CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208025Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

EXCLUSIVITY SUMMARY

NDA # 208025 SUPPL # HFD # 560

Trade Name

Generic Name lansoprazole delayed-release, orally disintegrating tablet

Applicant Name Dexcel Pharma Technologies

Approval Date, If Known 06/07/2016

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

Application is 505(b)(2).

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 sponsor has conducted a bioequivalence study and a comparative bioavailability study (food effect) to provide the scientific bridge to the agency's finding of safety and efficacy for Prevacid 24HR (NDA 022327).

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:

N/A

c) Did the applicant request exclusivity?

YES ☐ NO ☒

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

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

YES ☐ NO ☒

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

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

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

YES ☐ NO ☒

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

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

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

YES ☒ NO ☐

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

NDA# 022327

NDA# 021428

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:

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

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

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

Investigation #1 YES ☐ NO ☐

Investigation #2 YES ☐ NO ☐

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

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

Investigation #1 YES ☐ NO ☐

Investigation #2 YES ☐ NO ☐

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

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

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 # YES ☐ ! NO ☐
! Explain:

Investigation #2 !
!
IND # YES ☐ ! NO ☐
! Explain:

(b) For each investigation not carried out under an IND or for which the applicant was

not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1	!
	!
YES ☐	! NO ☐
Explain:	! Explain:

Investigation #2	!
	!
YES ☐	! NO ☐
Explain:	! Explain:

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

YES ☐ NO ☐

If yes, explain:

==========

Name of person completing form: Alina Salvatore
Title: Regulatory Project Manager
Date: 05/02/2016

Name of Office/Division Director signing form: Karen Murry Mahoney, MD, FACE
Title: Deputy Director

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/

ALINA W SALVATORE
06/06/2016

KAREN M MAHONEY
06/07/2016

Dexcel Pharma Technologies Ltd
1 Dexcel St., Or-Akiva 3060000, Israel • Tel: 972-4636-4070 • Fax: 972-4636-4004 • E-mail: Reg@dexcel.com, Pv@dexcel.com

Certificate of Debarment

Dexcel Pharma Technologies Ltd. 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.

Name: Uri Oren

Title: Vice President & COO

Signature: _____

Date: Sep 21, 2014

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION[1]

NDA # 208025 BLA #	NDA Supplement # BLA Supplement #	If NDA, Efficacy Supplement Type: *(an action package is not required for SE8 or SE9 supplements)*
Proprietary Name: Established/Proper Name: lansoprazole delayed-release Dosage Form: orally disintegrating tablet		Applicant: Dexcel Pharma Technologies Agent for Applicant (if applicable): Camargo Pharmaceuticals
RPM: Alina Salvatore		Division: Nonprescription Drug Products

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)

For ALL 505(b)(2) applications, two months prior to EVERY action:

- **Review the information in the 505(b)(2) Assessment and submit the draft[2] to CDER OND IO for clearance.**
- **Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity)**

☒ No changes
☐ New patent/exclusivity *(notify CDER OND IO)*
Date of check: 04/27/2016

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.

Actions	
• Proposed action • User Fee Goal Date is June 7, 2016	☒ AP ☐ TA ☐ CR
• Previous actions *(specify type and date for each action taken)*	☐ None RTF 02/06/2015
❖ 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) ssessment to CDER OND IO unless the Assessment has been substantively revised (e.g., new listed drug, patent certification vised).

[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): New Formulation
(confirm chemical classification at time of approval)

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

(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

BLAs: Subpart E
☐ Accelerated approval (21 CFR 601.41)
☐ Restricted distribution (21 CFR 601.42)
Subpart H
☐ 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

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)? • If so, specify the type	☒ No ☐ Yes
❖ 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 *(including approval letter with final labeling)*	Action(s) and date(s) RTF: 02/06/2015 Approval: 06/07/2016
Labeling	
❖ Package Insert *(write submission/communication date at upper right of first page of PI)*	
• Most recent draft labeling *(if it is division-proposed labeling, it should be in track-changes format)*	☐ Included N/A
• Original applicant-proposed labeling	☐ Included N/A
❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling *(write submission/communication date at upper right of first page of each piece)*	☐ Medication Guide ☐ Patient Package Insert ☐ Instructions for Use ☐ Device Labeling ☒ None
• Most-recent draft labeling *(if it is division-proposed labeling, it should be in track-changes format)*	☐ Included
• Original applicant-proposed labeling	☐ Included
❖ Labels (**full color** carton and immediate-container labels) *(write submission/communication date on upper right of first page of each submission)*	
• Most-recent draft labeling	☒ Included
Proprietary Name • Acceptability/non-acceptability letter(s) *(indicate date(s))* • Review(s) *(indicate date(s)*	N/A
❖ Labeling reviews *(indicate dates of reviews)*	RPM: ☒ None DMEPA: ☐ None 04/22/16 DMPP/PLT (DRISK): ☒ None OPDP: ☒ None SEALD: ☒ None CSS: ☒ None Product Quality ☒ None Other: ☐ None DNDP: 06/03/16, 04/25/16, 09/21/15 (Filing Review)
Administrative / Regulatory Documents	
❖ RPM Filing Review[4]/Memo of Filing Meeting *(indicate date of each review)* ❖ All NDA 505(b)(2) Actions: Date each action cleared by 505(b)(2) Clearance Committee	RPM 1st Filing Reviw:02/06/2015 RPM 2nd Filing Review10/09/2015 ☐ Not a (b)(2) 05/09/16
❖ NDAs only: Exclusivity Summary *(signed by Division Director)*	☒ 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 o If yes, Center Director's Exception for Review memo *(indicate date)* o If yes, OC clearance for approval *(indicate date of clearance communication)*	☐ Yes ☒ No ☐ Not an AP action
❖ Pediatrics *(approvals only)* • Date reviewed by PeRC 06/08/2016 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) *(include only the completed template(s) and not the meeting minutes)*	
• CDER Medical Policy Council Brief – Evaluating a Breakthrough Therapy Designation for Rescission Template(s) *(include only the completed template(s) and not the meeting minutes)* *(completed CDER MPC templates can be found in DARRTS as clinical reviews or on the MPC SharePoint Site)*	
❖ 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.) *(do not include OPDP letters regarding pre-launch promotional materials as these are non-disclosable; do not include Master File letters; do not include previous action letters, as these are located elsewhere in package)*	RTF letter: 02/06/15 Type A Meeting Minutes: 09/02/15 (DARRTS) Filing Review Issues Identified: 10/16/15 Information Requests: 05/18/16, 05/05/16, 03/15/16, 03/03/16
❖ 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 *(indicate date of mtg)*	☒ N/A or no mtg
• Pre-NDA/BLA meeting *(indicate date of mtg)*	☒ No mtg
• EOP2 meeting *(indicate date of mtg)*	☒ No mtg
• Mid-cycle Communication *(indicate date of mtg)*	☒ N/A
• Late-cycle Meeting *(indicate date of mtg)*	☒ N/A
• Other milestone meetings (e.g., EOP2a, CMC focused milestone meetings) *(indicate dates of mtgs)*	Type C Guidance Meeting to discuss results of BE study 09/26/14 Type B Pre-IND Mtg: 09/26/13

Advisory Committee Meeting(s)	☒ No AC meeting
• Date(s) of Meeting(s)	
Decisional and Summary Memos	
❖ Office Director Decisional Memo *(indicate date for each review)*	☒ None
Division Director Summary Review *(indicate date for each review)*	☐ None 06/07/16
Cross-Discipline Team Leader Review *(indicate date for each review)*	☐ None 05/21/16
PMR/PMC Development Templates *(indicate total number)*	☒ None
Clinical	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) *(indicate date for each review)*	☒ No separate review
• Clinical review(s) *(indicate date for each review)*	05/16/16, 05/04/16, and 10/09/15 (Filing)
• Social scientist review(s) (if OTC drug) *(indicate date for each review)*	☒ 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 *(indicate date of review/memo)*	See Medical Officer's Review
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers *(indicate date of each review)*[5]	☒ None
Controlled Substance Staff review(s) and Scheduling Recommendation *(indicate date of each review)*	☒ N/A
❖ Risk Management • REMS Documents and REMS Supporting Document *(indicate date(s) of submission(s))* • REMS Memo(s) and letter(s) *(indicate date(s))* • Risk management review(s) and recommendations (including those by OSE and CSS) *(indicate date of each review and indicate location/date if incorporated into another review)*	N/A ☐ None
❖ OSI Clinical Inspection Review Summary(ies) *(include copies of OSI letters to investigators)*	☒ None requested
Clinical Microbiology ☒ None	
❖ Clinical Microbiology Team Leader Review(s) *(indicate date for each review)*	☐ No separate review
Clinical Microbiology Review(s) *(indicate date for each review)*	☐ None
Biostatistics ☒ None	
❖ Statistical Division Director Review(s) *(indicate date for each review)*	☐ No separate review
Statistical Team Leader Review(s) *(indicate date for each review)*	☐ No separate review
Statistical Review(s) *(indicate date for each review)*	☐ None

For Part 3 combination products, all reviews from the reviewing Center(s) should be entered into the official archive (for further instructions, see "Section 508 Compliant Documents: Process for Regulatory Project Managers" located in the CST electronic repository).

Clinical Pharmacology ☐ None	
❖ Clinical Pharmacology Division Director Review(s) *(indicate date for each review)*	☒ No separate review
Clinical Pharmacology Team Leader Review(s) *(indicate date for each review)*	☒ No separate review
Clinical Pharmacology review(s) *(indicate date for each review)*	☐ None 05/16/16, 09/25/15 (Filing)
❖ OSI Clinical Pharmacology Inspection Review Summary *(include copies of OSI letters)*	☒ None requested OSIS recommended acceptance of data without on-site inspection 11/10/16
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 04/25/16, 09/18/15 (Filing)
❖ 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[6]	
• 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 04/22/16, 09/25/15 (Filing Review)
❖ 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)*	04/20/16
☐ 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: 02/2016 ☐ Withhold recommendation ☐ Not applicable

[6] Do not include Master File (MF) reviews or communications to MF holders. However, these documents should be made available upon signatory request.

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 *(Notify CDER OND IO)*
• Finalize 505(b)(2) assessment	☒ Done
❖ For Breakthrough Therapy (BT) Designated drugs: • Notify the CDER BT Program Manager	☐ Done **N/A** *(Send email to CDER OND IO)*
❖ 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 **N/A**
❖ 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 **N/A**
❖ Ensure that proprietary name, if any, and established name are listed in the *Application Product Names* 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

From:	Salvatore, Alina
To:	"Stevens, Ruth"
Cc:	Salvatore, Alina
Subject:	NDA 208025 Labeling IR
Date:	Wednesday, May 18, 2016 9:58:00 AM

Hi Ruth,

By COB Friday, May 20th, please submit the smaller cartons that will be used with the 7-count blister cards and an additional clarification on the consumer information leaflet as proposed in your email response of May 5.

Thank you,
Alina

Alina W. Salvatore, RPh, MS, RAC
CDR, United States Public Health Service
Regulatory Project Manager
Division of Nonprescription Drug Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research
Phone: 240-402-0379

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

/s/

ALINA W SALVATORE
05/18/2016

From:	Salvatore, Alina
To:	Stevens, Ruth
Cc:	Salvatore, Alina
Subject:	Labeling comments for NDA 208025
Date:	Thursday, May 05, 2016 7:30:22 AM
Attachments:	NDA 208025 labeling comments to sponsor.doc

Dear Ruth,

Please see the attached labeling comments from the FDA and confirm receipt. We may have an additional minor comment from CMC on the inactive ingredient and will have this comment to you by tomorrow.

Please respond to the labeling comments by COB Wednesday, May 11th.

Thank you,
Alina

Alina W. Salvatore, RPh, MS, RAC
CDR, United States Public Health Service
Regulatory Project Manager
Division of Nonprescription Drug Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research
Phone: 240-402-0379

NDA 208025 Lansoprazole DR ODT Labeling Comments:

Non Drug Facts Labeling

a. For the proposed 7-count blister package, provide data to demonstrate that consumers understand labeled instructions that two packaged (b) (4) blisters represent a full course of treatment. (b) (4)

b. Increase the relative prominence of "Lansoprazole" on the cartons and bottle label consistent with the PDP design of the proposed labeling submitted on December 8, 2014, and discussed at the April 13, 2015 meeting between FDA and Dexcel. Because the established name will be the name marketed to the consumer, the other text on the submitted label competes for the consumer's attention on the PDP and may be confusing.

c. Submit 14-count bottle carton and 14-count bottle carton with window labels that display the name "Lansoprazole" on the PDP when printed.

d. Remove (b) (4) that is located adjacent to the tablet (b) (4) statement "May take 1 to 4 days for full effect, although some people get complete relief of symptoms within 24 hours", (b) (4) .

e. For the blister carton labels, add the statement "Keep the carton and package insert. They contain important information" to the carton. This is approved labeling for the reference listed drug, and is included in the draft labeling for the bottle cartons.

f. For the 14-, 28- and 42-count bottle carton with window labels, remove the bulleted statements:
• May take 1 to 4 days for full effect, although some people get complete relief of symptoms within 24 hours
• Clinically Proved to Treat Frequent Heartburn
The window design serves to shift the entire PDP to the bottom half of the carton. With half as much area, the additional text affects the prominence of required items such as the statement of identity and the declaration of net quantity of

contents. 21 CFR 201.15(a)(4) and 201.15(a)(6) state that required statements can lack the required prominence by reason of "…use of label space for any word, statement, design, or device which is not required by or under authority of the act to appear on the label;" and "…crowding with other written, printed or graphic matter". The two bulleted statements are not required labeling, and should be removed from the PDP of the bottle carton with window.

g. Revise the consumer information leaflet to reflect the related changes to the Drug Facts label.

Drug Facts Label

a. Under the heading "14-Day Course of Treatment" in the ***Directions*** section, revise the bullets and bold the second bullet to state:

- take 1 tablet before eating in the morning
- **do not crush or chew tablets**
- place the tablet on tongue; tablet disintegrates, with or without water. The tablets can also be swallowed whole with water.
- take every day for 14 days
- do not take more than 1 tablet a day
- do not use for more than 14 days unless directed by your doctor
- do not take this medicine with alcohol

b. Revise the last bullet in the ***Directions*** section, to be identical to the approved statement in the reference listed drug:

• Children under 18 years of age: ask a doctor before use. Heartburn in children may sometimes be caused by a serious condition.

c. Revise the ***Questions?*** section to contain a telephone number.

d. For all blister carton labels, place a bar line between the warning, **Stop use and ask a doctor if** and the pregnancy/breastfeeding warning as required in 21 CFR 201.66(d)(5).

e. Revise the visual graphic arrows on the Drug Facts label of the 14-count inner and outer blister cartons to properly signal the continuation of the Drug Facts label, and properly format the ***Questions?*** section of the Drug Facts label to comply with 21 CFR 201.66(d)(5) and 201.66(d)(7).

f. For all bottle cartons, revise the ***Other Information*** and ***Inactive Ingredients*** sections so that they are listed in the order required by 21 CFR 201.66(c)(7) and

201.66(c)(8).

g. Revise all the 14- and 28-count bottle cartons so that the visual graphic arrows properly signal the continuation of the Drug Facts label to the next adjacent panel as required in 21 CFR 201.66(d)(5).

h. Revise both 28-count bottle cartons so that the last panel of the Drug Facts label complies with 21 CFR 201.66(d)(7).

We also recommend that you make the following revisions:

Drug Facts label:

a. ***Questions or comments*** section: include the time that the toll-free number is in operation.

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/s/

ALINA W SALVATORE
05/05/2016

From: Salvatore, Alina
To: "Stevens, Ruth"
Cc: Pham, Jade
Subject: 2nd Labeling Information Request for NDA 208025
Date: Tuesday, March 15, 2016 10:34:00 AM

Hi Ruth,

Please confirm receipt of this email.

Below is a second labeling information request for the lansoprazole NDA referenced above. Please submit a response by March 22, 2016. I will be on leave but Jade Pham (cc'd) has graciously agreed to oversee my assignments during this time period; please include her on your email response. Please also remember to send a copy of your response to the document room and reference your NDA.

1. Submit three tablets of the proposed tablet.
2. Submit the proposed 14-count blister and 14-ct bottle cartons to be marketed.
3. Describe how the "actual size" claim on the principal display panel will be controlled for accuracy with varying package sizes, configurations and vendors.

Thank you,
Alina

Alina W. Salvatore, RPh, MS, RAC
CDR, United States Public Health Service
Regulatory Project Manager
Division of Nonprescription Drug Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research
Phone: 240-402-0379

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/s/

ALINA W SALVATORE
03/15/2016

From: Salvatore, Alina
To: "RStevens@camargopharma.com"
Subject: Information Request for NDA 208025 (Lansoprazole 15mg)
Date: Thursday, March 03, 2016 11:53:00 AM

Hi Ruth:

Please confirm receipt of this email and provide a response to the below information request by March 9, 2016.

Identify the purpose of the 7-count immediate container (blister) submitted on 8/06/2015.

Thank you,
Alina

Alina W. Salvatore, RPh, MS, RAC
CDR, United States Public Health Service
Regulatory Project Manager
Division of Nonprescription Drug Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research
Phone: 240-402-0379

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/s/

ALINA W SALVATORE
03/03/2016

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 208025

FILING COMMUNICATION -
FILING REVIEW ISSUES IDENTIFIED

Dexcel Pharma Technologies Ltd.
c/o Camargo Pharmaceutical Services LLC
Attention: Ruth E. Stevens, PhD, MBA
Chief Scientific Officer, Executive Vice President
9825 Kenwood Road, Suite 203
Cincinnati, OH 45242

Dear Dr. Stevens:

Please refer to your New Drug Application (NDA) dated August 6, 2015, received August 7, 2015, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA), for lansoprazole delayed-release, orally disintegrating tablets, 15 mg.

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 June 7, 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 May 10, 2016.

During our filing review of your application, we identified the following potential review issues. We request that you submit the following information by December 4, 2015.

Biopharmaceutics:

1. Provide a complete in vitro dissolution method development report and your rationale for selecting the rotational speed of (b) (4) rpm instead of 75 rpm.

2. Revise the following description of dissolution acceptance criterion from [redacted] to the "Acid Stage" and "Buffer Stage". In addition, your proposed dissolution acceptance criterion for both drug release and shelf-life is too liberal: buffer stage NLT [redacted]% (Q) at [redacted] (60 min after acid stage). Revise the specification to buffer stage: NLT [redacted]% (Q) at [redacted] min. The final determination of dissolution acceptance criterion will be made after a thorough review based on the totality of the dissolution profile data submitted in the NDA.

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. If you respond to these issues during this review cycle, we may not consider your response before we take an action on your application.

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.

REQUEST FOR PROPRIETARY NAME REVIEW

If you intend to have a proprietary name for the proposed product, please submit a new, complete, request for proprietary name review. Include the statement "**REQUEST FOR PROPRIETARY NAME REVIEW,"** in bold capital letters, at the top of your cover letter and on the first page of the main submission document. The review of this name will be initiated when the new submission is received.

If you require additional information on developing proprietary names for drugs or proposing alternative proprietary names for consideration, we refer you to the following documents:

- Draft Guidance for Industry Best Practices in Developing Proprietary Names for Drugs, (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM398997.pdf)
- 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 questions, contact Jeffrey Buchanan, Regulatory Health Project Manager, at (301) 796-1007.

Sincerely,

{See appended electronic signature page}

Karen Murry Mahoney, MD
Deputy Director
Division of Nonprescription Drug Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

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/s/

KAREN M MAHONEY
10/16/2015

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 208025

MEETING MINUTES

Dexcel Pharma Technologies, Ltd.
c/o Camargo Pharmaceutical Services, LLC
Attention: Ruth E. Stevens, Ph.D., M.B.A.
Chief Scientific Officer, Executive Vice President
9825 Kenwood Road, Suite 203
Cincinnati, OH 45242

Dear Dr. Stevens:

Please refer to your New Drug Application (NDA), dated December 5, 2014, submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for lansoprazole delayed-release, orally-disintegrating tablets, 15 mg.

We also refer to the meeting between representatives of your firm and the FDA on April 13, 2015. The purpose of the meeting was to discuss FDA's Refusal-to-File correspondence, dated February 6, 2015.

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

If you have questions, contact Jeffrey Buchanan, Regulatory Health Project Manager, at (301) 796-1007.

Sincerely,

{See appended electronic signature page}

Theresa Michele, M.D.
Director
Division of Nonprescription Drug Products
Office of Drug Evaluation IV
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:	Type A
Meeting Category:	Other (post-RTF)
Meeting Date and Time:	Monday, April 13, 2015 at 3:00 P.M.
Meeting Location:	FDA White Oak Campus 10903 New Hampshire Avenue White Oak Building 22, Conference Room: 1315 Silver Spring, Maryland 20903
Application Number:	NDA 208025
Product Name:	Lansoprazole delayed-release, orally-disintegrating tablets, 15 mg
Indication:	Treatment of frequent heartburn
Sponsor/Applicant Name:	Dexcel Pharma Technologies, Ltd.

FDA ATTENDEES

Office of Drug Evaluation IV
Jagjit Grewal, M.P.H., Associate Director for Regulatory Affairs

Division of Nonprescription Drug Products
Theresa Michele, M.D., Director
Jane Filie, M.D., Medical Officer Team Leader
Mona Khurana, M.D., Medical Officer
Ruth E. Scroggs, Pharm.D., Associate Director for Labeling
Steven Adah, Ph.D., Interdisciplinary Scientist Team Leader
Mary R. Vienna, R.N., M.H.A., Interdisciplinary Scientist
Karen Livornese, R.N., M.S.N., Interdisciplinary Scientist
Dan Brum, Pharm.D., M.B.A., B.C.P.S., R.A.C., Chief, Project Manager Staff
Jeffrey Buchanan, Regulatory Health Project Manager

Division of Gastroenterology and Inborn Errors Products
Jessica Lee, M.D., Medical Officer Team Leader
Kerry Jo Lee, M.D., Medical Officer

Division of New Drug Products II
Eric Duffy, Ph.D., Director

Division of Biopharmaceutics
Tien-Mien Chen, Ph.D., Biopharmaceutics Reviewer

Office of Clinical Pharmacology
Dilara Jappar, Ph.D., Clinical Pharmacology Reviewer

Office of Surveillance and Epidemiology
Grace Jones, Pharm.D., Safety Evaluator, Division of Medication Error and Analysis
Peter Diak, Pharm.D., Team Leader, Division of Pharmacovigilance

SPONSOR ATTENDEES

Dexcel Pharma Technologies, Ltd.
Tomer Gold, VP, Research and Development
Alona Korol, Head of Regulatory Affairs and Pharmacovigilance
Sigalit Melcer, Manager, Clinical Trials Department

Camargo Pharmaceutical Services, LLC
Ruth E. Stevens, Ph.D., M.B.A., Executive VP and Chief Scientific Officer
Lynn Gold, Ph.D., VP, Chemistry, Manufacturing, and Controls
Josh Johnson, Ph.D., Research Scientist
K. Gary Barnette, Ph.D., VP, Drug Development

1.0 BACKGROUND

On December 8, 2014, Dexcel Pharma Technologies (Dexcel) submitted an original NDA, dated December 5, 2014, for a proposed over-the-counter (OTC) lansoprazole delayed-release, orally-disintegrating tablet (ODT), 15 mg. Following a multi-discipline filing review of the application, FDA issued a Refusal-to-File correspondence on February 6, 2015. On March 5, 2015, Dexcel submitted a Type A meeting request and background package, received March 6, 2015, to discuss the application deficiencies listed in FDA's Refusal-to-File correspondence. FDA granted the Type A meeting on March 17, 2015. FDA's Preliminary Comments were sent to Dexcel on April 10, 2015, and the meeting was held April 13, 2015.

Dexcel's questions are in **bold** type, FDA's preliminary responses are in *italics*, and the discussion is recorded in normal font.

2. DISCUSSION

1. **Does the Agency agree that the plan for the proposed ISS section and draft ISS tables seems reasonable and sufficient to accept the application for review?**

FDA Preliminary Response:
We agree with your description and we have the following additional comments:

- *Include a description of your pooling strategy.*
- *Describe your safety endpoints and reporting definitions for adverse events, serious adverse events, significant adverse events, and treatment emergent adverse events.*

- *Include a list of tables, a list of figures, a master abbreviations list, and a list of abbreviations for MedDRA System Organ Classifications (SOC).*
- *We agree with the proposed shells for tables 1.1, 1.2, 1.4, 1.5, 1.6, 2.1.*
- *For table shell 1.3 (adverse dropouts), include a separate column for the verbatim terms.*
- *For table shell 2.2 (vital signs summary), specify the number and percent of subjects in each treatment arm who met your pre-specified definitions of bradycardia, tachycardia, hypo/hypertension, fever, or tachypnea/bradypnea.*

Discussion:
Dexcel stated they have conducted a comparative bioavailability (BA) study and a food-effect study each of which included a lansoprazole treatment arm in which a single 15 mg delayed ODT was allowed to disintegrate for 60 seconds and then swallowed without water. Dexcel stated they plan to pool adverse events from this treatment arm in both studies. Dexcel does not intend to pool data from the other treatment arms. FDA agreed that the approach was reasonable and asked Dexcel to describe the pooling strategy in the NDA resubmission.

2. **Does the Agency agree that the datasets provided are sufficient to accept the application for review and in a form that would allow analyses of the results?**

FDA Preliminary Response:
We agree with your proposal.

3. **Does the Agency agree that the details of the coding and adjudication of the verbatim reported adverse events to preferred terms provided are sufficient to accept the application for review?**

FDA Preliminary Response:
We agree with your proposal.

4. **Does the Agency agree that the information above provides an adequate description of the conduct of the oropharyngeal safety assessments and the severity of the observed oropharyngeal AEs and physical exam findings such that the application can be accepted for filing?**
FDA Preliminary Response:
We agree with your proposal.

5. **Does the Agency agree that the in vitro bridge to Prevacid 24 HR and the scientific bridge to Prevacid 24 HR provide sufficient safety data to support the 14 day dosing of Lansoprazole DR ODT 15 mg OTC?**

FDA Preliminary Response:
No, we do not agree. Both pivotal PK studies included in your application to establish the scientific bridge to the listed drug (LD) were single-dose studies, so the data generated from the oropharyngeal assessments conducted in both studies would not be

supportive of repeated use of the proposed product. We refer you to the minutes of the pre-IND meeting held on September 26, 2013, specifically Question 4.

We acknowledge your application includes an in vitro bridge study to demonstrate similar dissolution profiles between the proposed product and the LD. While you may rely on the Agency's previous findings of safety for the LD as part of a 505(b)(2) submission, the data upon which you would be relying would support the safety of the active moiety only, but would not address our concerns about the potential safety of the ODT dosage form in the OTC setting. The dosage form of the LD is different from that of the proposed product. The LD is a capsule dosage form that contains pellets while the proposed product is an ODT. We note in the FAERS data you provided, that 887 adverse events (AEs) associated with 15 mg and 30 mg ODT of lansoprazole available by prescription were reported to FDA from the 1st quarter of 2008 through the 2nd quarter of 2014. Provide a description of the severity of the AEs, the number of AEs with a serious outcome, and the associated System Organ Classifications, Preferred Terms, and verbatim terms.

Discussion:
Dexcel inquired if FDA's request for oropharyngeal safety assessment is driven by the drug product's excipients. Given that the listed drug (LD) is ingested and not an orally-disintegrating product, FDA clarified that the different dosage forms raise safety concerns and, specifically, about the excipients to which the oropharyngeal cavity is exposed while the ODT disintegrates. Dexcel provided the attached Inactive Ingredient Database (IID) summary tables which listed the 20 excipients present in the proposed product. Dexcel explained that all of the proposed product's excipients are at or below the IID levels. Eleven of the excipients comprise the ODT [redacted] (b) (4) which are not exposed to the oral cavity. They are released in the gastrointestinal tract only. This is Dexcel's rationale for not conducting the oropharyngeal safety assessment.

FDA stated that the additional excipient information provided by Dexcel may provide a sufficient basis to justify not conducting a 14-day safety study but that Dexcel should articulate and justify their rationale in the NDA resubmission. FDA stated that the justification provided by Dexcel would be a review issue, not a filing issue.

6. **Does the Agency agree that the safety information from a complete set of post-marketing databases covering an adequate timeframe will be sufficient?**

FDA Preliminary Response:
Present the retrieved FAERS data for all reports as well as the serious non-fatal reports and serious fatal reports. Similarly present the retrieved FAERS data when stratifying by age group, sex, dose group, formulation, or other sub-groups. Provide tabular summaries of all serious reports in each subgroup analysis with the reported MedDRA SOC and Preferred Terms in decreasing order of frequency.

Provide DAWN data in tables by year for all emergency department visits with lansoprazole or other proton pump inhibitors as one of the drug exposures. Provide tabular summaries of the demographic and emergency department visit characteristics for the retrieved reports.

Extract all AE cases involving lansoprazole from the WHO database. Separate U.S. from ex-U.S. cases. Present the demographic characteristics, drug source, and frequencies of reported MedDRA SOC and Preferred Terms. Stratify the AEs by age group, sex, formulation, and dose.

Discussion:
Dexcel explained that lansoprazole is not a drug of abuse, stated they had provided the Agency with information from DAWN, and asked if they needed to submit retrieved reports from DAWN. FDA responded that the utility of the DAWN database is not limited to drug abuse but also to drug misuse and that the Agency is interested in understanding any health hazards associated with lansoprazole misuse from the DAWN database. FDA stated the DAWN information provided by Dexcel is limited and requested a summary of all reports including an analysis of basic demographic information, visit type and characteristics, and disposition. FDA stated similar analyses should be provided for the data retrieved from the WHO and the FAERS databases. FDA stated the tables summarizing sub-group analyses of the retrieved FAERS data provided in the background information are difficult to interpret without correlating the sub-group characteristics with the actual adverse events. FDA further clarified that the post-marketing safety assessment from all databases should focus only on lansoprazole and not all proton pump inhibitors (PPIs). FDA suggested that Dexcel focus their post-marketing safety assessment from all databases on known safety signals associated with the PPIs as well as on detection of any new safety signals associated with lansoprazole use.

7. **Do the post-marketing safety data as presented in the Type A meeting package provide the Division with enough information to provide an assessment of the risk-benefit for use in the OTC setting, with particular attention to AEs inherent to this class of drugs?**

FDA Preliminary Response:
In addition to your proposal, we also request safety data of your own post-marketing safety database on lansoprazole ODT (if available) and other dosage forms. Provide an overall assessment of the risk-benefit taking into consideration all of the information you collect and submit.

8. **Do the references, as summarized in this Type A meeting package, provide sufficient support for the risk-benefit assessment of this product?**

FDA Preliminary Response:
No, we do not agree. Focus the literature review to retrieve publications relevant to safety issues specific to proton pump inhibitors. Include both a tabular summary and an

analysis of the findings from the retrieved publications. Also provide a copy of the articles as well as English translation of the publications that are not in English.

Discussion:
Dexcel asked for clarification about whether the Agency was requiring a summary of the published safety literature for all PPIs in the resubmission of the NDA. FDA clarified that Dexcel should focus the published literature search only on lansoprazole and not on all PPIs. FDA requested Dexcel provide not just a tabular summary but also an analysis of the retrieved publications, focusing on the known safety signals associated with the PPIs and detecting any new safety signals associated with lansoprazole use. FDA also requested that Dexcel separate the safety data obtained from the label of the prescription drug product, Prevacid SoluTab, from the safety data retrieved from the published literature search.

9. **Does the Agency agree that the safety summary provided for the inactive ingredient maltitol is sufficient to support the safe use of this ingredient in Lansoprazole Delayed-release ODT 15 mg OTC?**

FDA Preliminary Response:
Submit the safety data for maltitol to the NDA. The safety summary provided for maltitol will be reviewed during the NDA review cycle.

Discussion:
Dexcel has submitted maltitol safety data. FDA explained that the agency's preliminary response was a reminder to resubmit the data.

10. **Does the Agency agree that sufficient data are provided to support the robustness of the (b) (4) on the physical attributes of Lansoprazole DR ODT 15 mg OTC?**

FDA Preliminary Response:
The robustness of the (b) (4) will be reviewed during the NDA review cycle.

11. **Does the Agency agree that the method used and the data presented are sufficient to characterize the alcohol dose dumping of OTC Lansoprazole DR ODT 15 mg? Does the Agency agree that the current label text under "How to manage heartburn" is sufficient warning about the use of this drug with alcohol?**

FDA Preliminary Response:
The in vitro method used and the in vitro data presented are sufficient to permit review of the alcohol dose dumping of OTC lansoprazole DR ODT 15 mg. To facilitate review in the future NDA resubmission, provide the assay method validation report and the assay in-study performance QC report. However, as noted in the Refusal-to-File letter, dated February 26, 2015, preliminary review of the in vitro data suggests that significant dose-dumping occurred in the presence of 40% alcohol. Whether or not additional data from

an in vivo alcohol dose-dumping study are needed or the issue can be addressed with labeling will be a review issue.

With regard to your labeling suggestion, information on the drug facts label (DFL) is data driven, whereas the information in the consumer leaflet reflects general advice on the management of heartburn. Therefore, general recommendations for heartburn management may not adequately address this issue. In your NDA submission, we recommend that you provide an analysis of potential clinical implications of the in vitro findings, keeping in mind the "worst case scenario" for the consumer related to safety and efficacy of your proposed product. Also provide specific plans to address this concern.

Discussion:
Dexcel has conducted an alcohol dose-dumping study and compared their drug product to Prevacid 24HR. Dexcel explained that the comparative alcohol dose-dumping study yielded similar results for both products. Dose-dumping occurs at 40% ethanol for both products. FDA explained there has been an evolution of thought at the Agency since the approval of the first PPIs, including the LD, when FDA didn't routinely ask about alcohol dose-dumping. FDA acknowledged the Agency did not require the innovator of the LD to conduct such studies, but stated the Agency is now requiring an evaluation of the alcohol dose-dumping potential of every product. FDA stated that, if Dexcel chooses not to conduct an *in vivo* alcohol dose-dumping study, the lack of *in vivo* data would not be a filing issue but rather a review issue. FDA further stated that Dexcel would need to justify not conducting such an *in vivo* alcohol dose-dumping PK study and address how the safety and/or efficacy of the proposed product may be compromised when used with alcohol as either a single dose or as multiple doses and how Dexcel would plan to mitigate the risk.

12. **Would the Division confirm that 1) the font specifications in the example label are acceptable for all draft labeling, 2) the draft 14-count inner carton is satisfactory to contain the blisters inside the 28- and 42-count blister cartons, and 3) the "labeling outsert" file contained in SN0000, Module 1, Section 1.14.1.3, contains what the Division was requesting as the consumer information leaflet?**

FDA Preliminary Response:
The font specifications and the 14-count inner carton included in the meeting package are acceptable for filing the NDA. The "labeling outsert" file contained in SN0000, Module 1, Section 1.14.1.3 of the NDA application does not contain what was requested as the consumer information leaflet. Module 1, Section 1.14.1.3 contains the text of the draft carton and consumer information leaflet labels. Submit a draft consumer information leaflet as a label in Module 1, Section 1.14.1.1, in the form it will appear to the consumer.

13. **DPT provides an example of the labeling documents (14 count inner carton) as part of this meeting package; does the provided document meet the Agency's resolution criteria?**

FDA Preliminary Response:
The resolution of the sample label provided in the meeting package is acceptable.

14. Does DCNE agree that the appropriate listed drug for OTC Lansoprazole Delayed-release ODT 15 mg is OTC Prevacid 24 HR (NDA 022327)?

FDA Preliminary Response:
The Agency typically does not advise a sponsor on the selection of a particular listed drug that may be relied upon to support approval of a proposed product. However, your proposal to rely on Prevacid 24 HR appears acceptable.

In addition, you assert that it is appropriate to consider your proposed lansoprazole delayed-release ODT to be a pharmaceutical equivalent to Prevacid 24 HR because they contain identical amounts of the same active ingredient, deliver (b) (4) *amounts of the active drug over the same dosing period, and both dosage forms are comprised of delayed-release,* (b) (4) *granules. However, pharmaceutical equivalents are drug products* (b) (4) *do not necessarily contain the same inactive ingredients, and meet the* (b) (4) *compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates [see 21 CFR 320.1(c) and FDA's "Approved Drug Products with Therapeutic Equivalence Evaluations" (the Orange Book)]. The dosage form of your proposed product is a delayed-release, orally-disintegrating tablet which is the same as Takeda's Prevacid SoluTab (lansoprazole) delayed-release ODT (NDA 021428). Your proposed lansoprazole delayed-release ODT 15 mg is a pharmaceutical equivalent to Takeda's Prevacid SoluTab (lansoprazole) delayed-release ODT 15 mg. Therefore, we maintain our comment that if there is a listed drug that is a pharmaceutical equivalent to the drug proposed in a 505(b)(2) application, that drug should also be identified as a listed drug consistent with FDA's draft Guidance for Industry: Applications Covered by Section 505(b)(2) located at the following web address:*
www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm079345.pdf

Discussion:
Dexcel stated they have established a scientific bridge to Prevacid 24 HR and do not intend to identify Takeda's Prevacid SoluTab as a relied upon listed drug in their resubmission. FDA reiterated their position as noted in the preliminary comment and also indicated that an applicant may rely upon more than one listed drug in support of a 505(b)(2) application. Dexcel inquired if this would be a filing issue. FDA responded that this would not be a filing issue, but it is a review issue that will be discussed with the Agency's 505(b)(2) Committee. Dexcel acknowledged issuance of the Agency's February 6, 2015 proposed rule (Docket No. FDA–2011–N–0830) which includes a provision that a 505(b)(2) applicant must identify any approved drug that is a pharmaceutical equivalent to the proposed product as a relied upon listed drug. Dexcel inquired if FDA had established a timeframe for finalizing the rule. FDA could not predict when the proposed rule may become final.

15. DPT plans to submit a request for review of a proposed proprietary name after the application is resubmitted, and once a distributor is identified. Is this plan acceptable?

FDA Preliminary Response:
Yes, this is acceptable. Note that there is a separate PDUFA clock for proprietary name submission. If you require information on PDUFA performance goals associated with proprietary name reviews, we refer you to the PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2013 through 2017 (http://www.fda.gov/downloads/ForIndustry/UserFees/PrescriptionDrugUserFee/UCM270412.pdf). The acceptability of the proposed proprietary name requires a promotional and safety assessment. DMEPA will perform such an assessment once they receive a formal request for review from you. The content requirements for such a submission can be found in the draft Guidance for Industry entitled, Contents of a Complete Submission for the Evaluation of Proprietary Names located at the following web address: (http://www.fda.gov/downloads/ucm075068.pdf). Further information about how FDA evaluates propriety names for drug products is available in the following guidance, Best Practices in Developing Proprietary Names for Drugs located at the following web address: (http://www.fda.gov/downloads/UCM398997.pdf).

3.0 ADMINISTRATIVE COMMENTS

505(b)(2) REGULATORY PATHWAY

The Division recommends that sponsors considering the submission of an application through the 505(b)(2) pathway consult the Agency's regulations at 21 CFR 314.54, and the draft guidance for industry *Applications Covered by Section 505(b)(2)* (October 1999), available at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm. In addition, FDA has explained the background and applicability of section 505(b)(2) in its October 14, 2003, response to a number of citizen petitions that had challenged the Agency's interpretation of this statutory provision (see Docket FDA-2003-P-0274-0015, available at http://www.regulations.gov).

If you intend to submit a 505(b)(2) application that relies for approval, in part, on FDA's finding of safety and/or effectiveness for one or more listed drugs, you must establish that such reliance is scientifically appropriate, and must submit data necessary to support any aspects of the proposed drug product that represent modifications to the listed drug(s). You should establish a "bridge" (e.g., via comparative bioavailability data) between your proposed drug product and each listed drug upon which you propose to rely to demonstrate that such reliance is scientifically justified.

If you intend to rely, in part, on literature or other studies for which you have no right of reference but that are necessary for approval, you also must establish that reliance on the studies described in the literature or on the other studies is scientifically appropriate. You should include a copy of such published literature in the 505(b)(2) application and identify any listed drug(s) described in the published literature [e.g., trade name(s)].

If you intend to rely, in part, on the Agency's finding of safety and/or effectiveness for a listed drug(s) or published literature describing a listed drug(s) (which is considered to be reliance on FDA's finding of safety and/or effectiveness for the listed drug(s)), you should identify the listed drug(s) in accordance with the Agency's regulations at 21 CFR 314.54. It should be noted that 21 CFR 314.54 requires identification of the "listed drug for which FDA has made a finding of safety and effectiveness," and thus an applicant may only rely upon a listed drug that was approved in an NDA under section 505(c) of the FD&C Act. The regulatory requirements for a 505(b)(2) application (including, but not limited to, an appropriate patent certification or statement) apply to each listed drug upon which a sponsor relies.

If you propose to rely on FDA's finding of safety and/or effectiveness for a listed drug that has been discontinued from marketing, the acceptability of this approach will be contingent on FDA's consideration of whether the drug was discontinued for reasons of safety or effectiveness.

We encourage you to identify each section of your proposed 505(b)(2) application that relies on FDA's finding of safety and/or effectiveness for a listed drug(s) or on published literature. In your 505(b)(2) application, we encourage you to clearly identify (for each section of the application, including the labeling): (1) the information for the proposed drug product that is provided by reliance on FDA's finding of safety and/or effectiveness for the listed drug or by reliance on published literature; (2) the "bridge" that supports the scientific appropriateness of such reliance; and (3) the specific name (e.g., proprietary name) of each listed drug named in any published literature on which your marketing application relies for approval. If you are proposing to rely on published literature, include copies of the article(s) in your submission.

In addition to identifying in your annotated labeling the source(s) of information essential to the approval of your proposed drug that is provided by reliance on FDA's previous finding of safety and efficacy for a listed drug or by reliance on published literature, we encourage you to also include that information in the cover letter for your marketing application in a table similar to the one below.

List the information essential to the approval of the proposed drug that is provided by reliance on the FDA's previous finding of safety and efficacy for a listed drug or by reliance on published literature	
Source of information (e.g., published literature, name of listed drug)	**Information Provided (e.g., specific sections of the 505(b)(2) application or labeling)**
1. Example: Published literature	*Nonclinical toxicology*
2. Example: NDA XXXXXX "TRADENAME"	*Previous finding of effectiveness for indication X*
3. Example: NDA YYYYYY "TRADENAME"	*Previous finding of safety for Carcinogenicity, labeling section XXX*

4.	

Please be advised that circumstances could change that would render a 505(b)(2) application for this product no longer appropriate. For example, if a pharmaceutically equivalent product were approved before your application is submitted, such that your proposed product would be a "duplicate" of a listed drug and eligible for approval under section 505(j) of the FD&C Act, then it is FDA's policy to refuse to file your application as a 505(b)(2) application (21 CFR 314.101(d)(9)). In such a case, the appropriate submission would be an Abbreviated New Drug Application (ANDA) that cites the duplicate product as the reference listed drug.

4.0 SUMMARY OF KEY DISCUSSION POINTS AND ACTION ITEMS

1. FDA stated that the additional excipient information provided by Dexcel may provide a sufficient basis to justify not conducting a 14-day safety study. Dexcel agreed to articulate and justify their rationale in the resubmission of their application. Dexcel understood that the justification they provide will be a review issue, but not a filing issue.
2. A decision to not list Takeda's Prevacid SoluTab as an LD in the resubmission will be a review issue.
3. Dexcel's proposed pooling strategy for the BA and food-effect study arms appeared reasonable.
4. Dexcel will focus the ISS on lansoprazole only rather than on all PPIs and that the post-marketing safety analyses for lansoprazole will focus on known safety signals associated with PPIs and any potential new safety signals.
5. A decision to not conduct an *in vivo* alcohol dose-dumping study would be a review issue.
6. Dexcel will provide more granular data and analyses of the DAWN, WHO, and FAERS databases for lansoprazole-specific post-marketing safety data. Dexcel understood the sub-group analyses of the FAERS data should be correlated to the reported MedDRA Preferred Terms and SOCs.

5.0 ATTACHMENTS AND HANDOUTS

DPT submitted the following two pages of supplemental information for Question 5 to be referenced and discussed during the meeting.

Dexcel Pharma Technologies Ltd

1 Dexcel St., Or-Akiva 3060000, Israel • Tel: 972-4636-4070 • Fax: 972-4636-4004 • E-mail: Reg@dexcel.com, Pv@dexcel.com

NDA 208025 (Reference ID: 3730324)
For Scheduled Type A Meeting: April 13, 2015

Supplemental information for Question 5:

Inactive Ingredient Database Summary

- All 20 excipients are present in IID in oral products at or below the maximum potency listed (as described in SN0000, 3.2.P.1).
- Table 1: 11 excipients comprise the ODT (b) (4) (exposed in the oral cavity) all are at or below the maximum potency listed.
- Table 2: (b) excipients comprising the (b) (4) (exposed in the oral cavity) all are at or below the maximum potency listed.
- Table 3: (b excipients comprising the (b) (4) (not exposed in the oral cavity) and require no further discussion.

Table 1 Excipients in Lansoprazole DR ODT (b) (4) to the Maximum Potency Stated in the FDA Inactive Ingredient Database (IID) (without the (b) (4) Pellets, Excipients (b) (4))

Blend Ingredient	Amount per unit of Lansoprazole DR ODT Tablets, 15 mg (mg)	IID Maximum Potency As Oral Disintegrating Tablet	Safety Margin (IID/Daily dose)
Crospovidone	(b) (4)		7
Copovidone			36.5
Sucralose			12.8
Ascorbic acid			1
Strawberry flavor			1
Colloidal silicon dioxide			2.5
Sodium stearyl fumarate			9
Sorbitol			45.2
Mannitol			7.3
Microcrystalline cellullose			10.1
Maltitol			93[1]

[1]The liquid product (b) (4) contains maltitol, a daily dose is (b) (4) of maltitol a day, a 20,000-fold safety factor. There are two additional approved products, Baraclude™ and Keppra™ (oral solutions), contain total daily doses of (b) (4) maltitol, respectively.

Table 2 Excipients in Lansoprazole DR ODT (b) (4) Pellets to the Maximum Potency Stated in the FDA Inactive Ingredient Database (IID) (b) (4)

Pellet Enteric Layer Excipients	Amount per unit of Lanosprazole DR ODT, 15 mg	IID Maximum Potency mg	Dosage form of IID entry	Safety Margin (IID/Daily dose)
Hypromellose (b) (4)	(b) (4)			1.48
Cetyl Alcohol				10.73
Triethyl Citrate				8.07
Talc				1.0
Titanium Dioxide				1.0

(b) (4)

Table 3 Comparison of Lansoprazole DR ODT (b) (4) to the Maximum Potency Stated in the FDA Inactive Ingredient Database (IID)

Ingredient*	Amount per unit of Lansoprazole DR ODT Tablets, 15 mg (mg)	IID Maximum Potency	Safety Margin (IID/Daily dose)
Sugar Spheres	(b) (4)		7.92
Meglumine			5.22
Polysorbate 80			89.01
Hypromellose (b) (4)			3.55

(b) (4)

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/s/

THERESA M MICHELE
09/02/2015

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

PIND 118528

ADVICE/INFORMATION REQUEST

Camargo Pharmaceutical Services, LLC
Attention: Ruth E. Stevens, Ph.D., M.B.A.
Chief Scientific Officer, Executive Vice President
(U.S. Agent for Dexcel Pharma Technologies)
9825 Kenwood Road, Suite 203
Cincinnati, OH 45242-6252

Dear Dr. Stevens:

Please refer to your Pre-Investigational New Drug Application (PIND) file for lansoprazole delayed-release, orally-disintegrating tablets, 15 mg.

We also refer to your amendment dated February 28, 2014 containing your initial Pediatric Study Plan (iPSP) for this drug product. We have completed our review of your submission. Attached is a copy of your iPSP to which our edits in track changes have been provided.

You are required to submit an agreed iPSP no later than 90 calendar days after the date of this communication. FDA is then required to confirm whether it agrees with your agreed iPSP no later than 30 calendar days after the date that it receives your agreed iPSP.

Secure email between CDER and sponsors 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 (except for 7-day safety reports for INDs not in eCTD format).

The FDA Electronic Submissions Gateway (ESG) is the central transmission point for sending information electronically to the FDA and enables the secure submission of regulatory information for review. If your IND is in eCTD format, you should obtain an ESG account. For additional information, see
http://www.fda.gov/ForIndustry/ElectronicSubmissionsGateway/.

If you have any questions, contact Celia Peacock, Regulatory Project Manager, at (301) 796-4154.

Sincerely,

{See appended electronic signature page}

Theresa Michele, M.D.
Director
Division of Nonprescription Clinical Evaluation
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

Enclosure:
Camargo Pharmaceutical Services, LLC iPSP lansoprazole delayed-release, orally-disintegrating tablets, 15 mg. dated February 28, 2014 with FDA edits in track changes

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/s/

THERESA M MICHELE
06/02/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 208025

REFUSAL TO FILE

Dexcel Pharma Technologies Ltd.
c/o Camargo Pharmaceutical Services LLC
Attention: Ruth E. Stevens, Ph.D., M.B.A.
Chief Scientific Officer, Executive Vice President
9825 Kenwood Road, Suite 203
Cincinnati, OH 45242

Dear Dr. Stevens:

Please refer to your New Drug Application (NDA) dated December 5, 2014, received December 8, 2014, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA), for lansoprazole delayed-release, orally-disintegrating tablets, 15 mg.

After a preliminary review, we find your application is not sufficiently complete to permit a substantive review. Therefore, we are refusing to file this application under 21 CFR 314.101(d) for the following reasons:

1. The application is incomplete because it does not on its face contain information required under section 505(b) of the FD&C Act and § 314.50.

    a. The following section is required by regulation and is missing in your application:
        - Integrated Summary of Safety: We refer you to CFR 314.50(d)(5)(vi) regarding the contents of an Integrated Summary of Safety.

    b. In addition, the following clinical deficiencies preclude us from conducting a review of your application:
        - The application fails to provide datasets containing safety data obtained for all study subjects in both pivotal pharmacokinetic studies (Project 120383 and Project 120384) including all adverse events and results of all vital signs, laboratory tests and electrocardiogram results in a format that would allow analyses of the results.
        - The application fails to provide the details on the coding and adjudication of the verbatim reported adverse events to preferred terms.
        - The application fails to provide a clear description of the conduct of the oropharyngeal safety assessments and the severity of observed oropharyngeal adverse events and physical exam findings.
        - The application does not provide safety information to support the repeated use of the product over 14 days.

- The application does not provide sufficient safety information from a complete set of post-marketing databases. No data are provided from the National Poison Data System (NPDS) from the American Association of Poison Control Centers (AAPCC) and the Drug Abuse Warning Network (DAWN). Although limited data from the FDA Adverse Event Reporting System (FAERS), World Health Organization (WHO), and published literature are provided, the provided data do not cover an adequate timeframe (2008 to time of application).

2. The application is not submitted in the form required under § 314.50.

- Contents of the clinical portion of the application are presented in a form that renders it unable to be reviewed:
  - The post-marketing safety data of each safety database searched are not summarized and analyzed by formulation, marketing status (Rx vs. OTC), dose, duration of use, year of reporting, seriousness, and age to provide an assessment of the risk-benefit for use in the over-the-counter setting, with particular attention to adverse events inherent to this class of drugs.
  - The references provided have not been summarized to provide support for the risk-benefit assessment of this product.

The information provided in response to our request is considered not adequate. Further delay on filing this application will compromise the ability of the review team to comply with good review management practices.

While the following issues are not related to our refusal to file decision for this application, you should address them if the application is resubmitted.

1. The safety evaluation summary review of the inactive ingredient, maltitol, to support the amount of its use in your product will be assessed during review of the NDA.

2. The evaluation of debossing on your finished product with respect to potential effects on the physical attributes of the orally-disintegrating tablet will be assessed during review of the NDA (b) (4).

3. Pending a thorough review, it appears that significant dose-dumping of lansoprazole occurred in the presence of 40% alcohol based on *in vitro* studies. Comment on the clinical relevance of this finding, and your specific plans to address this concern for your proposed OTC drug product.

4. Submit revised labeling for all submitted labels to include font specifications for the Drug Facts label. Submit the consumer information leaflet as part of labeling. Also, submit a 14-count inner carton label to be used with the 28- and 42-ct blister cartons. OTC PPI products are to be packaged in 14-day containers to promote compliance with the 14-day course of treatment.

5. Submit legible (sharp/clear) labeling that is the actual to-be-marketed package size. Provide the dimensions.

   The basis for our request is as follows: Your submitted portable document format (PDF) files appear to be image-based PDF files with a resolution of 111 dots per inch (dpi). For a sharp/clear readable image that can be used in reviews and action letters, the DPI needs to be at least set to 300 dpi. Scanned documents are generally more difficult to read especially if the resolution is less than 300 dpi. Avoid image-based PDF files whenever possible. For questions regarding the technical specifications, contact CDER at esub@fda.hhs.gov

   The following Guidance for Industry *Providing Regulatory Submissions in Electronic Format – Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications* contains the technical specifications for portable document format (PDF):
   http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM163565.pdf

6. It is noted that various sections of your NDA submission contain references to the "Approved Labeling for Prevacid (Takeda Pharmaceuticals America, 2012)" (Takeda's Prevacid). These references note that Dexcel Pharma Technologies proposes, in part, to rely upon the approved labeling for Takeda's Prevacid for the approval of the proposed lansoprazole delayed-release ODT. Specifically, you cite reliance on the approved labeling for Takeda's Prevacid for the following information in your NDA:

   - primary pharmacology
   - mutagenicity and genotoxicity
   - carcinogenicity studies
   - impairment of fertility
   - animal toxicology
   - clinical pharmacology
   - pharmacokinetic profile
   - ADME of lansoprazole
   - drug-drug interactions
   - specific populations
   - safety of lansoprazole

   We also refer to your February 3, 2015, correspondence containing your responses to our requests for information dated January 30, 2015. Your response states that you are relying upon the approved labeling for Takeda's Prevacid for the clinical safety of your proposed lansoprazole delayed-release ODT.

   Furthermore, if there is a listed drug that is a pharmaceutical equivalent to the drug proposed in a 505(b)(2) application, that drug should be identified as a listed drug (see draft Guidance for Industry: Applications Covered by Section 505(b)(2) http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079345.pdf). Per your NDA submission, your proposed lansoprazole delayed-release ODT 15 mg is a pharmaceutical equivalent to Takeda's Prevacid SoluTab (lansoprazole) delayed-release ODT 15 mg (NDA 021428).

In your NDA submission, you should specify the listed drug(s) [by brand name (if applicable), active ingredient, and NDA number] that you are relying upon for approval of your application. For each listed drug relied upon, you must comply with the 505(b)(2) regulatory requirements, including (but not limited to) submission of (1) an appropriate patent certification or statement with respect to any relevant patents that claim the listed drug and (2) a bridge between your proposed drug product and each listed drug upon which you propose to rely to demonstrate that such reliance is scientifically justified. In addition, you must provide an updated FDA form 356h identifying the listed drug(s) upon which you are relying for approval of your application.

Note that this filing review represents a preliminary review of the application and is not indicative of deficiencies that would be identified if we performed a complete review.

We will refund 75% of the total user fee submitted with the application.

Within 30 days of the date of this letter, you may request in writing a Type A meeting about our refusal to file the application. A meeting package should be submitted with this Type A meeting request. To file this application over FDA's protest, you must avail yourself of this meeting.

If, after the meeting, you still do not agree with our conclusions, you may request that the application be filed over protest. In that case, the filing date will be 60 days after the date you requested the meeting. The application will be considered a new original application for user fee purposes, and you must remit the appropriate fee.

PROPOSED PROPRIETARY NAME

If you intend to have a proprietary name for the above-referenced product, submit a request for review of a proposed proprietary name when you resubmit the application. For questions regarding proprietary name review requests, contact the OSE Project Management Staff via telephone at (301) 796-3414 or via email at OSECONSULTS@cder.fda.gov.

If you have questions, contact Jeffrey Buchanan, Regulatory Health Project Manager, at (301) 796-1007.

Sincerely,

{See appended electronic signature page}

Theresa Michele, M.D.
Director
Division of Nonprescription Drug Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

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/s/

THERESA M MICHELE
02/06/2015

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

PIND 118528

**MEETING REQUEST-
WRITTEN RESPONSES**

Camargo Pharmaceutical Services, LLC
Attention: Ruth E. Stevens, Ph.D., M.B.A.
Chief Scientific Officer, Executive Vice President
(U.S. Agent for Dexcel Pharma Technologies, Ltd.)
9825 Kenwood Road, Suite 203
Cincinnati, OH 45242

Dear Dr. Stevens:

Please refer to your Pre-Investigational New Drug Application (PIND) file for lansoprazole delayed-release, orally-disintegrating tablets, 15 mg.

We also refer to your submission dated July 10, 2014, containing a Type C, Written Responses Only meeting request. The purpose of the submission was to inquire about the results of a bioequivalence study conducted by Dexcel Pharma Technologies, Ltd.

The enclosed document constitutes our written responses to the questions contained in your July 10, 2014 briefing package.

If you have questions, contact Jeff Buchanan, Regulatory Project Manager, at (301) 796-1007.

Sincerely,

{See appended electronic signature page}

Theresa Michele, M.D.
Director
Division of Nonprescription Clinical Evaluation
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

Enclosure:
Written Responses

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

WRITTEN RESPONSES

Meeting Type: Type C
Meeting Category: Guidance

Application Number: PIND 118528
Product Name: lansoprazole delayed-release, orally-disintegrating tablets, 15 mg

Indication: Treatment of frequent heartburn
Sponsor/Applicant Name: Camargo Pharmaceutical Services, LLC
(U.S. Agent for Dexcel Pharma Technologies, Ltd.)

Regulatory Pathway: 505(b)(2)

1.0 BACKGROUND

Dexcel Pharma Technologies Ltd. (DPT) intends to submit an NDA pursuant to section 505(b)(2) for an over-the-counter (OTC) lansoprazole delayed-release, orally-disintegrating tablet for the treatment of frequent heartburn.

FDA met with the sponsor on September 26, 2013, to discuss DPT's proposed regulatory submission pathway, as well as chemistry, nonclinical, and clinical data requirements for a marketing application. DPT conducted a randomized, open-label, 4-way crossover bioequivalence study of lansoprazole delayed-release, orally-disintegrating tablet (DPT) and Prevacid® 24HR (RLD) following a 15 mg dose in healthy subjects under fasted conditions.

On July 10, 2014, DPT requested a Type C guidance meeting to discuss the results of the bioequivalence study.

The sponsor's question is in **bold** type, and FDA's written response is in *italics*.

2.0 QUESTION

1. **Does the Division consider the ODT product to be bioequivalent with and/or without water to Prevacid under the three different treatment conditions?**

   FDA Response:
   A definitive determination regarding the bioequivalence of the product will be made after review of the data in the NDA.

Based on a cursory review of the results provided in your briefing package, your product appears to be bioequivalent to the reference product when your product was dissolved on the tongue and swallowed without water. However, when your product was dissolved on the tongue and swallowed with water, the C_{max} value of lansoprazole did not meet the bioequivalence criteria (mean ratio=87.26%, 90% CI: 78.59 - 96.90%). Given this issue, we recommend that you address the clinical implication of the results and proposed labeling in your NDA.

3.0 ADDITIONAL ADMINISTRATIVE COMMENTS

LABELING REGULATIONS AND GUIDANCES

As you develop your label and labeling, we call your attention to the following pertinent labeling regulations and guidances:

Regulations under the Code of Federal Regulations (CFR)
When you prepare your NDA for submission to FDA, include the following:

1. All of the proposed labels and labeling (i.e., all count sizes with immediate container and carton labeling, including samples, and consumer information leaflet if proposed) as required under 21 CFR 314.50.
    a. "clean" labeling and marked up labeling (i.e., annotated) defining the information in the summary and technical sections of the application that support the inclusion of each statement in the proposed labeling.
    b. font and format specified under 21 CFR 201.66 as part of the annotated labeling or detailed in a separate document.

2. In addition to the format and content requirements for over-the-counter (OTC) drug product labeling (21 CFR 201.66), we refer you to the following:
    a. 21 CFR, Part 201 Subpart A-General Labeling Provisions and
    b. Subpart C-Labeling Requirements for Over-the-Counter Drugs, which provides the labeling required for packaging (Principal Display Panel (PDP)-21 CFR 201.60 and statement of identity- 21CFR 201.61 etc.).

Guidances

1. See "Guidance for Industry– Labeling OTC Human Drug Products –Questions and Answers" (December 2008) for assistance with OTC labeling development. http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM078792.pdf

2. We recommend that you formally submit your proposed labeling in portable document format (PDF) electronically to your NDA. See "Guidance for Industry – Providing Regulatory Submissions in Electronic Format – General Considerations" (January 1999). http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072390.pdf

a. To ensure electronic storage, retrieval, and viewability of the submitted labeling, which are often oversized and complex documents (i.e., OTC labeling usually has complex graphics and large file size), follow FDA's portable document format (PDF) specifications detailed in the document found at the following URL: http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM163565.pdf

b. Questions and general information regarding the preparation of submissions in electronic format may be directed to CDER at esub@fda.hhs.gov.

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. 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 Pediatric and Maternal Health Staff 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

DATA STANDARDS FOR STUDIES

CDER strongly encourages IND sponsors to consider the implementation and use of data standards for the submission of applications for investigational new drugs and product registration. Such implementation should occur as early as possible in the product development lifecycle, so that data standards are accounted for in the design, conduct, and analysis of clinical and nonclinical studies. CDER has produced a web page that provides specifications for sponsors regarding implementation and submission of clinical and nonclinical study data in a standardized format. This web page will be updated regularly to reflect CDER's growing experience in order

to meet the needs of its reviewers. The web page may be found at: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm

LABORATORY TEST UNITS FOR CLINICAL TRIALS

CDER strongly encourages IND sponsors to identify the laboratory test units that will be reported in clinical trials that support applications for investigational new drugs and product registration. Although Système International (SI) units may be the standard reporting mechanism globally, dual reporting of a reasonable subset of laboratory tests in U.S. conventional units and SI units might be necessary to minimize conversion needs during review. Identification of units to be used for laboratory tests in clinical trials and solicitation of input from the review divisions should occur as early as possible in the development process. For more information, please see CDER/CBER Position on Use of SI Units for Lab Tests (http://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/default.htm).

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/s/

THERESA M MICHELE
09/26/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

PIND 118528

MEETING MINUTES

Camargo Pharmaceutical Services, LLC
Attention: Ruth E. Stevens, Ph.D., M.B.A.
Chief Scientific Officer, Executive Vice President
(U.S. Agent for Dexcel Pharma Technologies)
9825 Kenwood Road, Suite 203
Cincinnati, OH 45242-6252

Dear Dr. Stevens:

Please refer to your Pre-Investigational New Drug Application (PIND) file for lansoprazole delayed-release, orally-disintegrating tablets, 15 mg.

We also refer to the meeting between representatives of your firm and the FDA on September 26, 2013. The purpose of the meeting was to discuss your drug product development program.

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

If you have questions, contact Jeff Buchanan, Regulatory Project Manager, at 301-796-1007.

Sincerely,

{See appended electronic signature page}

Theresa Michele, M.D.
Acting Director
Division of Nonprescription Clinical Evaluation
Office of Drug Evaluation IV
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-IND
Meeting Date and Time:	September 26, 2013 at 11:00 A.M.
Meeting Location:	FDA/White Oak 10903 New Hampshire Avenue Building 22/Room 1421 Silver Spring, MD 20993
Application Number:	118528
Product Name:	lansoprazole delayed-release, orally-disintegrating tablets, 15 mg
Indication:	Treatment of frequent heartburn
Sponsor/Applicant Name:	Dexcel Pharma Technologies (U.S. Agent, Camargo Pharmaceutical Services, LLC)
Meeting Chair:	Theresa Michele, M.D.
Meeting Recorder:	Jeffrey Buchanan

FDA ATTENDEES

Division of Nonprescription Clinical Evaluation

Theresa Michele, M.D., Acting Director
Joel Schiffenbauer, M.D., Deputy Director
Lesley Furlong, M.D., Medical Team Leader
Lolita Lopez, M.D., Medical Officer
Jane Filie, M.D., Medical Officer
Cindy Li, Ph.D., Pharmacology/Toxicology Reviewer
Dan Brum, Pharm.D., M.B.A., B.C.P.S., R.A.C., Chief, Project Manager Staff
Jeffrey Buchanan, Regulatory Health Project Manager

Office of New Drug Quality Assessment

Swapan De, Ph.D., Pharmaceutical Assessment Lead
Muthukumar Ramaswamy, Ph.D., Chemistry Reviewer
Tapash Ghosh, Ph.D., Biopharmaceutics Team Leader
Tien Mien Chen, Ph.D., Biopharmaceutics Reviewer

Office of Clinical Pharmacology

Insook Kim, Ph.D., Clinical Pharmacology Reviewer

SPONSOR ATTENDEES

Dexcel Pharma Technologies

Tomer Gold, Vice President, Research and Development
Alona Korol, Head of Regulatory Affairs and Pharmacovigilance
Sigalit Melcer, Manager, Clinical Trials Department

Camargo Pharmaceutical Services, LLC

Ruth E. Stevens, Ph.D., M.B.A., Chief Scientific Officer, Executive Vice President
K. Gary Barnette, Ph.D., Vice President of Drug Development
Josh Johnson, Ph.D., Research Scientist

1.0 BACKGROUND

This was a Type B, Pre-IND meeting held September 26, 2013 at 11:00 A.M. between representatives of the Division of Nonprescription Clinical Evaluation (DNCE) and Dexcel Pharma Technologies (DPT) and their U.S. agent, Camargo Pharmaceutical Services, LLC (Camargo). The meeting was held in response to a pre-IND meeting request submitted May 1, 2013.

The purpose of the meeting was to discuss DPT's drug product development program for lansoprazole delayed-release, orally-disintegrating tablets, 15 mg.

Preliminary responses, based on the August 13, 2013 meeting background package, were provided to Camargo on September 24, 2013. Discussion at the meeting centered on questions 3, 4, 10 and the additional administrative comments.

Where no additional discussion appears after a preliminary response, no further discussion occurred at the meeting. The sponsor's questions are in ***bold;*** the Division's response is in *italics;* and the discussion is in normal font.

2.0 DISCUSSION

QUESTIONS:

1. **DPT plans to submit an NDA via the 505(b)(2) regulatory pathway for an OTC Lansoprazole Delayed-release Orally Disintegrating Tablet for the treatment of frequent heartburn. Is the Agency in agreement with the 505(b)(2) regulatory pathway for the proposed product?**

   DPT plans to rely on data in the public domain to satisfy the nonclinical requirements of the NDA and to demonstrate the clinical safety and efficacy of Lansoprazole Delayed-release Orally Disintegrating Tablets.

   FDA Preliminary Response:
   A 505(b)(2) application would be an acceptable approach at this time, based on the information provided. The Division recommends that sponsors considering the submission of an application through the 505(b)(2) pathway consult the Agency's regulations at 21 CFR 314.54, and the draft guidance for industry Applications Covered by Section 505(b)(2) (October 1999), available at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm. In addition, FDA has explained the background and applicability of section 505(b)(2) in its October 14, 2003, response to a number of citizen petitions that had challenged the Agency's interpretation of this statutory provision (see Docket FDA-2003-P-0274-0015, available at http://www.regulations.gov).

If you intend to submit a 505(b)(2) application that relies for approval on FDA's finding of safety and/or effectiveness for one or more listed drugs, you must establish that such reliance is scientifically appropriate, and must submit data necessary to support any aspects of the proposed drug product that represent modifications to the listed drug(s). You should establish a "bridge" (e.g., via comparative bioavailability data) between your proposed drug product and each listed drug upon which you propose to rely to demonstrate that such reliance is scientifically justified.

If you intend to rely on literature or other studies for which you have no right of reference but are necessary for approval, you also must establish that reliance on the studies described in the literature or on the other studies is scientifically appropriate. You should include a copy of such published literature in the 505(b)(2) application and identify any listed drug(s) described in the published literature (e.g. trade name(s)).

If you intend to rely on the Agency's finding of safety and/or effectiveness for a listed drug(s) or published literature describing a listed drug(s) (which is considered to be reliance on FDA's finding of safety and/or effectiveness for the listed drug(s)), you should identify the listed drug(s) in accordance with the Agency's regulations at 21 CFR 314.54. It should be noted that 21 CFR 314.54 requires identification of the "listed drug for which FDA has made a finding of safety and effectiveness," and thus an applicant may only rely upon a listed drug that was approved in an NDA under section 505(c) of the FD&C Act. The regulatory requirements for a 505(b)(2) application (including, but not limited to, an appropriate patent certification or statement) apply to each listed drug upon which a sponsor relies.

If you propose to rely on FDA's finding of safety and/or effectiveness for a listed drug that has been discontinued from marketing, the acceptability of this approach will be contingent on FDA's consideration of whether the drug was discontinued for reasons of safety or effectiveness.

We encourage you to identify each section of your proposed 505(b)(2) application that relies on FDA's finding of safety and/or effectiveness for a listed drug(s) or on published literature. In your 505(b)(2) application, we encourage you to clearly identify (for each section of the application, including the labeling): (1) the information for the proposed drug product that is provided by reliance on FDA's finding of safety and/or effectiveness for the listed drug or by reliance on published literature; (2) the "bridge" that supports the scientific appropriateness of such reliance; and (3) the specific name (e.g., proprietary name) of each listed drug named in any published literature on which your marketing application relies for approval. If you are proposing to rely on published literature, include copies of the article(s) in your submission.

In addition to identifying in your annotated labeling the source(s) of information essential to the approval of your proposed drug that is provided by reliance on FDA's previous finding of safety and efficacy for a listed drug or by reliance on published literature, we encourage you to also include that information in the cover letter for your marketing application in a table similar to the one below.

List the information essential to the approval of the proposed drug that is provided by reliance on the FDA's previous finding of safety and efficacy for a listed drug or by reliance on published literature	
Source of information (e.g., published literature, name of listed drug)	***Information Provided (e.g., specific sections of the 505(b)(2) application or labeling)***
1. Example: Published literature	*Nonclinical toxicology*
2. Example: NDA XXXXXX "TRADENAME"	*Previous finding of effectiveness for indication X*
3. Example: NDA YYYYYY "TRADENAME"	*Previous finding of safety for Carcinogenicity, labeling section XXX*
4.	

Please be advised that circumstances could change that would render a 505(b)(2) application for this product no longer appropriate. For example, if a pharmaceutically equivalent product were approved before your application is submitted, such that your proposed product would be a "duplicate" of a listed drug and eligible for approval under section 505(j) of the FD&C Act, then it is FDA's policy to refuse to file your application as a 505(b)(2) application (21 CFR 314.101(d)(9)). In such a case, the appropriate submission would be an Abbreviated New Drug Application (ANDA) that cites the duplicate product as the reference listed drug.

2. Does the Agency agree that for an OTC Lansoprazole Delayed-release Orally Disintegrating Tablets, Prevacid 24 HR (NDA 022327) is the appropriate Listed Drug (LD)?

FDA Preliminary Response:
Your choice of reference drug, Prevacid 24HR® capsule, for your lansoprazole orally-disintegrating tablet (ODT) product appears to be appropriate.

3. Does the Agency agree that a waiver for pediatric studies in children under the age of 18 is acceptable?

Use of OTC lansoprazole would not be consistent with the clinical practice recommendations for all pediatric age groups since the underlying causes for heartburn in children should be evaluated by a healthcare professional.

FDA Preliminary Response:
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. Your plan to request a waiver of the requirement for pediatric studies in patients under the age of 18 years appears reasonable at this time.

However, 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 held on or after November 6, 2012. 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," located at the following web address: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM360507.pdf. In addition, you may contact the Pediatric and Maternal Health Staff 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.

Discussion:
DPT requested clarification of the timing of the PSP submission. FDA confirmed the PSP should be submitted 210 days prior to the submission of the NDA, or earlier.

4. **The proposed bioequivalence and food-effect study protocols are included in this meeting package (Sections 15.2 and 15.1, respectively).Will the two proposed studies described below be sufficient to build a pharmacokinetic bridge between the proposed product and Prevacid 24 HR?**
   a. **The bioequivalence study will be a single-center, open-label, randomized, single-dose, 4-period, 4-sequence, crossover design in 60 healthy adult volunteers. The 4 study groups are as follows:**
      1. **Lansoprazole Delayed-release Orally Disintegrating Tablet (1 × 15 mg) placed on the tongue until disintegration and then swallowed without water**
      2. **Lansoprazole Delayed-release Orally Disintegrating Tablet (1 × 15 mg) placed on the tongue until disintegration and then swallowed with water**
      3. **Lansoprazole Delayed-release Orally Disintegrating Tablet (1 × 15 mg) swallowed with water**

4. **Prevacid 24 HR administered as (1 × 15 mg) swallowed with water**

b. The food-effect study is planned to be a single-center, comparative bioavailability, open-label, randomized, single-dose, 2-period, 2-sequence, crossover food-effect design. The Lansoprazole Delayed-release Orally Disintegrating Tablet (1 × 15 mg) will be placed on the tongue until disintegration and then swallowed without water under fasting and fed conditions.

FDA Preliminary Response:
We agree that the planned BE study may be used to establish the bridge between the proposed product and Prevacid 24HR®. The proposed food effect study appears acceptable for supporting the dosing instructions.

We recommend that in vivo disintegration time be recorded and provided in the NDA.

We also recommend that your protocol include a safety assessment of the oropharyngeal area after study drug administration.

We recommend you consult the Agency's guidance on ODT to define a product as an ODT: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm070578.pdf

Discussion:
DPT requested clarification of the FDA-recommended safety assessment of the oropharyngeal area after study drug administration. FDA reminded the sponsor that safety information should support the repeated use of the product over 14 days. A 14-day safety assessment may be necessary if the drug delivery technology is novel. If the ingredients have been used in this manner in other ODT products, DPT should include this information in their submission and provide a rationale as to why a 14-day safety assessment is not necessary. DPT proposed assessing the oropharyngeal area before and shortly after study drug administration. FDA recommended an additional assessment just prior to discharge from the study site. FDA advised that protocols should be submitted for review and comments. The sponsor replied that they will not be submitting an IND because they are performing a bioequivalence study.

5. DPT's proposed OTC Lansoprazole Delayed-release Orally Disintegrating Tablets are formulated as tablets, and as such, cannot be opened and taken with applesauce. Hence, DPT would like to request a biowaiver for the applesauce sprinkle study that is suggested in the FDA guidance on lansoprazole. Is the Agency in agreement?

FDA Preliminary Response:
We agree.

6. If the proposed OTC lansoprazole drug product is determined to be bioequivalent with the LD (Prevacid 24 HR) regardless of whether the tablet is allowed to disintegrate on

the tongue and regardless of whether the product is swallowed with or without water, does the Agency agree with the proposed Dosage and Administration section: " (b) (4) **"?**

FDA Preliminary Response:
Note that the OTC Drug Facts label does not have a "Dosage and Administration" section; instead, it has a "Directions" section.

Final labeling is an application review issue. The directions for use in the OTC Drug Facts label should not only reflect the results of the proposed trials but also the manner in which they are conducted. For example, your proposed language regarding the duration of time the tablet disintegrates should be supported by data and will be a review issue.

We anticipate that the other content of the Directions section of the OTC Drug Facts label (for example, the 14-day course of treatment and time to effect) will not be different from the reference drug.

In terms of the NDA submission, we remind you that your labeling should follow the "Drug Facts" labeling format and content requirements as specified in 21 CFR 201.66(c) and (d), and the general labeling provisions of 21 CFR 201 and 211.

7. **Will the Agency require label comprehension studies as a result of the proposed change from the LD in the Dosage and Administration information?**

FDA Preliminary Response:
With regard to your proposed difference from the listed drug in the Directions section of the label, it is unlikely that a label comprehension study will be needed. However, if other clinically important text in your label is significantly different from text in the listed drug's label, then consumer study(ies) may be needed.

8. **If the proposed OTC lansoprazole drug product is determined to be bioequivalent to the LD (Prevacid 24 HR), does the Agency agree that a survey of the available clinical and nonclinical literature, FDA adverse event database, World Health Organization (WHO) adverse event database, and past Agency findings will be adequate to demonstrate the safety and efficacy of the proposed OTC Lansoprazole Delayed-release Orally Disintegrating Tablet, and that no additional clinical safety and efficacy trials will be required for approval of the 505(b)(2) NDA?**

FDA Preliminary Response:
In addition to your proposal to include safety information from the above (FAERS, WHO, and clinical literature) databases, you need to submit the following safety information for lansoprazole at the time of your NDA submission:

- *Safety information from clinical trials using your proposed product*
- *Drug Abuse and Overdose Data:*
    - *National Poison Data (NPDS) from American Association of Poison Control Centers (AAPCC)*
    - *Drug Abuse Warning Network (DAWN)*

If you feel that information from a particular Drug Abuse and Overdose database listed above will not be useful for the assessment of the drug's safety for OTC use, you may provide a rationale for why such data is not needed.

Data from all sources should be summarized and analyzed by formulation, marketing status (Rx vs. OTC), dose, duration of use, year of reporting, and age.

You should also include a list of countries where the product is marketed nonprescription, foreign labels with English translation, and information on whether the product or the active ingredient has ever been withdrawn due to safety reasons.

We encourage you to come for a pre-NDA meeting at the appropriate time, and look forward to discussing with you the specific content and format of the safety information needed for your NDA submission.

9. Based on the bioequivalence of the proposed OTC lansoprazole product with the LD, the Sponsor believes that its proposed OTC lansoprazole product presents no new safety risks, and intends to rely on the nonclinical data for 15 mg Prevacid 24 HR to satisfy the safety requirements for NDA approval for its lansoprazole product by the 505(b)(2) regulatory pathway. Does the Agency agree with this approach?

FDA Preliminary Response:
Yes, you may rely on the nonclinical data for 15 mg Prevacid 24HR® to satisfy the safety requirements for NDA approval if the new orally-disintegrating tablet formulation does not present new pharmacokinetics/dynamics profile or toxicity patterns which differ from that obtained for the 15 mg Prevacid 24HR® product.

10. Does the Agency agree that the proposed lansoprazole raw material, finished product release, and finished product stability specifications are acceptable for NDA submission?

FDA Preliminary Response:
Your proposed specification for lansoprazole drug substance is acceptable. However, your proposed limits for (b) (4) *impurities in drug product exceed the ICH Q3B limits. Impurity levels that exceed the limits specified under ICH Q3B guidance*

warrant qualification. You may provide adequate justification to support the proposed limits.

Discussion:
DPT intends to submit 12 months of stability data from two demonstration batches and 6 - 9 months of stability data for three pivotal batches at the time of NDA submission (see Attachment 2: Stability Table). The demonstration batches are identical in batch size to the pivotal (production) batches except that they were manufactured at a different manufacturing site. FDA advised they would need more information submitted to the IND before commenting as this is a review issue; however, it is possible that the stability package will be acceptable if DPT can demonstrate that the products being manufactured at two different sites are comparable. DPT should submit stability data from accelerated and intermediate storage conditions. Dissolution data will be needed as well.

DPT stated they intend to bypass submission of an IND and proceed directly to submission of an NDA given this will be a bioequivalence (BE) study. FDA recommended that drug/alcohol interaction data be presented at a pre-NDA meeting.

ADDITIONAL ADMINISTRATIVE COMMENTS:

CDER strongly encourages IND sponsors to consider the implementation and use of data standards for the submission of applications for investigational new drugs and product registration. Such implementation should occur as early as possible in the product development lifecycle, so that data standards are accounted for in the design, conduct, and analysis of clinical and nonclinical studies. CDER has produced a web page that provides specifications for sponsors regarding implementation and submission of clinical and nonclinical study data in a standardized format. This web page will be updated regularly to reflect CDER's growing experience in order to meet the needs of its reviewers. The web page may be found at: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm

We encourage you to submit your requests for FDA review of your proposed proprietary name during the IND phase of your drug development program. The content requirements for such a submission can be found in the draft Guidance for Industry entitled, "Contents of a Complete Submission for the Evaluation of Proprietary Names," located at the following web address: (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075068.pdf). Please note that such a request can be made as early as at the end of phase 2 of the IND review process.

Your pre-IND has been assigned the number 118528. Please reference this number on all submissions and correspondence. Please note studies in humans may not be conducted under this PIND number. Before you may conduct studies in humans under this application number, you must submit an Investigational New Drug Application (IND, see 21 CFR Part 312) to the Division of Nonprescription Clinical Evaluation.

Discussion:
FDA stated that data files can be submitted in .xpt or SAS format, and that a file for adverse events (AEs) should be included in the NDA submission. DPT stated that AEs will be included as line listings with analysis and description in the ICH study report. FDA agreed.

3.0 SUMMARY OF KEY DISCUSSION POINTS AND ACTION ITEMS

1. DPT agreed to perform oropharyngeal safety assessments before and after drug product administration, including just prior to discharge from the study site. DPT acknowledged the need for 14-day safety assessments if the drug product delivery technology is novel.

2. DPT agreed to submit the PSP 210 days prior to the submission of the NDA, or earlier.

3. DPT agreed to submit their pharmacokinetic data files in .xpt or SAS format and to include an AE file as part of their NDA submission.

4. DPT stated that they will follow the ICHQ1A (R2) guidance for the stability testing for the drug product.

4.0 POST-MEETING ADDENDUM

Because this is an (b) (4) dosage form, an *in vitro* alcohol dose-dumping study is needed. Evaluate the alcohol-induced dose dumping of (b) (4) product by first conducting an *in vitro* alcohol dose-dumping test. Depending on the result of the *in vitro* testing, you may have to follow-up with an *in vivo* alcohol dose-dumping study. Note that if the results show an interaction of your (b) (4) product with alcohol, discuss these results with FDA prior to NDA submission.

Consider the following points during the development of the *in vitro* alcohol dose dumping study for your (b) (4) product:

- Conduct dissolution testing for all the proposed strengths using the optimal dissolution apparatus and agitation speed. Generate dissolution data from 12 dosage units (n=12) at multiple time points to obtain a complete dissolution profile.

- The following alcohol concentrations for the *in vitro* dissolution studies are recommended: 0, 5, 10, 20, and 40%.

- In general;
  - If the optimal dissolution medium is 0.1 N HCl, dissolution profiles in 0.1 N HCl (pH 1.2) containing the above range of alcohol concentrations would be sufficient.

- If the optimal dissolution medium is NOT 0.1 N HCl, dissolution profiles using the above range of alcohol concentrations in 0.1 N HCl and in the optimal dissolution medium are recommended.
- If the optimal dissolution medium has not been identified, dissolution profiles using the above range of alcohol concentrations in three physiologically relevant pH media (pH 1.2, 4.5, and 6.8) are recommended.
- If the dissolution of the (b) (4) product is pH independent, then dissolution data in 0.1 N HCl with the above range of alcohol concentrations is sufficient.

- Compare the shape of the dissolution profiles to determine if the (b) (4) characteristics are maintained, especially in the first 2 hours.

- Estimate the f2 values assessing the similarity (or lack thereof) between the dissolution profiles (using 0% alcohol as the reference). Provide 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 to us for review and comments.

5.0 ATTACHMENTS

Attachment 2: Stability Table

Batch Number	Batch Size (Tablets)	Stability		Manufacturing Site
		Start Date	Data available at NDA submission SEP 2014	
Pivotal # 1	(b) (4)			
Pivotal #2 and #3				
Demonstration batch #1***				
Demonstration batch #2***				
Supporting Batch #R1070711A*				
Supporting Batch #R1401211A*				
Supporting Batch #R1041012				
Supporting Batch #TBD				

(b) (4)

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

/s/

THERESA M MICHELE
10/25/2013