrections in your procedures to assure that the findings noted above are not repeated in any ongoing or future studies.

We acknowledge your assurances that corrective actions have been taken to prevent similar findings from occurring in any future studies. Any response and all correspondence will be included as a permanent part of your file.

We appreciate the cooperation shown Investigator Barreto-Pettit during the inspection. Should you have any questions or concerns regarding this letter or the inspection, please contact me by letter at the address given below.

Sincerely,

{See appended electronic signature page}

Constance Lewin, M.D., M.P.H.
Branch Chief, Good Clinical Practice Branch I
Division of Scientific Investigations
Office of Compliance
Center for Drug Evaluation and Research
Food and Drug Administration
Bldg. 51, Rm. 5354
10903 New Hampshire Avenue
Silver Spring, MD 20993

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

/s/

Constance Lewin
8/22/2008 02:30:45 PM



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-287

INFORMATION REQUEST LETTER

Takeda Pharmaceuticals North America, Inc.
Attention: Nancianne Knipfer, Ph.D.
Project Manager, Regulatory Affairs
One Takeda Parkway
Deerfield, IL 60015

Dear Dr. Knipfer:

Please refer to your December 28, 2007 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for dexlansoprazole.

We also refer to your submissions dated February 5, 18, & 19, 2008; March 7 & 26, 2008; April 28 & 29, 2008; May 5, 22, & 30, 2008; June 24, 26, & 30; and July 15, 2008.

We are reviewing the Clinical section of your submission and have the following information requests:

1. Please provide in tabular formats, the percentage of Phase 3 study population with cardiovascular risk factors at baseline, presented by:
 - a) Study indication
 - b) Treatment group
 - c) Overall Phase 3 safety population

For the following information requests, please do not include open-label safety data in the requested tables.

2. All treatment-emergent adverse events for Phase 3 controlled studies listed by subject and by patient-month.
3. All treatment-emergent serious adverse events for Phase 3 controlled studies listed by subject and by patient-month.
4. Narrative reports for all non-serious adverse events for Phase 3 controlled studies encompassed by the following High-level terms (HLTs):
 - Limb injuries NEC
 - Lower limb fractures/dislocations
 - Muscle/tendon/ligament injuries
 - Non-site specific injuries NEC
 - Site-specific injuries NEC
 - Thoracic cage fractures/dislocations
 - Upper limb fractures/dislocations

We request a prompt written response in order to continue our evaluation of your NDA.

If you have any questions, call Chantal Phillips, Regulatory Project Manager, at 301-796-2259.

Sincerely,

{See appended electronic signature page}

Brian Strongin, R.Ph., M.B.A.
Chief, Project Management Staff
Division of Gastroenterology Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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

/s/

Brian Strongin
8/13/2008 10:56:00 AM



NDA 22-287

INFORMATION REQUEST LETTER

TAP Pharmaceutical Products Inc.
Attention: Nancianne Knipfer, Ph.D.
Project Manager, Regulatory Affairs
675 North Field Drive
Lake Forest, IL 60045

Dear Dr. Knipfer:

Please refer to your December 28, 2007 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for dexlansoprazole.

We also refer to your submissions dated February 5, 18, & 19, 2008; March 7 & 26, 2008; April 28 & 29, 2008; and May 5, 22, & 30, 2008.

We are reviewing the Clinical Pharmacology section of your submission and have the following information requests.

- Please submit the genotyping analytical report to include:
 - a) primers and probes used
 - b) method of analysis for all the genotyping studies

We request a prompt written response in order to continue our evaluation of your NDA.

If you have any questions, call Chantal Phillips, Regulatory Project Manager, at 301-796-2259.

Sincerely,

{See appended electronic signature page}

Brian Strongin, R.Ph., M.B.A.
Chief, Project Management Staff
Division of Gastroenterology Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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

/s/

Brian Strongin

6/27/2008 01:00:20 PM



NDA 22-287

INFORMATION REQUEST LETTER

TAP Pharmaceutical Products Inc.
Attention: Nancianne Knipfer, Ph.D.
Project Manager, Regulatory Affairs
675 North Field Drive
Lake Forest, IL 60045

Dear Dr. Knipfer:

Please refer to your December 28, 2007 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for dexlansoprazole.

We also refer to your submissions dated February 5, 18, & 19, 2008; March 7 & 26, 2008; April 28 & 29, 2008; and May 5, 22, & 30, 2008.

We are reviewing the Clinical section of your submission; specifically the tables: "Potential Cardiovascular Adverse Events in Phase 3 Studies" (Table 3.7.6.7.1 in the Integrated Summary of Safety 2008) and "Treatment-Emergent Potential Cardiovascular Adverse Events per 100PM . . ." (Table 24 in 4-Month Safety Update), and have the following information requests:

- Please provide detailed narratives of all 281 treatment-emergent potential cardiovascular adverse events. This includes both serious and nonserious adverse events.
- Please indicate which of the 5 treatment groups the subject was assigned.
- We request this information on all 281 potential cardiovascular adverse events and have special interest in those recorded as chest pain and chest discomfort.
- For ease of review, please provide this information collectively in one submission, even if a portion of this data is available in prior submissions.

We request a prompt written response in order to continue our evaluation of your NDA.

If you have any questions, call Chantal Phillips, Regulatory Project Manager, at 301-796-2259.

Sincerely,

{See appended electronic signature page}

Brian Strongin, R.Ph., M.B.A.
Chief, Project Management Staff
Division of Gastroenterology Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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

/s/

Brian Strongin
6/6/2008 09:06:45 AM



NDA 22-287

INFORMATION REQUEST LETTER

TAP Pharmaceutical Products Inc.
Attention: Nancianne Knipfer, Ph.D.
Project Manager, Regulatory Affairs
675 North Field Drive
Lake Forest, IL 60045

Dear Dr. Knipfer:

Please refer to your December 28, 2007 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for dexlansoprazole.

We also refer to your submissions dated February 5, 18, & 19, 2008; March 7 & 26, 2008; and April 28 & 29, 2008.

We are reviewing the Clinical Pharmacology section of your submission and have the following comments and information requests.

- 1) Please submit the control strings (software codes) for population kinetic analysis (T-P105-129)
- 2) Regarding all the studies with genotyped subjects, please pool the data together and analyze the pharmacokinetic (PK), pharmacodynamic (PD), and adverse events based on the CYP 2C19 genotypes to determine whether an association between genotypes and exposure, PD response, and adverse events in the combined data exists.
- 3) In the hepatic impairment study, you re-genotyped Subject 805. Please submit the new detailed genotype results of this subject.
- 4) For the gender/age study, please submit the new detailed genotype results of Subject 119 if this subject was re-genotyped.

We request a prompt written response in order to continue our evaluation of your NDA.

If you have any questions, call Chantal Phillips, Regulatory Project Manager, at 301-796-2259.

Sincerely,

{See appended electronic signature page}

Brian Strongin, R.Ph., M.B.A.
Chief, Project Management Staff
Division of Gastroenterology Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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

/s/

Brian Strongin
5/20/2008 10:27:30 AM



NDA 22-287

INFORMATION REQUEST LETTER

TAP Pharmaceutical Products Inc.
Attention: Nancianne Knipfer, Ph.D.
Project Manager, Regulatory Affairs
675 North Field Drive
Lake Forest, IL 60045

Dear Dr. Knipfer:

Please refer to your December 28, 2007 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for dexlansoprazole.

We also refer to your submissions dated February 5, 18, & 19, 2008, and March 7, 2008.

We are reviewing the Clinical Pharmacology 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.

- Please list all the bioanalytical sites for all the human PK/PD studies (including DDI, special populations, single dose, multiple doses) and confirm that no PK assay was done at **(b) (4)** [redacted] between 2000 and 2004.

If you have any questions, call Chantal Phillips, Regulatory Project Manager, at 301-796-2259.

Sincerely,

{See appended electronic signature page}

Brian Strongin, R.Ph., M.B.A.
Chief, Project Management Staff
Division of Gastroenterology Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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

/s/

Brian Strongin
5/1/2008 10:41:04 AM



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

FILING COMMUNICATION

NDA 22-287

TAP Pharmaceutical Products Inc.
Attention: Nancianne Knipfer, Ph.D., RAC
Principal Regulatory Adviser
675 N. Field Drive
Lake Forest, IL 60045

Dear Dr. Knipfer:

Please refer to your new drug application (NDA) dated December 28, 2007, received December 31, 2007, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act, for dexlansoprazole Delayed Release Capsules, 30 mg, 60 mg, (b) (4).

We also refer to your submissions dated February 5, 18, & 19, 2008.

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 was 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 31, 2008.

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

Labeling

Highlights:

- The initial U.S. Approval should be 2004 as this enantiomer, dexlansoprazole, is part of the racemate, lansoprazole, which was originally approved on this date. **Please see 21 CFR 201.57 (a) (3).**

Full Prescribing Information (FPI):

- Do not refer to adverse reactions as "adverse events". Please correct this throughout the label. **Please refer to the Guidance for Industry: Adverse Reactions Sections of Labeling for Human Prescription Drug and Biological Products – Content and Format,** available at <http://fda.gov/cder/guidance>.

- Full prescribing information must be limited in length to one-half page, in 8 point font type, two-column format. **Please see CFR 201.57 (d) (8).**
- The Patient Counseling Information section must reference any FDA-approved patient labeling or Medication Guide. [See 21 CFR 201.57(c)(18)] The reference [See FDA-Approved Patient Labeling] or [See Medication Guide] should appear at the beginning of the Patient Counseling Information section to give it more prominence.

Patient Counseling Information must follow after How Supplied/Storage and Handling section. [See 21 CFR 201.56(d)(1)] This section must not be written for the patient but rather for the prescriber so that important information is conveyed to the patient to use the drug safely and effectively. [See 21 CFR 201.57 (c)(18)] You have not identified any specific instructions to be relayed to the patient by the prescriber.

- Refer to <http://www.fda.gov/cder/regulatory/physLabel/default.htm> for fictitious examples of labeling in the new format.
- Regarding information at the end of the labeling, company website addresses are not encouraged. Please delete from package insert labeling. The same applies to the patient package insert and Medication Guide.

Clinical

- You have proposed the following indication for your product:
“Treating (b) (4) : heartburn (b) (4) associated with GERD.”

(b) (4)

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.

We also request that you submit the following information:

- Updated proposed label to reflect the recommendations and comments listed above.

If you have not already done so, you must submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at <http://www.fda.gov/oc/datacouncil/spl.html>. The content of labeling must be in the Prescribing Information (physician labeling rule) format.

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.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We note that you have not fulfilled the requirements. We acknowledge receipt of your request for a waiver of pediatric studies for this application for pediatric patients aged 0 to 1 months.

We also acknowledge receipt of your request for a deferral of pediatric studies for this application for pediatric patients aged 1 month to 17 years.

If you have any questions, call Chantal Phillips, Regulatory Project Manager, at (301) 796-2259.

Sincerely,

{See appended electronic signature page}

Brian Strongin, R.Ph., M.B.A.
Chief Project Management Staff
Division of Gastroenterology Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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

/s/

Brian Strongin
3/13/2008 12:24:42 PM



NDA 22-287

NDA ACKNOWLEDGMENT

TAP Pharmaceutical Products Inc.
Attention: Nancianne Knipfer, PhD, RAC
Principal Regulatory Adviser
675 North Field Drive
Lake Forest, IL 60045

Dear Dr. Knipfer:

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

Name of Drug Product: (dexlansoprazole) Delayed Release Capsules, 30, 60, (b) (4) mg

Date of Application: December 28, 2007

Date of Receipt: December 31, 2007

Our Reference Number: NDA 22-287

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 29, 2008, in accordance with 21 CFR 314.101(a).

If you have not already done so, promptly submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at <http://www.fda.gov/oc/datacouncil/spl.html>. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action under 21 CFR 314.101(d)(3). The content of labeling must be in the Prescribing Information (physician labeling rule) format.

The NDA number provided above must 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 Gastroenterology 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, call me at (301) 796-2259.

Sincerely,

{See appended electronic signature page}

Chantal Phillips, LCDR, B.S.N.
Regulatory Project Manager
Division of Gastroenterology Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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

/s/

Chantal N. Phillips
1/4/2008 11:45:48 AM

From: Simon, Anna Maria
Sent: Monday, January 12, 2009 3:00 PM
To: 'Knipfer, Nancianne (TGRD)'
Subject: Clinical questions for today's T-Con NDA 22-287

Attachments: NDA 22287 Dexlansoprazole labeling discussion questions on 1 (3).doc

Nanci,

I have attached clinical questions for today's labeling meeting. I do not have the questions from Stats



NDA 22287
exlansoprazole labe.

Thank you
Anna

Anna Maria Simon MSN, CPNP
Regulatory Health Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Gastroenterology Products
White Oak BLDG 22, Room 5473

anna.simon@fda.hhs.gov
(301) 796-3509 Phone
(301) 796-9905 Fax

Appears This Way On Original

NDA 22287 Dexlansoprazole labeling discussion questions on 1/12/09

We need to be able to compare baseline (at entry to each of the following studies) and at the end of each of the studies for following 4 populations:

Patients who entered the healing study
Patients who entered the extension study
Patients who did not enter the extension study
Patients who entered the GERD study

- 1) Provide the distribution of baseline number of days and mean severity of heartburn for each population listed above, including the baseline at the extension study entry.
- 2) What was the Diary compliance for each study listed above, and for each of the populations listed above (i.e. what was the compliance in the healing study for the subgroup of the patients who entered the extension study)?
- 3) How did the patients who entered the extension study baseline symptoms compare to the baseline symptoms of the patients in their same group in the healing study who didn't enter the extension study?
- 4) What happened to the baseline symptoms during the course of the healing study in those patients who entered the extension study, and compared to the same information for the others in their treatment group in the healing study who didn't enter the extension study?
- 5) What was the distribution and proportion of 4 week healers vs. 8 week healers in the patients who entered the extension study, compare between the extension study arms?
- 6) What proportion of the extension study had been on lanso on the healing study, what was the distribution of healing study lansoprazole patients across arms in the extension study, and were the baseline symptoms at healing and extension study entry points for these patients different from the other patients?
- 7) Other supportive information, including severity, physician assessment of symptoms, and rescue medication was collected. Can you give us the tables for these from the healing study, extension study and GERD study for each of the above study populations, including subset results of the population during the healing study for those who ultimately entered the maintenance study – comparing to those who did not enter the maintenance study? Please provide baseline at maintenance study entry for those patients who entered the maintenance study.
- 8) The GERD study collected data on the patients' description of the symptoms. Were these data collected in the healing and extension study? If so, can you provide the tables for baseline and outcome in each. For the extension study need the relative comparison by treatment in the healing study of the patients at extension study entry and baseline at healing study entry.

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

/s/

Anna Maria Simon
1/13/2009 10:26:45 AM
CSO

Anna Maria Simon
1/13/2009 10:27:19 AM
CSO

From: Simon, Anna Maria
Sent: Monday, January 12, 2009 4:36 PM
To: 'Knipfer, Nancianne (TGRD)'
Cc: Phillips, Chantal
Subject: Stats question for NDA 22-287
Nanci,

Please see the question below from STATS.

Using compliance definition of % days with both day and night heartburn diary entries, please provide a summary table on patients' compliance for the maintenance studies. Furthermore, please provide summary tables on percentage of days with neither day or night heartburns for those patients who had more than 50%, 60%, 70%, 80%, or 90% compliance. The summary tables should present the results for each treatment arm, each month during the 6-month treatment period, and the whole treatment period.

We will speak to you again on Wednesday. Please confirm whether we should use the same call in number as today.

Thank you,
Anna

Anna Maria Simon MSN, CPNP
Regulatory Health Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Gastroenterology Products
White Oak BLDG 22, Room 5473

anna.simon@fda.hhs.gov
(301) 796-3509 Phone
(301) 796-9905 Fax

Appears This Way On Original

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

/s/

Anna Maria Simon
1/13/2009 10:33:30 AM
CSO

Anna Maria Simon
1/13/2009 10:33:59 AM
CSO

MEMORANDUM OF TELECON

DATE: November 5, 2008

APPLICATION NUMBER: NDA 22-287

BETWEEN:

Name: Nancianne Knipfer, PhD, Manager, Regulatory Affairs Strategy
Donna Helms, BS, MBA, Director Regulatory Affairs Strategy
Dean Sundberg, Sr. Vice President, Regulatory Affairs
David Recker, MD, Sr. Vice President, Clinical Sciences
Galen Witt, MS, Associate Director, Statistics
Nancy Siepman, PhD, Vice President, Analytical Sciences
Maria Paris, MD, Sr. Vice President, Pharmacovigilance

Phone: International line provided by sponsor

Representing: Takeda

AND

Name: Ruyi He, M.D., Medical Team Leader, DGP
Tamara Johnson, M.D., Medical Officer, DGP
Sue Chih Lee, Ph.D., Team Leader Clinical Pharmacology
Jane Bai, Ph.D., Reviewer, Clinical Pharmacology
Kristina Estes, LT, Pharm D., Regulatory Reviewer, Clinical Pharmacology
Mike Welch, Ph.D., Statistical Team Leader, Division of Biometrics III
Stella Grosser, Math Statistician, Division of Biometrics III
Freda Cooner, Ph.D., Statistical Reviewer, Division of Biometrics III
Chantal Phillips, LCDR, M.S.H.S., Regulatory Project Manager, DGP
Anna Simon, MSN, CPNP, Regulatory Project Manager, DGP
Division of Gastroenterology Products, HFD-180

SUBJECT: (b) (4)

SUMMARY:

• (b) (4)

(b) (4)

- Sponsor will speak with Agency via teleconference on November 17, 2008 regarding other areas of labeling.

- Sponsor will provide Agency with additional labeling comments.
- Sponsor will provide Agency with a revised Pediatric Assessment Plan to include sample size and where appropriate, the power for the study.

Anna M. Simon, MSN, CPNP
Regulatory Health Project Manager
Division of Gastroenterology Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Appears This Way On Original

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

/s/

Anna Maria Simon
11/12/2008 02:31:11 PM
CSO

2 Page(s) Withheld

√ Trade Secret / Confidential (b4)

 Draft Labeling (b4)

 Draft Labeling (b5)

 Deliberative Process (b5)

Withheld Track Number: Administrative- 2

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

/s/

Chantal N. Phillips
10/29/2008 01:31:42 PM
CSO

MEMORANDUM OF TELECON

DATE: March 19, 2008

APPLICATION NUMBER: NDA 22-287

BETWEEN:

TAP Pharmaceutical Products Inc.

Donna Helms, Director, Regulatory Strategy
Binita Kwankin, Associate Director, Regulatory Strategy
Nancianne Knipfer, Ph.D., Principal Regulatory Advisor
Maria Paris, MD, Senior Director Clinical Safety Pharmacovigilance
Nancy Siepman, Ph.D., Director Scientific Data Analysis
Galen Witt, Assistant Director, Statistics

(b) (4) Attendees (b) (4)

(b) (4)

(b) (4) performed readings):

(b) (4)

Phone: Secure line provided by sponsor

Representing: TAP Pharmaceutical Products

AND

Christine Garnett, Pharm.D., QT-IRT Scientific Leader, Clinical Pharmacology Reviewer, OTS
Chantal Phillips, LCDR, Regulatory Project Manager, Division of Gastroenterology Products

Division of Cardiovascular and Renal Products

Suchitra Balakrishnan, M.D., Ph.D., QT-IRT Medical Officer
Devi Kozeli, QT-IRT Regulatory Project Manager
Norman Stockbridge, M.D., Ph.D., Director

Division of Cardio/Renal consulted by Division of Gastroenterology Products, HFD-180

SUBJECT: NDA 22-287, Dexlansoprazole (TQT Study Report No. T-P104-092)

BACKGROUND:

NDA 22-287 was submitted to DGP on December 28, 2007 and is currently under the GRMP pilot study. Biopharmaceutical review team requested a consult to the Division of Cardiovascular and Renal Products for QTIRT review for Study # T-P104-092 .

DCaRP requested a telecon with the sponsor and the core lab, prior to proceeding with the review of the TQT Study Report No. T-P104-092. There are concerns regarding the QT interval interpretation. The sponsor was also provided an ECG screenshot example via email as an example to be discussed during the telecom.

DISCUSSION:

The following issues were raised by the Agency:

- Primary lead not-pre-specified in protocol.
- Baseline and on-treatment QT measurements have not been based on the same lead.
- 69% of annotations have been in non-primary lead.
- Annotations have been at multiple leads at same and adjacent time points for no clear reason- even when lead II or V2 waveforms are of good quality.
- Annotations were made in leads with low T wave amplitude.
- A comparison between the reported QT interval and a measurement based on an automatic algorithm demonstrates that the distribution of QT measurements is broader than it is with most of the other studies that we have reviewed.

Sponsor believes that what they did was a conservative approach. Agency states that this is approach produces excess noise in the ECG reading. Sponsor has agreed to re-interpret ECGs for a sample of the subjects and send their proposal of the plan to the Agency for agreement.

Chantal Phillips, LCDR
Regulatory Project Manager

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

/s/

Chantal N. Phillips
3/20/2008 04:16:28 PM
CSO

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: January 28, 2009

SUBJECT: **Labeling Negotiation**
NDA 22-287, Kapidex (Dexlansoprazole) Delayed Release
Capsules

Brief Teleconference held with Sponsor regarding labeling for NDA 22-287, Kapidex (Dexlansoprazole) Delayed Release Capsules. Labeling received January 27, 2009, acceptable with the exception of Table 4: Mean (CV%) Pharmacokinetic Parameters for Subjects on Day 5 After Administration of KAPIDEX. Sponsor was directed to modify data in Table 4 to include the Cmax and AUC data without dose normalization. Sponsor was agreeable.

Appears This Way On Original

From: Knipfer, Nancianne (TGRD) [nancianne.knipfer@tgrd.com]
Sent: Wednesday, January 28, 2009 2:51 PM
To: Simon, Anna Maria
Subject: FW: NDA 22-287 Labeling REVISED

Attachments: DEXLANSOPRAZOLE_FULL PRESCRIBING INFORMATION_PI1002 R1-Clean (2).doc; annotated (2)
DEXLANSOPRAZOLE_FULL PRESCRIBING INFORMATION28jan2009.doc
Anna-

As we discussed on the phone, I have updated the label to move the line for the highlights section from the top of page 2 to the bottom of page 1.

Please use these files instead of the ones sent earlier today. These will be included in the formal submission.

Thanks, Nanci

Nancianne Knipfer, Phd, RAC
Manager, Regulatory Affairs Strategy
Takeda Global Research and Development Center, Inc.

Phone: 847-582-2193
Cell: 773-531-7300
Fax: 847-582-2880
nancianne.knipfer@tgrd.com

From: Knipfer, Nancianne (TGRD)
Sent: Wednesday, January 28, 2009 1:37 PM
To: 'Simon, Anna Maria'
Subject: RE: NDA 22-287 Labeling

Yes.

Nancianne Knipfer, Phd, RAC
Manager, Regulatory Affairs Strategy
Takeda Global Research and Development Center, Inc.

Phone: 847-582-2193
Cell: 773-531-7300
Fax: 847-582-2880
nancianne.knipfer@tgrd.com

From: Simon, Anna Maria [mailto:anna.simon@fda.hhs.gov]
Sent: Wednesday, January 28, 2009 1:16 PM
To: Knipfer, Nancianne (TGRD)
Subject: RE: NDA 22-287 Labeling

Nanci,
I just sent this to Drs Griebel, He and Bai for review. Will the letter have today's date?
Thanks again!
Anna

Anna M. Simon
Regulatory Project Manager
Division of Gastroenterology Products
CDER/OND/ODE III

White Oak BLDG 22, Room 5473

anna.simon@fda.hhs.gov

) 796-3509 Phone

) 796-9905 Fax

From: Knipfer, Nancianne (TGRD) [mailto:nancianne.knipfer@tgrd.com]

Sent: Wednesday, January 28, 2009 2:13 PM

To: Simon, Anna Maria

Cc: Phillips, Chantal

Subject: NDA 22-287 Labeling

Anna-

Attached are the revised annotated and clean versions of the label in word format. Per our discussion today we have modified the data in table 4 to include the Cmax and AUC data without dose normalization.

We will formally submit these documents today. I will forward a copy of the submission.

If you have any questions, please let me know.

Thanks, Nanci

Nancianne Knipfer, Phd, RAC

Manager, Regulatory Affairs Strategy

da Global Research and Development Center, Inc.

Phone: 847-582-2193

Cell: 773-531-7300

Fax: 847-582-2880

nancianne.knipfer@tgrd.com

###

This message is for the designated recipient only and may contain privileged or confidential information. If you have received it in error, please notify the sender immediately and delete the original. Any other use of the email by you is prohibited.

###

Appears This Way On Original

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

/s/

Anna Maria Simon
1/28/2009 03:50:30 PM
CSO

Anna Maria Simon
1/28/2009 03:50:54 PM
CSO



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

IND 69,927

TAP Pharmaceutical Products, Inc.
Attention: Nancianne Knipfer, Ph.D.
Senior Regulatory Product Manager
675 North Field Drive
Lake Forest, IL 60045

Dear Dr. Knipfer:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Dexlansoprazole Modified-Release Capsules.

We also refer to the meeting between representatives of your firm and the FDA on October 1, 2007. The purpose of the Pre-NDA meeting was to discuss non-clinical and clinical information.

The official minutes of that meeting are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 796-2259.

Sincerely,

{See appended electronic signature page}

Chantal Phillips, LCDR, B.S.N.
Regulatory Project Manager
Division of Gastroenterology Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure

MEMORANDUM OF MEETING MINUTES

MEETING DATE: October 1, 2007
TIME: 2:30 pm to 3:30 pm EST
LOCATION: FDA ,White Oak
APPLICATION: IND 69,927
DRUG NAME: Dexlansoprazole Modified-Release Capsules
TYPE OF MEETING: Type B

MEETING CHAIR: Dr. Ruyi He

MEETING RECORDER: Chantal Phillips

FDA ATTENDEES:

Division of Gastroenterology Products

Joyce Korvick, M.D., M.P.H., Deputy Director
Ruyi He, M.D., Medical Team Leader
Marjorie Dannis, M.D., Medical Reviewer
Sushanta Chakder, Ph.D., Pharmacology Reviewer
Ke Zhang, Ph.D., Pharmacology Reviewer

Division of Biometrics III

Mike Welch, Ph.D, Statistical Team Leader

Office of Clinical Pharmacology and Biopharmaceutics

Sue-Chih Lee, Ph.D., Team Leader
Jane Bai, Ph.D., Reviewer

EXTERNAL CONSTITUENT ATTENDEES:

Nancy Joseph-Ridge, MD, Vice President, Research and Development, TAP
Dean Sundberg, Vice President, Regulatory Affairs, TAP
Donna Helms, BS, MBA, RAC, Director, Regulatory Affairs, TAP
Nancianne Knipfer, PhD, RAC, Principal Regulatory Adviser, TAP
Stuart Atkinson, MD, Senior Scientific Director, Head Therapeutic Areas, TAP
Robert Jackson, MD, Head of Clinical Development, Outcomes and External Research, TAP
Maria Claudia Perez, MD, Medical Director, GI Therapeutic Areas
Maria Paris, MD, PhD, Senior Director, Clinical Safety Pharmacovigilance, TAP
Nancy Siepman, PhD, Director, Statistics and Study Programming, TAP
Galen Witt, Assistant Director, Statistics, TAP
Steve Elrod, Vice President, Scientific Affairs, TAP
Darcy Mulford, PhD, Director, Drug Metabolism and Pharmacokinetics, TAP
Harriet Glassman, Senior Director, Project Management, Operations, and Scientific Communications, TAP
Takeshi Seita, Takeda Liaison, TAP

BACKGROUND:

Tap Pharmaceutical Products submitted a Pre-NDA meeting for Dexlansoprazole on June 18, 2007. Dexlansoprazole is currently under a Tradename review and the proposed indication is for healing of erosive esophagitis; maintenance healing of erosive esophagitis (b) (4) and treatment of (b) (4) heartburn. Tap Pharmaceutical Products plans to submit an NDA in late 2007.

MEETING OBJECTIVES:

The objective of the meeting is to discuss non-clinical and clinical information related to Dexlansoprazole.

DISCUSSION POINTS:

In response to questions in the August 9, 2007, background package, the following responses were given. The format provides the firm's questions in italics followed by FDA responses in bold lettering. Questions, responses, and additional comments are indicated with headings.

CLINICAL QUESTIONS

Question 1.

As planned in the protocols, Studies T-EE04-084 and T-EE04-085 were designed to demonstrate noninferiority of dexlansoprazole (b) 60 mg and 90 mg to lansoprazole 30 mg for the healing of EE, and, if noninferiority was established for either or both doses in these studies, superiority to lansoprazole 30 mg would also be assessed. Results from both of these studies demonstrate noninferiority of dexlansoprazole (b) 60 mg and 90 mg to lansoprazole 30 mg for the healing of EE in the primary analysis (life-table method). In addition to achieving noninferiority to lansoprazole 30 mg for the primary efficacy endpoint for both dexlansoprazole (b) 60 mg and 90 mg in 2 studies,

Does the Agency agree that these studies are adequate to support the approval of dexlansoprazole (b) for the EE healing indication?

FDA Response:

The adequacy of the studies to support approval will be determined during the review process. Non-inferiority studies, in particular, require a substantial level of justification to support the chosen margin, assay sensitivity and constancy of control assumptions. (Refer

to ICH E10). Regarding your multiple objectives, you will need to clearly establish prospectively defined procedures for experiment-wise Type I error control

Additional Comment:

The sponsor concurred with these requirements and indicated they will be documented within their submission.

Question 2.

Studies T-EE04-084 and T-EE04-085 are identical in design and have similar patient populations and baseline characteristics. In order to provide additional statistical power to evaluate subjects with moderate to severe grades of EE (Los Angeles [LA] Classification Grades C and D [23% and 6% of overall enrolled subjects, respectively]), TAP plans to present an analysis of combined data from both studies to demonstrate efficacy of dexlansoprazole MR in Grades C and D combined. Does the Agency agree that the combined analysis from the 2 EE healing studies demonstrates the added clinical benefit of dexlansoprazole MR 90 mg over lansoprazole 30 mg in Grades C and D?

FDA Response:

We do not agree. The combining or pooling of studies to show a clinically and statistically significant effect within a subgroup would generally be considered an exploratory analysis. The statistical significance and clinical benefit of dexlansoprazole MR 90 mg over lansoprazole 30 mg should be demonstrated within the individual studies as prospectively planned.

Additional Comment:

We discussed the concept that the individual studies will be the primary data and the combined analysis will be used as supportive data. The significance of the combined analysis will be a review issue.

Question 3.

Does the Agency agree with the proposed dosing recommendations for EE healing?

FDA Response:

The adequacy of the studies to support approval will be determined during the review process.

Question 4.

TAP conducted 2 large, robust Phase 3, controlled studies in subjects with healed EE (T-EE04-086 and T-EE05-135). As discussed with the Agency in the 01 March 2006 teleconference, both studies included the 60-mg dose, and only one of these studies (T-EE05-135) included the 30-mg dose. Does the Agency agree that the single study (T-EE05-135), a large, adequate, and well-controlled study that demonstrates clinically and statistically significant superiority of dexlansoprazole MR 30 mg and 60 mg over placebo ($p < 0.00001$), is acceptable for the approval of dexlansoprazole MR for the maintenance of healed EE indication?

FDA Response:

A single superiority study would need to demonstrate high statistical significance with demonstrable clinical efficacy. A single study would need to show consistent results across subgroups, centers, secondary endpoints, and other factors. Adequacy of the studies to support approval would be determined during the review process.

Question 5.

Based on subgroup analysis for Grades C and D, dexlansoprazole MR 60 mg demonstrated a higher percentage of subjects with maintenance of healed EE than dexlansoprazole MR 30 mg in Study T-EE05-135. This was also observed using combined data from Studies T-EE05-135 and T-EE04-086. Does the Agency agree that these data demonstrate the added clinical benefit of dexlansoprazole MR 60 mg in Grades C and D combined?

FDA Response:

Unplanned or retrospective subgroup analyses are considered exploratory and would not support labeling claims. During the review process, subgroup differences may be found

that would appear to be of clinical significance; however, such results would generally need confirmation in a new, adequately controlled study. Also see response to question 2.

Question 6.

Does the Agency agree with the proposed dosing recommendations for maintenance of healed EE?

FDA Response:

The adequacy of the studies to support approval will be determined during the review process.

Question 7.

As discussed with the Agency in the 01 March 2006 teleconference, the primary analyses for studies to support the EE healing and maintenance of healed EE indications utilized life-table methods and the log-rank test was used for comparisons between treatment groups. For assessing these indications, does the Agency have any preference regarding choice of discrete time units (day-based or interval-based)?

FDA Response:

Life table methods may be informative; however, we recommend the primary analyses be based on proportions of subjects who are healed by a specific time point. Adequacy of your study design and analyses to support your indications will be determined during the review process.

Additional Comment:

We discussed the primary endpoint analysis. It was agreed that the sponsor will change their primary analysis to compare the proportions of patients responding at a specified time point, e.g., eight weeks,(crude rate analysis), and use the time to event, life- table method, as a supportive analysis.

Sponsor will submit an amendment in their submission to this effect.

Question 8.

In addition, does the Agency find the assumptions used to implement the life-table method as summarized in Appendix B acceptable, including the methods of censoring and the choice of discrete time units for estimating rates?

FDA Response:

Please refer to the response for question 7. Agency review of your statistical analysis plan is best accomplished prior to starting your phase 3 studies. As this is a preNDA meeting, we assume that at this time, your analysis plan has been prospectively defined and finalized. The adequacy of your analyses will be addressed during review of your submission.

Question 9.

Does the Agency agree that the single study (T-GD05-137), a large, adequate, and well-controlled study that demonstrated clinically and statistically significant superiority of dexlansoprazole MR 30 mg over placebo ($p < 0.00001$), is acceptable for approval of dexlansoprazole MR for the symptomatic GERD indication?

FDA Response:

A single study will need to demonstrate high statistical significance with consistent levels of efficacy across subgroups, centers, secondary endpoints, and other factors. This will be determined during the review process.

Question 10.

Does the Agency agree with the proposed dosing recommendations for symptomatic GERD?

FDA Response:

The adequacy of the studies to support approval will be determined during the review process.

Question 11.

Based on the pharmacodynamic and pharmacokinetic data from Study T-P106-146 summarized in Section 9.2.2, does the Agency agree that dexlansoprazole MR can be taken without regard to the timing of food?

FDA Response:

This is a review issue and will be determined during the review process.

Question 12.

- a) *The safety profile of dexlansoprazole MR is similar to lansoprazole and appears to be consistent with other proton pump inhibitors (PPIs). Does the Agency have any questions or concerns regarding the safety profile of dexlansoprazole MR based on the data summarized in the briefing document?*

FDA Response:

The adequacy of the studies to support approval will be determined during the review process.

- b) *Does the Agency agree that the long-term patient exposure data to be included in the original NDA and the 4-Month Safety Update (described in Table 9.4.1.a)) are adequate to support the NDA filing?*

FDA Response:

It is acceptable.

Question 13.

Does the Agency agree with the proposed strategy for the Integrated Summaries of Efficacy (ISE) and Summaries of Clinical Efficacy for each indication, as described in Section 12.1.1? Specifically:

- a) *TAP's proposal to split each of the ISEs for the healing of EE and maintenance of healed EE indications, as described in the June 2007 draft Guidance for Industry, "Integrated Summaries of Effectiveness and Safety: Location Within the Common Technical Document." As described in Sections III.C and V.D of the draft guidance, TAP plans to place the text portion of each ISE in Module 2.7.4 (Summary of Clinical Efficacy) and the tables, appendices, and datasets in Module 5.3.5.3. Statistical tables referenced in the text (Module 2.7.4) will be electronically hyperlinked to the tables located in Module 5.*

FDA Response:

This appears to be acceptable; however, confirmatory evidence of efficacy should be based on the individual studies; data from the ISE are mainly used for supportive and/or exploratory purposes and do not constitute substantial evidence for labeling purposes.

- b) *TAP's proposal to have only a Summary of Clinical Efficacy and no ISE for the symptomatic GERD indication, as integration of the 2 symptomatic GERD studies is not warranted.*

FDA Response:

No.

Question 14.

Does the Agency have any questions or comments about the proposed study groupings or the data presentation for the Integrated Summary of Safety (ISS) as described in Section 12.1.2?

FDA Response:

No.

Question 15.

Does the Agency have any comments on the validation data for the Patient Assessment of Upper Gastrointestinal Disorders-Symptom Severity Index (PAGI-SYM) and Patient Assessment of Upper Gastrointestinal Disorders Quality-of-Life Index (PAGI-QOL) questionnaires previously

submitted to IND 69,927 on 13 April 2006 (Serial No. 0039) and 10 August 2006 (Serial No. 0058)?

FDA Response:

Pending SEALD response. (Not addressed during meeting).

LABELING

Question 16.

For the NDA, the full prescribing information will be provided in portable document file (PDF) and Microsoft Word formats. Structured product labeling (SPL) will not be submitted with the NDA, but will be submitted after approval once the full prescribing information is agreed upon. Is this acceptable?

FDA Response:

No, we expect PLR and SPL format to be submitted with the original NDA submission. By regulation [21 CFR 314.50(l), 314.94(d), and 601.14(b); Guidance for Industry: *Providing Regulatory Submissions in Electronic Format — Content of Labeling* (April 2005); <http://www.fda.gov/ohrms/dockets/dockets/92s0251/92s-0251-m000032-vol1.pdf>], you are required to submit to FDA prescribing and product information (i.e., the package insert or label) in SPL format. FDA will work closely with applicants during the review cycle to correct all SPL deficiencies before approval. Please email spl@fda.hhs.gov for individual assistance.

Question 17.

For the NDA, labels for the primary packaging will be provided in Microsoft Word and PDF format as text, and color mock-ups will be submitted during the review. Is this acceptable?

FDA Response:

No, please submit with the original application.

OVERALL QUESTIONS

Question 18.

Has the Agency identified any issues that could affect the filing of the NDA under 21 CFR 314.101?

FDA Response:

This will be determined at the time of filing.

Question 19.

Has the Agency identified any review issues?

FDA Response:

This will be determined during the review process.

Regulatory

Question 20.

The NDA will contain financial disclosure for the following six Phase 3 studies, which meet the definition of a “covered study” per 21 CFR 54:

- *EE healing (T-EE04-084, T-EE04-085)*
- *Maintenance of healed EE (T-EE04-086, T-EE05-135)*
- *Symptomatic GERD (T-GD05-137, T-GD04-082)*

Financial disclosure will not be included for any Phase 1 study or for the Phase 3 Study T-GI04-088 (an uncontrolled, open-label, long-term extension study), as these studies are not considered “covered” studies per the regulations. Is this acceptable?

FDA Response:

No, the financial disclosure should be provided for all Phase 3 studies.

Question 21.

- a) *For the NDA, electrocardiogram (ECG) findings will be included in the data listings of each clinical study report. ECG tracings will be available upon request. Is this acceptable?*

FDA Response:

Yes, this is acceptable.

- b) *TAP plans to submit Council for International Organization of Medical Sciences (CIOMS) reports in place of text narratives for deaths and other serious adverse events (SAEs). Narratives for premature discontinuations due to adverse events will also be submitted. Is this acceptable?*

FDA Response:

No, you should provide text narrative for all patient deaths and serious adverse events as well as all premature discontinuations.

Additional Comment:

The CIOMS format is acceptable in place of text narratives for patient deaths and serious adverse events as long as all of the relevant information is included.

The patient profile format should be provided for all premature discontinuations.

- c) *The dexlansoprazole MR NDA will cross-reference lansoprazole clinical and nonclinical study reports previously submitted under IND 30,159 and NDA 20-406 for Prevacid (lansoprazole) Delayed-Release Capsules. TAP does not plan to resubmit these reports, but will include cross-references to their locations in the respective locations. Is this acceptable?*

FDA Response:

Yes.

Question 22.

Does the Agency have any questions or comments regarding the test submission with datasets in Clinical Data Interchange Standards Consortium (CDISC) format as submitted on 13 July 2007?

FDA Response:

CDISC format is acceptable.

NONCLINICAL QUESTIONS

Question 23.

The Agency and TAP discussed at the Type C meeting (teleconference) held on 06 October 2004 that based on FDA's Policy Statement for the Development of New Stereoisomeric Drugs, the following nonclinical studies would support the bridging strategy for dexlansoprazole, the R-enantiomer of lansoprazole:

- *In vitro Purkinje fiber study*
- *3-month repeat-dose toxicity study in rats*
- *3-month repeat-dose toxicity study in dogs*
- *Reproductive toxicity segment II study in rabbits*

In each in vivo study, lansoprazole was used as a comparator.

Additional nonclinical studies were performed including in vitro and in vivo pharmacodynamic and pharmacokinetic/drug metabolism studies, a 4-week, repeat-dose toxicity study in rats, and an Ames test with follow-up studies (Table 10.1.a). No additional studies are planned. Does the Agency agree that the above studies support the bridging strategy for filing an NDA for dexlansoprazole MR?

FDA Response:

No, please see our response to Question 24 below.

Question 24.

Has the Agency identified any issues based on the nonclinical study summaries provided in Section 10?

FDA Response:

Yes. Based on the results of the recent Ames tests, please conduct additional genotoxicity studies including an in vitro mouse lymphoma cell tk assay or an in vitro test with cytogenetic evaluation of chromosomal damage with mammalian cells, and an in vivo mouse micronucleus test.

Additional Comments:

Sponsor agrees to conduct the studies and plans to submit the draft report with the NDA submission.

We agree that sponsor can submit draft full reports with the initial NDA submission.

Office of Surveillance and Epidemiology (OSE)

Additional Comments:

- **If the sponsor and/or FDA believe that there are product risks that merit more than conventional professional product labeling (i.e. package insert (PI) or patient package insert (PPI)) and post marketing surveillance to manage risks, then the Sponsor is encouraged to engage in further discussions with FDA about the nature of the risks and the potential need for a Risk Minimization Action Plan (RiskMAP). If you plan to submit a RiskMAP with the original submission, please remember to submit all planned materials identified within the RiskMAP that will be necessary to implement your proposal.**
- **For the most recent publicly available information on CDER's views on RiskMAPs, please refer to the following Guidance documents:**

Premarketing Risk Assessment: <http://www.fda.gov/cder/guidance/6357fnl.htm>

**Development and Use of Risk Minimization Action Plans:
<http://www.fda.gov/cder/guidance/6358fnl.htm>**

**Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment:
<http://www.fda.gov/cder/guidance/6359OCC.htm>**

- **If there is any information on product medication errors from the premarketing clinical experience, OSE requests that this information be submitted with the NDA/BLA application.**

DECISIONS (AGREEMENTS) REACHED:

See specific questions.

UNRESOLVED ISSUES OR ISSUES REQUIRING FURTHER DISCUSSION:

None.

ACTION ITEMS:

None.

ATTACHMENTS/HANDOUTS:

None.

Appears This Way On Original

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

/s/

Ruyi He
10/12/2007 03:39:01 PM

- 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?

N/A YES NO

CLINICAL MICROBIOLOGY N/A FILE REFUSE TO FILE

STATISTICS N/A FILE REFUSE TO FILE

BIOPHARMACEUTICS FILE REFUSE TO FILE

- Biopharm. study site audits(s) needed?
YES NO

PHARMACOLOGY/TOX N/A FILE REFUSE TO FILE

- GLP audit needed? YES NO

CHEMISTRY FILE REFUSE TO FILE

- Establishment(s) ready for inspection? YES NO
- Sterile product? YES NO
- If yes, was microbiology consulted for validation of sterilization? YES NO

ELECTRONIC SUBMISSION:

Any comments:

REGULATORY CONCLUSIONS/DEFICIENCIES:

(Refer to 21 CFR 314.101(d) for filing requirements.)

- The application is unsuitable for filing. Explain why:
- The application, on its face, appears to be well-organized and indexed. The application appears to be suitable for filing.
 - No filing issues have been identified.
 - Filing issues to be communicated by Day 74. List (optional):

ACTION ITEMS:

1. Ensure that the review and chemical classification codes, as well as any other pertinent classification codes (e.g., orphan, OTC) are correctly entered into COMIS.
2. If RTF, notify everybody who already received a consult request of RTF action. Cancel the EER.
3. If filed and the application is under the AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
4. If filed, complete the Pediatric Page at this time. (If paper version, enter into DFS.)

5. Convey document filing issues/no filing issues to applicant by Day 74.

Chantal Phillips
Regulatory Project Manager

Appears This Way On Original

Appendix A to NDA Regulatory Filing Review

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 ODE's Office of Regulatory Policy representative.

Appears This Way On Original

**Appendix B to NDA Regulatory Filing Review
Questions for 505(b)(2) Applications**

1. Does the application reference a listed drug (approved drug)? YES NO

If "No," skip to question 3.

2. Name of listed drug(s) referenced by the applicant (if any) and NDA/ANDA #(s):
3. Is this application for a drug that is an "old" antibiotic (as described in the draft guidance implementing the 1997 FDAMA provisions? (Certain antibiotics are not entitled to Hatch-Waxman patent listing and exclusivity benefits.) YES NO

If "Yes," skip to question 7.

4. Is this application for a recombinant or biologically-derived product? YES NO

If "Yes" contact your ODE's Office of Regulatory Policy representative.

5. The purpose of the questions below (questions 5 to 6) 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.
- (a) Is there a pharmaceutical equivalent(s) to the product proposed in the 505(b)(2) application that is already approved? YES NO

(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))

If "No," to (a) skip to question 6. Otherwise, answer part (b and (c)).

- (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 approved pharmaceutical equivalent(s) cited as the listed drug(s)? YES NO

If "Yes," (c), list the pharmaceutical equivalent(s) and proceed to question 6.

If "No," to (c) list the pharmaceutical equivalent and contact your ODE's Office of Regulatory Policy representative.

Pharmaceutical equivalent(s):

6. (a) Is there a pharmaceutical alternative(s) already approved? YES NO

(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.)

If "No," to (a) skip to question 7. Otherwise, answer part (b and (c)).

- (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) cited as the listed drug(s)? YES NO

If "Yes," to (c), proceed to question 7.

NOTE: *If there is more than one pharmaceutical alternative approved, consult your ODE's Office of Regulatory Policy representative to determine if the appropriate pharmaceutical alternatives are referenced.*

If "No," to (c), list the pharmaceutical alternative(s) and contact your ODE's Office of Regulatory Policy representative. Proceed to question 7.

Pharmaceutical alternative(s):

7. (a) Does the application rely on published literature necessary to support the proposed approval of the drug product (i.e. is the published literature necessary for the approval)? YES NO

If "No," skip to question 8. Otherwise, answer part (b).

(b) Does any of the published literature cited reference a specific (e.g. brand name) product? Note that if yes, the applicant will be required to submit patent certification for the product, see question 12.

8. Describe the change from the listed drug(s) provided for in 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 capsules to solution").

9. Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? (Normally, FDA may refuse-to-file such NDAs (see 21 CFR 314.101(d)(9)).) YES NO

10. 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 314.54(b)(1)). If yes, the application may be refused for filing under 21 CFR 314.101(d)(9)). YES NO

11. Is the application for a duplicate of a listed drug whose only difference is YES NO

that the rate at which the product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the RLD (see 21 CFR 314.54(b)(2))? If yes, the application may be refused for filing under 21 CFR 314.101(d)(9).

12. Are there certifications for each of the patents listed in the Orange Book for the listed drug(s) referenced by the applicant (see question #2)? YES NO
(This is different from the patent declaration submitted on form FDA 3542 and 3542a.)

13. 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.)

- Not applicable (e.g., solely based on published literature. See question # 7)
- 21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA. (Paragraph I certification)
Patent number(s):
- 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):
- 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)
Patent number(s):

NOTE: IF FILED, and if the applicant made a "Paragraph IV" certification [21 CFR 314.50(i)(1)(i)(A)(4)], the applicant must **subsequently** submit a signed certification stating that the NDA holder and patent owner(s) were notified the NDA was filed [21 CFR 314.52(b)]. The applicant must also submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)]. OND will contact you to verify that this documentation was received.

- 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above).
Patent number(s):
- Written statement from patent owner that it consents to an immediate effective date upon approval of the application.
Patent number(s):
- 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):

14. Did the applicant:

- Identify which parts of the application rely on the finding of safety and effectiveness for a listed drug or published literature describing a listed drug or both? For example, pharm/tox section of application relies on finding of preclinical safety for a listed drug.

YES NO

If "Yes," what is the listed drug product(s) and which sections of the 505(b)(2) application rely on the finding of safety and effectiveness or on published literature about that listed drug

Was this listed drug product(s) referenced by the applicant? (see question # 2)

YES NO

- Submit a bioavailability/bioequivalence (BA/BE) study comparing the proposed product to the listed drug(s)?

N/A YES NO

15. (a) Is there unexpired exclusivity on this listed drug (for example, 5 year, 3 year, orphan or pediatric exclusivity)? Note: this information is available in the Orange Book.

YES NO

If "Yes," please list:

Application No.	Product No.	Exclusivity Code	Exclusivity Expiration

Appears This Way On Original

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

/s/

Chantal N. Phillips
2/15/2008 04:10:04 PM
CSO