

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

208056Orig1s000

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**

EXCLUSIVITY SUMMARY

NDA # 208056

SUPPL #

HFD #

Trade Name Dexilant SoluTab

Generic Name (dexlansoprazole delayed-release orally disintegrating tablet)

Applicant Name Takeda Development Center Americas, Inc. (Takeda)

Approval Date, If Known January 26, 2016

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)

b) 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.

The applicant evaluated Dexlansoprazole SoluTab in 7 phase 1 open-label bioequivalence/bioavailability studies in healthy volunteers. The studies are listed in the table below with a brief description of the investigations conducted during each study. There were 6 bioequivalence/bioavailability studies and 1 sensory evaluation study to determine the in-vivo disintegration time. While safety data were collected during these studies, and some studies included pharmacokinetic and pharmacodynamic assessments, there were no clinical efficacy and/or safety trials conducted and submitted in this NDA.

Study #	Objective(s)	Study Design	Treatment	Subjects
TAK-390MR(OD)_102	Bioequivalence	Phase 1, randomized, open-label, single-center, single-dose, 4-period, crossover study	A: Single oral dose of Dex 30 mg OD tablet Formulation X (Test) B: Single oral dose of Dex 30 mg OD tablet Formulation Y (Test) C: Single oral dose of Dex 30 mg OD tablet Formulation Z (Test) D: Single oral dose of Dex 30 mg capsule (Reference)	64 healthy adults
TAK-390MR(OD)_103	BA: Food effect study and effect of water rinse after administration	Phase 1, randomized, open-label, single-center, single-dose, 3-period crossover study	A: Dex 30 mg OD tablet administered on the tongue on Day 1, allowed to disintegrate, and swallowed without water 30 minutes after starting to ingest a high-fat meal (Test) B: Dex 30 mg OD tablet administered on the tongue on Day 1 after a 10-hour fast, allowed to disintegrate, swallowed without water, and followed with a 240-mL water rinse (Test) C: Dex 30 mg OD tablet administered on the tongue on Day 1 after a 10-hour fast, allowed to disintegrate, and swallowed without water (Reference)	72 healthy adults
TAK-390MR(OD)_106	BA: OD tablet administered without water, swallowed intact with water, or mixed with water and administered orally via syringe or via nasogastric tube	Phase 1, randomized, open-label, single-center, single-dose, 4-period crossover study	A: Single oral dose of Dex 30 mg OD tablet mixed with water and administered orally via syringe (Test). B: Single oral dose of Dex 30 mg OD tablet mixed with water and administered via NG tube (Test). C: Single oral dose of Dex 30 mg OD tablet, swallowed intact with water (Test). D: Single oral dose of Dex 30 mg OD tablet, administered on the tongue, allowed to disintegrate, and swallowed without water (Reference).	77 healthy adults
TAK-390MR(OD)_101	BA, PD (intragastric pH response), and safety of OD tablet versus capsules	Phase 1, randomized, open-label, single-center, multiple-dose, 4-period, 3-way crossover study	A: Dex 30 mg OD tablet Formulation A for 5 days, fasted. B: Dex 30 mg OD tablet Formulation B for 5 days, fasted. C: Dex 30 mg capsule for 5 days, fasted. D: Dex 30 mg OD tablet Formulation A for 1 day, fed. E: Dex 30 mg OD tablet Formulation B for 1 day, fed.	48 healthy adults
TAK-390MR(OD)_104	BA	Phase 1, randomized, open-label, single-center, multiple-dose, 2-period crossover study	A: Dex 2x30 mg OD tablet QD administered on the tongue, allowed to disintegrate, and swallowed without water for 5 days (Test). B: Dex 1x60 mg capsule QD for 5 days (Reference).	52 healthy adults
TAK-390MR(OD)_105	PK, PD, and BA	Phase 1, randomized, open-label, single-center, multiple-dose, 2-period crossover study	A: Dex 30 mg OD tablet administered on the tongue, allowed to disintegrate, and swallowed without water for 5 days (Test). B: Dex 30 mg capsules for 5 days (Reference).	52 healthy adults
TAK-390MR(OD)_107	Sensory evaluation (In vivo disintegration time)	Phase 1/2 open-label sensory evaluation	Dex 30 mg OD tablet administered on the tongue, allowed to disintegrate, then expectorated	8 healthy adults

(source: reproduced from clinical pharmacology review by Dr. Dilara Jappar, dated 12/23/2015)

§314.108(a).

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:

c) Did the applicant request exclusivity?

YES ☒ NO ☐

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

Three year period of marketing exclusivity for dextansoprazole delayed-release orally disintegrating tablets.

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

YES ☒ NO ☐

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

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# 22287

Dexilant (dexlansoprazole) delayed-release capsules

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 ☐

The application contains clinical investigations by virtue of a right of reference to clinical investigations conducted by the applicant in another application, NDA022287.

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 ☐

FDA relied on clinical investigations conducted by the applicant under NDA 022287.

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

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

YES ☒ NO ☐

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

YES ☐ NO ☒

If yes, explain:

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

YES ☐ NO ☒

If yes, explain:

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

Studies 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 ☐

Relied upon the clinical efficacy and safety phase 3 trials, conducted by the applicant, under NDA 22287 for the approved Dexilant (dexlansoprazole) delayed-release capsules.

Investigation #2

YES ☐ NO ☒

There were 6 bioequivalence/bioavailability studies and 1 sensory evaluation study to determine the in-vivo disintegration time that were submitted and reviewed in this application, NDA 208056.

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

Clinical efficacy and safety phase 3 trials, conducted by the applicant, under NDA 22287 for the approved Dexilant (dexlansoprazole) delayed-release capsules.

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

Investigation #1

YES ☐ NO ☒

Investigation #2

YES ☐ NO ☒

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

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

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 # 69927 YES ☒ !
(dexlansoprazole delayed-release capsules) ! NO ☐
! Explain:

Investigation #2
IND # 106858 YES ☒ !
(dexlansoprazole delayed-release orally disintegrating tablets) ! 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 ☐ !
Explain: ! NO ☐
! Explain:

Investigation #2
!

YES ☐

Explain:

! NO ☐

! 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: Juli Tomaino, M.D.

Title: Medical Team Leader

Date: January 20, 2016

Name of Office/Division Director signing form: Andrew Mulberg, M.D.

Title: Deputy Director, DGIEP

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05; removed hidden data 8/22/12

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

/s/

MAUREEN D DEWEY
01/26/2016

JULI A TOMAINO
01/26/2016

ANDREW E MULBERG
01/26/2016

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION ¹		
NDA # 208056	NDA Supplement # BLA Supplement #	If NDA, Efficacy Supplement Type: <i>(an action package is not required for SE8 or SE9 supplements)</i>
Proprietary Name: Dexilant SoluTab Established/Proper Name: dexlansoprazole delayed-release orally disintegrating tablet Dosage Form: 30 mg		Applicant: Takeda Development Center Americas, Inc. (Takeda) Agent for Applicant (if applicable):
RPM: Maureen Dewey		Division: DGIEP
NDA Application Type: ☒ 505(b)(1) ☐ 505(b)(2) Efficacy Supplement: ☐ 505(b)(1) ☐ 505(b)(2) BLA Application Type: ☐ 351(k) ☐ 351(a) Efficacy Supplement: ☐ 351(k) ☐ 351(a)		<u>For ALL 505(b)(2) applications, two months prior to EVERY action:</u> - Review the information in the 505(b)(2) Assessment and submit the draft² to CDER OND IO for clearance. - Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity) ☐ No changes ☐ New patent/exclusivity <i>(notify CDER OND IO)</i> Date of check: <i>Note: If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.</i>
❖ Actions		
- Proposed action (split originals) - User Fee Goal Date is <u>January 26, 2016</u>		☒ AP – Original ☐ TA ☐
Previous actions <i>(specify type and date for each action taken)</i>		☐ None
❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain _____		☐ Received
❖ Application Characteristics ³		

¹ The **Application Information** Section is (only) a checklist. The **Contents of Action Package** Section (beginning on page 2) lists the documents to be included in the Action Package.

² For resubmissions, 505(b)(2) applications must be cleared before the action, but it is not necessary to resubmit the draft 505(b)(2) Assessment to CDER OND IO unless the Assessment has been substantively revised (e.g., new listed drug, patent certification revised).

³ Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA.

Review priority: ☒ Standard ☐ Priority
Chemical classification (new NDAs only):
(confirm chemical classification at time of approval)

- | | |
|---|---|
| ☐ Fast Track | ☐ Rx-to-OTC full switch |
| ☐ Rolling Review | ☐ Rx-to-OTC partial switch |
| ☐ Orphan drug designation | ☐ Direct-to-OTC |
| ☐ Breakthrough Therapy designation | |

(NOTE: Set the submission property in DARRTS and notify the CDER Breakthrough Therapy Program Manager;
Refer to the "RPM BT Checklist for Considerations after Designation Granted" for other required actions: [CST SharePoint](#))

NDAs: Subpart H

- ☐ Accelerated approval (21 CFR 314.510)
☐ Restricted distribution (21 CFR 314.520)

Subpart I

- ☐ Approval based on animal studies

- ☐ Submitted in response to a PMR
☐ Submitted in response to a PMC
☐ Submitted in response to a Pediatric Written Request

BLAs: Subpart E

- ☐ Accelerated approval (21 CFR 601.41)
☐ Restricted distribution (21 CFR 601.42)

Subpart H

- ☐ Approval based on animal studies

- REMS: ☐ MedGuide
☐ Communication Plan
☐ ETASU
☐ MedGuide w/o REMS
☐ REMS not required

Comments:

❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 (approvals only)	☐ Yes ☐ No
❖ Public communications (approvals only)	
• Office of Executive Programs (OEP) liaison has been notified of action	☒ Yes ☐ No
• Indicate what types (if any) of information were issued	☐ None ☐ FDA Press Release ☐ FDA Talk Paper ☐ CDER Q&As ☐ Other
❖ Exclusivity	
• Is approval of this application blocked by any type of exclusivity (orphan, 5-year NCE, 3-year, pediatric exclusivity)?	☒ No ☐ Yes
• If so, specify the type	
❖ Patent Information (NDAs only)	
• Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought.	☒ Verified ☐ Not applicable because drug is an old antibiotic.
CONTENTS OF ACTION PACKAGE	
Officer/Employee List	
❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list (approvals only)	☒ Included
Documentation of consent/non-consent by officers/employees	☒ Included

Action Letters	
❖ Copies of all action letters <i>(including approval letter with final labeling)</i>	Actions and dates: Original 1: Approval 01/26/2016
Labeling	
❖ Package Insert <i>(write submission/communication date at upper right of first page of PI)</i>	
• Most recent draft labeling <i>(if it is division-proposed labeling, it should be in track-changes format)</i>	☒ Included (01/21/2016)
• Original applicant-proposed labeling	☒ Included 03/26/2015
❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling <i>(write submission/communication date at upper right of first page of each piece)</i>	☒ Medication Guide ☒ Patient Package Insert ☒ Instructions for Use ☐ Device Labeling ☐ None
• Most-recent draft labeling <i>(if it is division-proposed labeling, it should be in track-changes format)</i>	☒ Included
• Original applicant-proposed labeling	☒ Included 03/26/2015
❖ Labels (full color carton and immediate-container labels) <i>(write submission/communication date on upper right of first page of each submission)</i>	
• Most-recent draft labeling	☒ Included 11/05/2015
❖ Proprietary Name	07/27/2015
• Acceptability	07/19/2015
• Review	
❖ Labeling reviews <i>(indicate dates of reviews)</i>	RPM: ☒ None DMEPA: ☐ None 10/15/2015 DMPP/PLT : ☐ None 12/22/2015 OPDP: ☐ None 12/02/2015 SEALD: ☒ None CSS: ☒ None Product Quality ☒ None Other: ☒
Administrative / Regulatory Documents	
❖ RPM Filing Review ⁴ /Memo of Filing Meeting <i>(indicate date of each review)</i>	06/02/2015
❖ All NDA 505(b)(2) Actions: Date each action cleared by 505(b)(2) Clearance Committee	☒ Not a (b)(2)
❖ NDAs only: Exclusivity Summary <i>(signed by Division Director)</i>	☒ Included
❖ Application Integrity Policy (AIP) Status and Related Documents http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	

⁴ Filing reviews for scientific disciplines are NOT required to be included in the action package.

Applicant is on the AIP	☐ Yes ☒ No
- This application is on the AIP - If yes, Center Director's Exception for Review memo <i>(indicate date)</i> - If yes, OC clearance for approval <i>(indicate date of clearance communication)</i>	☐ Yes ☒ No ☐ Not an AP action
❖ Pediatrics <i>(approvals only)</i> Date reviewed by PeRC <u>12/9/2015</u> If PeRC review not necessary, explain: _____	
❖ Breakthrough Therapy Designation	☒ N/A
Breakthrough Therapy Designation Letter(s) (granted, denied, an/or rescinded)	
CDER Medical Policy Council Breakthrough Therapy Designation Determination Review Template(s) <i>(include only the completed template(s) and not the meeting minutes)</i>	
CDER Medical Policy Council Brief – Evaluating a Breakthrough Therapy Designation for Rescission Template(s) <i>(include only the completed template(s) and not the meeting minutes)</i> <i>(completed CDER MPC templates can be found in DARRTS as clinical reviews or on the MPC SharePoint Site)</i>	
❖ Outgoing communications: letters, emails, and faxes considered important to include in the action package by the reviewing office/division (e.g., clinical SPA letters, RTF letter, Formal Dispute Resolution Request decisional letters, etc.) <i>(do not include OPDP letters regarding pre-launch promotional materials as these are non-disclosable; do not include previous action letters, as these are located elsewhere in package)</i>	n/a
❖ Internal documents: memoranda, telecons, emails, and other documents considered important to include in the action package by the reviewing office/division (e.g., Regulatory Briefing minutes, Medical Policy Council meeting minutes)	n/a
❖ Minutes of Meetings	
If not the first review cycle, any end-of-review meeting <i>(indicate date of mtg)</i>	☒ N/A or no mtg
Pre-NDA/BLA meeting <i>(indicate date of mtg)</i>	09/03/2014 CMC pre NDA 02/13/2015 WRO pre NDA
EOP2 meeting <i>(indicate date of mtg)</i>	Type C Preliminary Comments 02/03/2012, Meeting Canceled by Sponsor
Mid-cycle Communication <i>(indicate date of mtg)</i>	☒ N/A
Late-cycle Meeting <i>(indicate date of mtg)</i>	☒ N/A
Other milestone meetings (e.g., EOP2a, CMC focused milestone meetings) <i>(indicate dates of mtgs)</i>	

❖ Advisory Committee Meeting(s)	☒ No AC meeting
• Date(s) of Meeting(s)	
Decisional and Summary Memos	
❖ Office Director Decisional Memo (<i>indicate date for each review</i>)	☒ None
Division Director Summary Review (<i>indicate date for each review</i>)	☐ None 01/25/2016
Cross-Discipline Team Leader Review (<i>indicate date for each review</i>)	☐ None 01/11/2016; 01/25/2016
PMR/PMC Development Templates (<i>indicate total number</i>)	☐ None (6) 01/20/2016
Clinical	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) (<i>indicate date for each review</i>)	☒ No separate review
• Clinical review(s) (<i>indicate date for each review</i>)	None
• Social scientist review(s) (if OTC drug) (<i>indicate date for each review</i>)	☒ None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here ☐ and include a review/memo explaining why not (<i>indicate date of review/memo</i>)	Review 01/25/2016; CDTL Review (page 25)
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers (<i>indicate date of each review</i>)	☐ None DPMH: 11/30/2015; 12/20/2015
❖ Controlled Substance Staff review(s) and Scheduling Recommendation (<i>indicate date of each review</i>)	☒ N/A
❖ Risk Management	
• REMS Documents and REMS Supporting Document (<i>indicate date(s) of submission(s)</i>)	
• REMS Memo(s) and letter(s) (<i>indicate date(s)</i>)	
• Risk management review(s) and recommendations (including those by OSE and CSS) (<i>indicate date of each review and indicate location/date if incorporated into another review</i>)	☒ None
❖ OSI Clinical Inspection Review Summary(ies) (<i>include copies of OSI letters to investigators</i>)	☒ None requested
Clinical Microbiology ☒ None	
❖ Clinical Microbiology Team Leader Review(s) (<i>indicate date for each review</i>)	☐ No separate review
Clinical Microbiology Review(s) (<i>indicate date for each review</i>)	☐ None
Biostatistics ☒ None	
❖ Statistical Division Director Review(s) (<i>indicate date for each review</i>)	☐ No separate review
Statistical Team Leader Review(s) (<i>indicate date for each review</i>)	☐ No separate review
Statistical Review(s) (<i>indicate date for each review</i>)	☐ None
Clinical Pharmacology ☐ None	
❖ Clinical Pharmacology Division Director Review(s) (<i>indicate date for each review</i>)	☒ No separate review
Clinical Pharmacology Team Leader Review(s) (<i>indicate date for each review</i>)	☒ No separate review
Clinical Pharmacology review(s) (<i>indicate date for each review</i>)	☐ None 12/23/2015
❖ OSI Clinical Pharmacology Inspection Review Summary (<i>include copies of OSI letters</i>)	☒ None performed due to previous inspection history.

Nonclinical ☐ None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) (indicate date for each review)	☒ No separate review
• Supervisory Review(s) (indicate date for each review)	☒ No separate review
• Pharm/tox review(s), including referenced IND reviews (indicate date for each review)	☐ None 12/22/2015
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer (indicate date for each review)	☒ None
❖ Statistical review(s) of carcinogenicity studies (indicate date for each review)	☒ No carc
❖ ECAC/CAC report/memo of meeting	☒ None Included in P/T review, page
❖ OSI Nonclinical Inspection Review Summary (include copies of OSI letters)	☒ None requested
Product Quality ☐ None	
❖ Product Quality Discipline Reviews	
• Tertiary review (indicate date for each review)	☐ None
• Secondary review (e.g., Branch Chief) (indicate date for each review)	☐ None
• Integrated Quality Assessment (contains the Executive Summary and the primary reviews from each product quality review discipline) (indicate date for each review)	☐ None 12/24/2015 DNDAPI/Branch II: 12/21/2015 DNDP II/ Branch IV: 12/24/2015 OPF//Branch V: 12/21/2015 OPQ/DB/Branch II: 11/19/2015
❖ Reviews by other disciplines/divisions/Centers requested by product quality review team (indicate date of each review)	☒ None
❖ Environmental Assessment (check one) (original and supplemental applications)	
☒ Categorical Exclusion (indicate review date)(all original applications and all efficacy supplements that could increase the patient population)	12/23/2015
☐ Review & FONSI (indicate date of review)	
☐ Review & Environmental Impact Statement (indicate date of each review)	
❖ Facilities Review/Inspection	
☒ Facilities inspections (action must be taken prior to the re-evaluation date) (only original applications and efficacy supplements that require a manufacturing facility inspection(e.g., new strength, manufacturing process, or manufacturing site change)	☒ Acceptable Re-evaluation date: ☐ Withhold recommendation ☐ Not applicable

Day of Approval Activities	
❖ For all 505(b)(2) applications: Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity)	☐ No changes ☐ New patent/exclusivity (<i>Notify CDER OND IO</i>)
Finalize 505(b)(2) assessment	☐ Done
❖ For Breakthrough Therapy (BT) Designated drugs: Notify the CDER BT Program Manager	☐ Done (<i>Send email to CDER OND IO</i>)
❖ For products that need to be added to the flush list (generally opioids): Flush List Notify the Division of Online Communications, Office of Communications	☐ Done
❖ Send a courtesy copy of approval letter and all attachments to applicant by fax or secure email	☒ Done
❖ If an FDA communication will issue, notify Press Office of approval action after confirming that applicant received courtesy copy of approval letter	☐ Done
❖ Ensure that proprietary name, if any, and established name are listed in the <i>Application Product Names</i> section of DARRTS, and that the proprietary name is identified as the “preferred” name	☐ Done
❖ Ensure Pediatric Record is accurate	☐ Done
❖ Send approval email within one business day to CDER-APPROVALS	☒ Done



IND 106585

MEETING MINUTES

Takeda Development Center Americas, Inc.
Attention: Valerie Tews, RAC
Manager, Regulatory Affairs Strategy
One Takeda Parkway
Deerfield, IL 60015

Dear Ms. Tews:

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

We also refer to the telecon between representatives of your firm and the FDA on July 9, 2014. The purpose of the meeting was to discuss the quality section of the NDA.

A copy of the official minutes of the telecon is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 796-3877.

Sincerely,

{See appended electronic signature page}

Cathy Tran-Zwanetz
Office of Pharmaceutical Quality
Office of Drug Evaluation
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type: B
Meeting Category: Pre-NDA

Meeting Date and Time: September 3, 2014, 1:00 PM- 2:00 PM
Meeting Location: Tele-conference

Application Number: IND 106858
Product Name: Dexlansoprazole
Indication: Symptomatic non-erosive gastroesophageal reflux disease, maintenance of healed erosive esophagitis and relief of heartburn
Sponsor Name: Takeda Development Center Americas, Inc.

Meeting Chair: Marie Kowblansky, Ph.D.
Meeting Recorder: Cathy Tran-Zwanetz

FDA ATTENDEES

Marie Kowblansky, Ph.D., CMC Lead
Tapash Ghost, Ph.D., Biopharmaceutical Lead
Cathy Tran-Zwanetz, Regulatory Project Manager

SPONSOR ATTENDEES

Jennifer Stanek, Director, Global Regulatory Affairs CMC
Nancianne Knipfer, Director, Global Regulatory Affairs
Haiyan Grady, Fellow, Pharmaceutical Sciences
Michael Kukulka, Sr. Clinical Pharmacologist
Takako Ono, Researcher, Analytical Development Laboratories

1.0 BACKGROUND

Takeda has previously sought advice on the development program of the dexlansoprazole ODT formulation. A Type B, Pre-IND Meeting was held with the Agency on 03 March 2010 after the completion of a pilot BA study [Study TAK-390MR(OD)_101] which demonstrated that ODT Formulations A and B were not bioequivalent to the capsule. Following the meeting, Takeda began reformulation work, selecting new ODT formulations to study clinically. After the completion of study [TAK-390MR\(OD\)_102](#), a Type C Meeting was scheduled for 07 February 2012 to gain agreement with the Agency on the development plan and regulatory path to approval for a dexlansoprazole ODT. However, on 03 February 2012 the meeting was cancelled based on the Preliminary Written Comments received from the Agency. Based on the Agency's

advice contained in the preliminary comments, additional studies to support the registration of the dextansoprazole ODT formulation were conducted. Additional studies were conducted to support the administration with food (TAK-390MR(OD)_103), the PK/PD profile (TAK-390MR(OD)_105), alternate administration options (TAK-390MR(OD)_106) and an assessment of the disintegration time (TAK-390MR(OD)_107). Also, Study TAK-390MR(OD)_104 is currently on-going; and the purpose of the study is to evaluate the relative bioavailability of two 30 mg dextansoprazole ODTs to one 60 mg dextansoprazole capsule. Study TAK-390MR(OD)_105 confirmed that a dextansoprazole 30 mg ODT is bioequivalent to a dextansoprazole 30 mg capsule. The purpose of this meeting is to discuss the quality control session of the NDA. FDA sent Preliminary Comments to Takeda on August 29, 2014.

2. DISCUSSION

1. Takeda proposes the following tests (Table 10.a) for dextansoprazole delayed release orally disintegrating tablets (ODT). The justification for the tests and acceptance criteria is provided in Section 11.2. Does the Agency agree with Takeda's proposed specification for dextansoprazole ODT for both release and stability?

FDA RESPONSE: Based on the information provided in your meeting package, we find the proposed drug product specification reasonable, but you will need to add disintegration time and moisture content to the release and stability specifications, unless you can adequately justify that these are not necessary. With regard to disintegration testing, we note that your proposed acceptance criterion is a disintegration time of < (b) (4) seconds (using the USP test), yet the in vitro disintegration time for your ODT tablets on stability testing ranged between 29 and 36 seconds. In view of these data, an acceptance criterion of < (b) (4) seconds is more appropriate than the (b) (4) seconds that you propose. With regard to your dissolution specification, we prefer to see the drug release not less than (b) (4) % at 60 minutes instead of your proposed (b) (4) minutes. And finally, please note that your proposed specification will be further evaluated in the context of your full NDA submission.

DISCUSSION:

The agency concern regarding moisture was its effect on disintegration and degradation of the product. Regarding moisture, FDA recommendation is to at least have an initial specification at release. A specification on stability may not be required due to the packaging. The applicant will propose a limit based on available data upon NDA filing. If the sponsor believes such a specification is not required on stability testing, data driven justification needs to be provided.

FDA agrees to add dissolution test at release and stability. Final specification will be justified based on all available data at time of filing. FDA has agreed, we will be flexible on the 30 seconds limit which is in the guidance.

All agree that in general FDA's recommendation on moving dissolution time point from (b) (4) 60 minutes but there will be new data available at time of filing and they may make changes based on that data.

2. Takeda has developed a dissolution method for the ODT product for both release and stability testing. The dissolution method description and justifications are provided in Section 11.3. Does the Agency agree that Takeda's proposed dissolution method is appropriate for testing product quality at both release and on stability?

FDA RESPONSE: Your dissolution method appears reasonable. Note that the final determination on the acceptability of the dissolution method is a review issue that can be determined during the IND or NDA. However, the acceptability of the proposed dissolution criterion for your product will be made during the NDA review process based on the totality of the provided dissolution data.

As a delayed-release product, the potential impact of alcohol induced dose dumping should be evaluated. Please conduct an in vitro alcohol dose dumping study in 0.1 N HCl dissolution media (representing acid-stage) containing 0%, 5%, 10%, 20% and 40% alcohol. Dissolution data should be generated from 12 dosage units (n=12) at multiple time points to obtain a complete dissolution profile. The shape of the dissolution profiles should be compared to determine if the delayed release characteristics are maintained. The f2 values assessing the similarity (or lack thereof) between the dissolution profiles should be estimated (using 0% alcohol as the reference). The report with the complete data (i.e., individual, mean, SD, comparison plots, f2 values, etc.) collected during the evaluation of the in vitro alcohol induced dose dumping study should be provided to FDA for review and comments.

Discussion:

The sponsor agrees to perform the recommendation dissolution test with alcohol. Dissolution will only be performed in .1 normal acid and F2 may not be applicable in this case but will depend on the data.

3. Dexlansoprazole delayed release ODT is designed as an orally disintegrating tablet, in terms of both the formulation and the manufacturing process. The characteristics of dexlansoprazole ODT were examined using in vitro and in vivo methods, including tests for disintegration time and administration acceptability. The in vitro and in vivo test results support the ODT designation for the product. Additional information is provided in Section 11.4. Does the Agency agree with Takeda's proposal for the dexlansoprazole ODT designation?

FDA RESPONSE: We agree with the designation of your product as an Orally Disintegrating Tablet, provided that the specification includes the < ^(b)₍₄₎ second acceptance criterion for in-vitro disintegration time.

Discussion; See Discussion from question 1, FDA will be reasonably flexible regarding the disintegration time.

(b) (4)

product. The relationships between multiple process parameters have been established for the dexlansoprazole delayed release ODT (b) (4). Development studies have shown (b) (4)

information is provided in Section 11.5. Does the Agency agree with Takeda's proposal to (b) (4) control tests?

FDA RESPONSE: No, we do not agree. Disintegration testing needs to be included in the drug product specification and tested at release and as part of your stability protocol. (b) (4) testing will also be required, but may remain as in-process controls.

Discussion:
No additional comments

5. For the dexlansoprazole delayed release orally disintegrating tablet NDA submission, Takeda would like to cross-reference to NDA 22-287 eCTD Sections 2.3.S and 3.2.S. These sections contain information on the dexlansoprazole drug substance, which is the active component of the ODT drug product. Also refer to Section 11.6. Does the Agency agree with Takeda's proposal to cross-reference to NDA 22-287 for the dexlansoprazole drug substance (Module 2.3.S and Module 3.2.S) for the dexlansoprazole ODT NDA?

FDA RESPONSE: Yes. It is acceptable for you to cross reference another NDA for all information regarding the drug substance. However, we request that you identify the drug substance manufacturing and testing sites and include the drug substance specification in the ODT NDA.

Discussion: No additional comments

ADDITIONAL FDA COMMENTS:

We are concerned that the enteric coating of your dexlansoprazole DR ODT may dissolve in the buccal cavity at saliva pH > 5.5 and dexlansoprazole may be released in the mouth. As a consequence, uncoated acid-labile dexlansoprazole may reach the stomach, get degraded and the proposed delayed release action of dexlansoprazole may be defeated. Please address our concerns.

Discussion:

The FDA has agreed that the applicant's approach to address the FDA's concern is reasonable, the actual data will be reviewed at the time the NDA is submitted. The sponsor has clinical data to address the FDA's concern of the tablet disintegrating in the mouth and will provide it during the NDA filing. Sponsor will do the alcohol interaction study to address the potential dose

dumping in the buffer stage will provide in NDA filing. FDA will be open to reviewing the sponsors protocol and data prior to filing.

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/s/

CATHERINE A TRAN-ZWANETZ
09/29/2015



NDA 208056

INFORMATION REQUEST

Takeda Development Center Americas, Inc.
Attention: Valerie Tews, RAC
Manager, Global Regulatory Affairs
One Takeda Parkway
Deerfield, IL 60015

Dear Ms. Tews:

Please refer to your New Drug Application (NDA) dated March 26, 2015, received March 26, 2015, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Dexilant SoluTab (dexlansoprazole delayed-release orally disintegrating tablet), 30 mg.

We are reviewing your application and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

1. In study TAK-390MR(OD)_103, administration of 30 mg dexlansoprazole orally disintegrating tablets with food (fed condition) reduced the C_{max} by 38%, and administration of 30 mg orally disintegrating tablets on the tongue without water, followed by administration of 240 mL of water reduced dexlansoprazole AUC by approximately 20% and C_{max} by 29%. Intragastric pH was not measured in this study. Based on the results of this study, you are proposing that dexlansoprazole orally disintegrating tablets can be taken without regard to food and with and without water in the proposed label. Provide supporting data that these lower exposures of dexlansoprazole are acceptable.
2. In the Clinical Summary of Safety, module 2.7.4 of your submission dated March 26, 2015, narratives were provided for two subjects (USUBJID TAK-390MR(OD)_105-6001-201 and TAK-390MR(OD)_106-7001-095) who experienced elevated creatinine phosphokinase (CPK) after administration of dexlansoprazole 30 mg orally disintegrating tablets. We note that these two reports are consistent with two reports of elevated CPK included in the Periodic Safety Update Report for Dexilant (NDA 22287), dated March 27, 2015. We are trying to better understand whether the events of elevated CPK could be related to the drug. The narrative for subject TAK-390MR(OD)_105-6001-201 states that he also experienced elevation of ALT and AST and that the changes were probably related to exercise. The narrative for subject TAK-390MR(OD)_106-7001-095 states that

this subject had no concomitant medications noted and no clinically significant abnormalities on ECG, physical exam, or vital signs.

Based on the information provided in the narratives, it is not clear that the elevated CPK was unrelated to the drug. Therefore, provide any additional available information for these two patients (e.g., type and duration of exercise, concomitant medications, including over-the-counter or supplements, or co-morbid medical conditions). Also include any reports of elevated CPK associated with use of the Dexilant delayed-release capsules that may have been reported since the last PSUR submission, dated March 27, 2015.

If you have any questions, please contact Maureen Dewey, Senior Regulatory Project Manager, at (301) 796-0845.

Sincerely,

{See appended electronic signature page}

Kevin Bugin, MS, RAC
Acting, Chief Project Management Staff
Division of Gastroenterology and Inborn
Errors Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

KEVIN B BUGIN
08/27/2015



DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

NDA 208056

**PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE**

Takeda Pharmaceuticals U.S.A., Inc.
One Takeda Parkway
Deerfield, IL 60015

ATTENTION: Valerie Tews, RAC
Manager, Global Regulatory Affairs

Dear Ms. Tews:

Please refer to your New Drug Application (NDA) dated and received March 26, 2015, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Dexlansoprazole Orally Disintegrating Tablets, 30 mg.

We also refer to your correspondence dated and received May 1, 2015, requesting review of your proposed proprietary name, Dexilant SoluTab.

We have completed our review of the proposed proprietary name, Dexilant SoluTab and have concluded that it is conditionally acceptable.

If any of the proposed product characteristics as stated in your May 1, 2015, submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you require information on submitting requests for proprietary name review or PDUFA performance goals associated with proprietary name reviews, we refer you to the following:

- Guidance for Industry Contents of a Complete Submission for the Evaluation of Proprietary Names
(<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075068.pdf>)
- PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2013 through 2017,
(<http://www.fda.gov/downloads/ForIndustry/UserFees/PrescriptionDrugUserFee/UCM270412.pdf>)

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Aleksander Winiarski, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-5295. For any other information regarding this application, contact Maureen Dewey, Regulatory Project Manager in the Office of New Drugs, at (301) 796-0845.

Sincerely,

{See appended electronic signature page}

Todd Bridges, RPh
Director
Division of Medication Error Prevention and Analysis
Office of Medication Error Prevention and Risk Management
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

TODD D BRIDGES
07/27/2015



NDA 208056

**FILING COMMUNICATION –
NO FILING REVIEW ISSUES IDENTIFIED**

Takeda Development Center Americas, Inc.
Attention: Valerie Tews, RAC
Manager, Global Regulatory Affairs
One Takeda Parkway
Deerfield, IL 60015

Dear Ms. Tews:

Please refer to your New Drug Application (NDA) dated March 26, 2015, received March 26, 2015 submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA), for Dexilant SoluTab (dexlansoprazole), delayed-release orally disintegrating tablets, 30 mg.

We also refer to your amendments dated May 1, May 4, May 15 and May 21, 2015.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is **Standard**. Therefore, the user fee goal date is January 26, 2016.

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, mid-cycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing commitment requests by December 9, 2015.

At this time, we are notifying you that, we have not identified any potential review issues. Please note that our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review.

We request that you submit the following information by July 15, 2015:

1. Provide the following information for the proposed in-process controls located in Table 2 in Section p.3.4.1 (Controls of Critical Steps and Intermediate):
 - A. In-process method/procedures and, if appropriate, method validation reports. If you have already submitted this information, please specify the location.
 - B. In-process sampling details for the tablets and for the enteric coated microgranules (b) (4) including a general plan for locations and frequency.
 - C. Correlation (in graphic format) (b) (4)
(b) (4)
ensure final drug product quality.
2. Provide sampling and analysis details for the testing results of (b) (4) and (b) (4) described in Section 3.2. P.2.3 (Manufacturing Process Development).
3. (b) (4)
4. You have stated (in Section 3.2.P.3.3 Description of Manufacturing Process and Process Controls) (b) (4)
(b) (4)
5. Since the (b) (4)
(b) (4) please provide an amendment that includes a description for the packaging process in Section 3.2. P.3.3. Also provide the executed batch record for packaging of a registration batch.
6. Provide actual finished drug product samples from the registration batches.
7. We acknowledge that you performed microbial limit testing using USP <61> and <62> methods and all results were in compliance with the acceptance criteria specified in USP <1111> for oral tablets. However, no microbial tests are proposed for future commercial batches. We remind you that if you propose to waive microbial limit test, you will need to address the issues listed below:
 - A. Identify and justify critical control points in the manufacturing process that could affect microbial load of the drug product. Specifically, you will need to:

- B. Describe microbiological monitoring and acceptance criteria for the critical control points that you have identified above. Conformance to the acceptance criteria established for each critical control point should be documented in the batch record in accordance with 21 CFR 211.188.
- C. Describe activities taken when microbiological acceptance criteria are not met at control points.
- D. In addition, you will need to minimally perform microbial limits testing at the initial stability testing time point. Provide an updated specification and stability schedule to reflect this testing.

Alternatively, you have the option to perform the microbial test for commercial batches, at release and during stability monitoring. We recommend that you continue to follow USP <1111>, and USP <61> and <62> for acceptance criteria and test methods.

PRESCRIBING INFORMATION

Your proposed prescribing information (PI) must conform to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57. As you develop your proposed PI, we encourage you to review the labeling review resources on the [PLR Requirements for Prescribing Information](#) website including:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products
- Regulations and related guidance documents
- A sample tool illustrating the format for Highlights and Contents
- The Selected Requirements for Prescribing Information (SRPI) – a checklist of 42 important format items from labeling regulations and guidances and
- FDA's established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

At the end of labeling discussions, use the SRPI checklist to ensure that the PI conforms with format items in regulations and guidances.

Please respond only to the above requests for 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.

PROMOTIONAL MATERIAL

You may request advisory comments on proposed introductory advertising and promotional labeling. Please submit, in triplicate, a detailed cover letter requesting advisory comments (list each proposed promotional piece in the cover letter along with the material type and material identification code, if applicable), the proposed promotional materials in draft or mock-up form with annotated references, and the proposed package insert (PI), Medication Guide, and Instructions for Use. Submit consumer-directed, professional-directed, and television advertisement materials separately and send each submission to:

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

Do not submit launch materials until you have received our proposed revisions to the package insert (PI), Medication Guide, and Instructions for Use, and you believe the labeling is close to the final version.

For more information regarding OPDP submissions, please see <http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm>. If you have any questions, call OPDP at 301-796-1200.

REQUIRED PEDIATRIC ASSESSMENTS

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

Pediatric studies conducted under the terms of section 505B of the Federal Food, Drug, and Cosmetic Act (the Act) may also qualify for pediatric exclusivity under the terms of section 505A of the Act. If you wish to qualify for pediatric exclusivity please consult Division of Gastroenterology and Inborn Errors Products. Please note that satisfaction of the requirements in section 505B of the Act alone may not qualify you for pediatric exclusivity under 505A of the Act.

We acknowledge receipt of your request for a partial waiver of pediatric studies for this application. Once we have reviewed your request, we will notify you if the partial waiver request is denied.

We acknowledge receipt of your request for a partial deferral of pediatric studies for this application. Once we have reviewed your request, we will notify you if the partial deferral request is denied.

If you have any questions, call Maureen Dewey, Senior Regulatory Project Manager, at (301) 796-0845.

Sincerely,

{See appended electronic signature page}

Andrew E. Mulberg, M.D., FAAP, CPI
Deputy Director
Division of Gastroenterology and Inborn Errors
Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

ANDREW E MULBERG
06/08/2015



NDA 208056

NDA ACKNOWLEDGMENT

Takeda Development Center Americas, Inc.
Attention: Valerie Tews, RAC
Manager, Global Regulatory Affairs
One Takeda Parkway
Deerfield, IL 60015

Dear Ms. Tews:

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

Name of Drug Product: Dexilant (dexlansoprazole delayed-release orally disintegrating tablets), 30 mg

Date of Application: March 26, 2015

Date of Receipt: March 26, 2015

Our Reference Number: NDA 208056

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 May 25, 2015, 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/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>. 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 conform to the content and format requirements of revised 21 CFR 201.56-57.

You are also responsible for complying with the applicable provisions of sections 402(i) and 402(j) of the Public Health Service Act (PHS Act) [42 USC §§ 282 (i) and (j)], which was amended by Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law No. 110-85, 121 Stat. 904).

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

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

Secure email between CDER and applicants is useful for informal communications when confidential information may be included in the message (for example, trade secrets or patient information). If you have not already established secure email with the FDA and would like to set it up, send an email request to SecureEmail@fda.hhs.gov. Please note that secure email may not be used for formal regulatory submissions to applications.

If you have any questions, call me, Regulatory Project Manager, at (301) 796-0845.

Sincerely,

{See appended electronic signature page}

Maureen Dewey, M.P.H.
Senior Regulatory Health Project Manager
Division of Gastroenterology and Inborn
Errors Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

MAUREEN D DEWEY
04/09/2015



IND106858

**MEETING REQUEST-
WRITTEN RESPONSES**

Takeda Development Center Americas, Inc.
Attention: Valerie Tews
One Takeda Parkway
Deerfield, IL 60015

Dear Ms. Tews:

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

We also refer to your submission dated December 4, 2014, containing a Type C meeting request. The purpose of the requested meeting was to discuss the content, organization and format of the Dexlansoprazole delayed-release orally disintegrating tablets NDA in eCTD format.

Further reference is made to our Meeting Granted letter dated December 24, 2014, wherein we stated that written responses to your questions would be provided in lieu of a meeting.

The enclosed document constitutes our written responses to the questions contained in your December 4, 2014 background package.

If you have any questions, call me, at (301) 796-0845.

Sincerely,

{See appended electronic signature page}

Maureen Dewey, M.P.H.
Senior Regulatory Health Project Manager
Division of Gastroenterology and Inborn Errors
Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure:
Written Responses



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

WRITTEN RESPONSES

Meeting Type:	C
Meeting Category:	Guidance
Application Number:	IND106858
Product Name:	Dexlansoprazole delayed-release orally disintegrating tablets
Indication:	(b) (4) b) maintaining healing of EE and relief of heartburn for up to 6 months. c) treating heartburn associated with symptomatic non-erosive gastroesophageal reflux disease (GERD) for four weeks.
Sponsor/Applicant Name:	Takeda Development Center Americas, Inc.
Regulatory Pathway:	505(b)1

1.0 BACKGROUND

A Type B, Pre-IND Meeting was held on March 3, 2010 after the completion of a pilot bioavailability (BA) study which demonstrated that ODT Formulations A and B were not bioequivalent to the capsule. A reformulation for a new ODT formulation was conducted.

IND 106858 became active on July 27, 2011.

A Type C Meeting was scheduled for February 7, 2012 to discuss the development plan and regulatory path for Dexlansoprazole ODT. However, on February 3, 2012 the meeting was cancelled by the sponsor based on the receipt of FDA's Preliminary Written Comments.

A CMC Type B, Pre-NDA meeting was requested on July 9, 2014 and Preliminary Written Comments were issued on August 29, 2014. The meeting was held on September 3, 2014.

FDA notified the sponsor on December 11, 2014 that the review of the November 19, 2014 submission containing an agreed initial Pediatric Study Plan was complete.

On December 4, 2014, the sponsor submitted a Type C meeting request to discuss the content, organization and format of the Dexlansoprazole delayed-release orally disintegrating tablets NDA in eCTD format. The meeting was granted on December 24, 2014 and sponsor was notified that Written Responses would be provided in lieu of a meeting.

The NDA for dexlansoprazole 30 mg ODT is planned for March 2015.

2.0 QUESTIONS AND RESPONSES

Clinical (Datasets)

Question 1

Takeda plans to provide the integrated safety datasets for the 6 Phase 1 studies included in the safety analyses, and not study level datasets for the individual studies, in the SAS XPORT transport format (Version 5). The integrated dataset files will contain subject demographic characteristics, treatment assignments, exposure, and adverse event data. All variables used in the integrated analyses, variables used in the calculations of the analysis variables, and variables indicating whether an observation is used in a particular analysis, and other variables will be included as appropriate. These integrated datasets will be structured in a CDISC ADaM-like model. Does FDA agree with the safety integrated analysis dataset approach?

FDA Response:

No, we do not agree with your proposed approach to submit only the integrated safety datasets. You also need to submit all study-level datasets utilized in the integration, along with their corresponding metadata file (i.e., define.xml) for each of the six phase 1 studies.

We agree with the proposed ADaM-like format for the integrated safety datasets; however, details regarding how the integration was implemented need to be included in the reviewer's guide that will accompany the define.xml file for the integrated safety datasets.

Question 2

In addition to the integrated datasets, a define.xml document and reviewer's guide will be provided in support of the integrated safety datasets. Does FDA agree with the documentation approach?

FDA Response:

Yes, we agree. Please also submit a define.pdf file for printing purposes unless you are planning to submit a define.xml v2.0 file. For details pertaining to the Analysis Data Reviewer's Guide (ADRG), refer to the recently published Study Data Technical Conformance Guide (<http://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/default.htm>).

Nonclinical

Question 3

As described in [Section 11.2.1.5](#) and [Appendix 1](#) of the CMC Pre-NDA Information Package submitted 01 August 2014 in Sequence No. 0035 for the meeting held 03 September 2014, Takeda has concluded that (b) (4) should not be controlled according to ICH M7 ([Appendix 1](#)). Does the Agency agree with Takeda's assessment for the (b) (4) impurity as described in Appendix 1?

FDA Response:

No, we do not agree with your assessment of the mutagenic potential of (b) (4). Specifically, we do not agree with your conclusion that your (Q)SAR (*in silico*) analysis results were indicative of a negative prediction for mutagenicity. However, given that the API (dexlansoprazole) is known to be mutagenic and the close structural relationship between (b) (4), it is acceptable to control the (b) (4) impurity level in Dexlansoprazole Delayed-Release ODT based on the recommendations in ICH guidance Q3B(R2).

We note that the applicable qualification threshold for impurities in your product is (b) (4) %, which would allow for a maximum daily intake of (b) (4) mcg, as recommended by ICH Q3B(R2). If you propose a limit for (b) (4) that allows for exposure greater than (b) (4) mcg/day, the qualification of (b) (4) would depend on the results of your 4-week toxicity study of TAK-390 and (b) (4) in rats.

Regulatory

Question 4

Takeda plans to include the new 4-week toxicity study that supports the qualification of the (b) (4) impurity in Module 4. Takeda plans to provide a cross-reference to the dexlansoprazole delayed release capsule NDA 022287 for all other nonclinical studies to support the dexlansoprazole delayed-release ODT NDA. Takeda will also summarize the results from the 4-week study in the appropriate Module 2 documents. Does the Agency agree with Takeda's strategy for the nonclinical cross-referencing?

FDA Response:

Your proposal appears to be acceptable. In your dexlansoprazole ODT NDA, you should clearly indicate which nonclinical studies were submitted under NDA 22287 and the dates of submission.

Your options of cross-referencing information submitted to another application would be to either place a cross-reference document under module m1.4.4 (cross reference to other applications), or use cross-application links.

1. To use the first option (placing a cross-reference document in m1.4.4), a table formatted document can be submitted in Section 1.4.4 of the eCTD, detailing previously submitted information (eCTD and/or non- eCTD) that is being referenced by the current application. The information in the document should include (1) the application number, (2) the date of submission (e.g., letter date), (3) the file name, (4) the page number (if necessary), (5) the eCTD sequence number, (6) the eCTD heading location (e.g., m3.2.p.4.1 Control of Excipients – Specifications), (7) the document leaf title, and (8) the submission identification (e.g., submission serial number, volume number, electronic folder, file name, etc.) of the referenced document along with a hypertext link to the location of the information, when possible.

2. To use the second option (cross-application links), both applications would need to be in eCTD format. The applications need to include the appropriate prefix in the href links (e.g. nda, ind). In the leaf titles of the documents, it is recommended that the leaf title indicate the word “cross reference to” and the application number (e.g. Cross Ref to NDAXXX). The cross-reference information in the leaf title allows the reviewer to know that the document resides in another application.

Prior to using cross application linking in an application, it is recommended that you submit an "eCTD cross application links" sample, to ensure successful use of cross-application links.

To submit an eCTD cross-application links sample, you would need to request two sample application numbers from the [ESUB team - esub@fda.hhs.gov](mailto:esub@fda.hhs.gov). For more information on eCTD sample, please refer to the Sample Process web page which is located at <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm174459.htm>

3.0 DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

As stated in our December 24, 2014 communication granting this meeting, if, at the time of submission, the application that is the subject of this meeting is for a new molecular entity or an original biologic, the application will be subject to “the Program” under PDUFA V. Therefore, at this meeting be prepared to discuss and reach agreement with FDA on the content of a complete application, including preliminary discussions on the need for risk evaluation and mitigation strategies (REMS) or other risk management actions. You and FDA may also reach agreement on submission of a limited number of minor application components to be submitted not later than 30 days after the submission of the original application. These submissions must be of a type that would not be expected to materially impact the ability of the review team to begin its review. All major components of the application are expected to be included in the original application and are not subject to agreement for late submission.

Discussions and agreements will be summarized at the conclusion of the meeting and reflected in FDA’s meeting minutes. If you decide to cancel this meeting and do not have agreement with FDA on the content of a complete application or late submission of any minor application components, your application is expected to be complete at the time of original submission.

In addition, we remind you that the application is expected to include a comprehensive and readily located list of all clinical sites and manufacturing facilities.

Finally, in accordance with the PDUFA V agreement, FDA has contracted with an independent contractor, Eastern Research Group, Inc. (ERG), to conduct an assessment of the Program. ERG will be in attendance at this meeting as silent observers to evaluate the meeting and will not participate in the discussion. Please note that ERG has signed a non-disclosure agreement.

Information on PDUFA V and the Program is available at
<http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm272170.htm>.

PREA REQUIREMENTS

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

Please be advised that under the Food and Drug Administration Safety and Innovation Act (FDASIA), you must submit an Initial Pediatric Study Plan (PSP) within 60 days of an End of Phase (EOP2) meeting. In the absence of an End-of-Phase 2 meeting, refer to the draft guidance below. The PSP must contain an outline of the pediatric study or studies that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation, and any previously negotiated pediatric plans with other regulatory authorities. The PSP should be submitted in PDF and Word format.

For additional guidance on the timing, content, and submission of the PSP, including a PSP Template, please refer to the draft guidance for industry, *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans* at: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM360507.pdf>. In addition, you may contact the Division of Pediatric and Maternal Health at 301-796-2200 or email pdit@fda.hhs.gov. For further guidance on pediatric product development, please refer to: <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm>.

PRESCRIBING INFORMATION

In your application, you must submit proposed prescribing information (PI) that conforms to the content and format regulations found at 21 [CFR 201.56\(a\) and \(d\)](#) and [201.57](#). As you develop your proposed PI, we encourage you to review the labeling review resources on the [PLR Requirements for Prescribing Information](#) website including:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products
- Regulations and related guidance documents
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) – a checklist of 42 important format items from labeling regulations and guidances.

Prior to submission of your proposed PI, use the SRPI checklist to ensure conformance with the format items in regulations and guidances.

MANUFACTURING FACILITIES

To facilitate our inspectional process, we request that you clearly identify *in a single location*, either on the Form FDA 356h, or an attachment to the form, all manufacturing facilities associated with your application. Include the full corporate name of the facility and address where the manufacturing function is performed, with the FEI number, and specific manufacturing responsibilities for each facility.

Also provide the name and title of an onsite contact person, including their phone number, fax number, and email address. Provide a brief description of the manufacturing operation conducted at each facility, including the type of testing and DMF number (if applicable). Each facility should be ready for GMP inspection at the time of submission.

Consider using a table similar to the one below as an attachment to Form FDA 356h. Indicate under Establishment Information on page 1 of Form FDA 356h that the information is provided in the attachment titled, “Product name, NDA/BLA 012345, Establishment Information for Form 356h.”

Site Name	Site Address	Federal Establishment Indicator (FEI) or Registration Number (CFN)	Drug Master File Number (if applicable)	Manufacturing Step(s) or Type of Testing [Establishment function]
1.				
2.				

Corresponding names and titles of onsite contact:

Site Name	Site Address	Onsite Contact (Person, Title)	Phone and Fax number	Email address
1.				
2.				

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

/s/

MAUREEN D DEWEY
02/13/2015



IND106858

MEETING PRELIMINARY COMMENTS

Takeda Global Research & Development Center, Inc.
Attention: Valerie Tews, RAC
Regulatory Strategy Product Manager
One Takeda Parkway
Deerfield, Illinois 60015

Dear Ms. Tews:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Dexilant (dexlansoprazole) delayed-release orally disintegrating tablets.

We also refer to your November 2, 2011, correspondence, received November 2, 2011, requesting a meeting to discuss development plans for a dexlansoprazole delayed-release orally disintegrating tablet formulation.

This material consists of our preliminary responses to your questions and any additional comments in preparation for the discussion at the teleconference scheduled for February 7, 2012 between Takeda and the Division of Gastroenterology and Inborn Errors Products. We are sharing this material to promote a collaborative and successful discussion at the meeting. The meeting minutes will reflect agreements, important issues, and any action items discussed during the meeting and may not be identical to these preliminary comments following substantive discussion at the meeting. However, if these answers and comments are clear to you and you determine that further discussion is not required, you have the option of cancelling the meeting (contact the regulatory project manager (RPM)). If you choose to cancel the meeting, this document will represent the official record of the meeting. If you determine that discussion is needed for only some of the original questions, you have the option of reducing the agenda and/or changing the format of the meeting (e.g., from face to face to teleconference). It is important to remember that some meetings, particularly milestone meetings, can be valuable even if the premeeting communications are considered sufficient to answer the questions. Note that if there are any major changes to your development plan, the purpose of the meeting, or the questions based on our preliminary responses, we may not be prepared to discuss or reach agreement on such changes at the meeting although we will try to do so if possible. If any modifications to the development plan or additional questions for which you would like CDER feedback arise before the meeting, contact the RPM to discuss the possibility of including these items for discussion at the meeting.

Clinical

1. The results from Takeda Study TAK-390MR(OD)_102 indicate that the dexlansoprazole 30 mg ODT Formulation Z achieved plasma dexlansoprazole exposure similar to the 30 mg dexlansoprazole capsule, as measured by AUC values. The 90% CIs for both AUC(0-t_{lqc}) and AUC(0-inf) were within the 0.80 to 1.25 equivalence range. The point estimate for dexlansoprazole C_{max} indicated that administration of the ODT Formulation Z resulted in a dexlansoprazole C_{max} central value that was 24% higher than that from the 30 mg capsule, which is the closest to the C_{max} of capsule among the three ODT formulations. The mean C_{max} value for the 30 mg ODT, Formulation Z (837 ng/mL), however, is less than the mean dexlansoprazole C_{max} following administration of the 60 mg dexlansoprazole capsule (1290 ng/mL). ODT Formulation Z was well-tolerated in Study TAK-390MR(OD)_102.

Based on the results of the TAK-390MR(OD)_102 study, Takeda plans to conduct a definitive food effect study, Study TAK-390MR(OD)_103 using Formulation Z.

Does the Agency agree that Studies TAK-390MR(OD)_102 and TAK-390MR(OD)_103 can support filing an NDA for dexlansoprazole delayed-release orally disintegrating tablets?

FDA Response:

From a clinical pharmacology standpoint, the proposed two studies (i.e., a relative bioavailability study and a food effect study) can support filing of an NDA. Nonetheless the adequacy of the study results will be determined at the time of NDA review. We note that the mean concentration-time profile of your product is different from that of dexlansoprazole capsule by having only one peak and lower plasma concentrations after 6 hours post-dose. You should provide a justification for why this difference will not significantly affect the efficacy of ODT. In your food effect study, we recommend that the effect of concomitant water be assessed since patients may want to rinse their mouth with water.

(b) (4)

We recommend that you evaluate the relative bioavailability between two 30 mg ODT and 60 mg Dexlansoprazole capsule to inform the safety evaluation.

2. The current ODT formulations X, Y and Z have a tablet weight of more than 500 mg. According to FDA's Guidance for Industry, Orally Disintegrating Tablets"[3], Takeda intends to use supporting data to justify the tablet weight. After receiving advice from the Agency on 20 May 2011, Takeda has been generating the supportive data. As part of Study TAK-390MR(OD)_102, a subject questionnaire was included to assess the tablet acceptability with respect to flavor, texture, and overall taste of the ODT formulations. Additionally, subjects were asked if they would take this product on a daily basis for 4 to 8 weeks. The rating scale was 1 (disliked very much) to 5 (liked very much). An average score of 4 or better was achieved for the ODT formulations in each of the categories. An actual usage study will be conducted in a questionnaire format in the upcoming Study TAK-390MR(OD)_103.

Separately, Takeda will also perform an *in vivo* disintegration test using a professional panel to measure the disintegration time on the tongue.

Are these evaluations acceptable to justify the tablet weight?

FDA Response:

No, in addition to your proposed *in vivo* disintegration test and patient questionnaire, you should also add an *in vitro* disintegration test to your product specification. For the patient questionnaire, you may also consider including a crude measure of tablet residue, such as estimating the amount of water needed to clear residue from mouth.

Chemistry, Manufacturing, and Controls

3. DEXILANT (dexlansoprazole) delayed-release capsules in its primary packaging have demonstrated excellent stability at room temperature. If the dexlansoprazole delayed release ODT product is as stable, Takeda proposes to submit 9-month stability data (b) (4) and the data from accelerated and intermediate conditions in the NDA, per ICH Guidance “Q1C Stability Testing for New Dosage Forms”[4].
 - a. Does the Agency agree that filing the Original NDA with 9-month stability data is acceptable?

FDA Response:

Yes, it is acceptable to submit your application with only 9 months of data. (See additional comments below.)

- b. Does the Agency agree that Takeda may update the stability data to 12 months while the Original NDA is under review?

FDA Response:

Yes, you may update the NDA with additional data, but it must be submitted no later than at the midpoint of the review clock (5 months after submission) for it to be considered in expiration dating your product.

- c. Does the Agency agree with Takeda's proposed (b) (4) month product expiration, if the stability data meets all acceptance criteria at long-term for 9 months and 12 months (data updated during review)?

FDA Response:

No, we do not agree. Although it is possible that a (b) (4) month expiration will be appropriate, the acceptability of your proposal will depend on the trends that are observed in the submitted stability data. Data from both long term and accelerated storage will need to be considered.

- d. (b) (4)

Is this proposal acceptable to the Agency?

FDA Response:

Yes, it is acceptable for you to store your stability samples (b) (4)

4. Takeda plans to manufacture NDA stability batches as provided in the ICH Guidance "Q1A (R2) Stability Testing of New Drug Substances and Products (Selection of Batches, Section 2.2.3)"[5]. Takeda plans to manufacture production batches. The packaging materials and configurations will be (b) (4) for the NDA stability batches and commercial batches. The process and manufacturing site for the NDA and production batches of the tablet dosage form (b) (4) the equipment used will be of the same operating principle. However, the packaging and stability study sites will be changed (b) (4).
- a. Does the Agency agree with Takeda's proposal to use a commercial packaging site that is different from that used for the NDA stability study?

FDA Response:

No, we do not agree. The environmental conditions at the two manufacturing sites may be sufficiently different to cause differences in the stability of product packaged at the two sites. You will need to submit at least three months of long term and accelerated stability data for product packaged at the new site for comparison with data from the original site. We recommend that you submit your NDA with data for product from the original site. After approval, you can submit a supplement with supporting data to change the packaging site.

- b. Does the Agency agree with Takeda's proposal to use a different commercial stability site from that used for the NDA stability study?

FDA Response:

Yes, that is acceptable.

- c. Takeda plans to include only NDA stability lot data and does not plan to include any production batch stability data in the Original NDA. Is this plan acceptable to the Agency?

FDA Response:

Yes, it is acceptable if the stability batches were prepared at least at 1/10 of the commercial scale, using equipment that is representative of production scale equipment.

You should provide, to the Regulatory Project Manager, a hardcopy or electronic version of any materials (i.e., slides or handouts) to be presented and/or discussed at the meeting.

If you have any questions, call Maureen Dewey, Senior Regulatory Project Manager, at (301) 796-0845.

Sincerely,

{See appended electronic signature page}

Maureen Dewey, M.P.H.
Senior Regulatory Project Manager
Division of Gastroenterology and Inborn Errors
Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

MAUREEN D DEWEY
02/03/2012