CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

214278Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

PIND 129881

MEETING MINUTES

Dexcel Pharma Technologies Ltd.
Attention: Monica Rohrschneider, PhD (Authorized Agent)
Managing Consultant, Regulatory Affairs
CBR International Corporation
2905 Wilderness Place, Ste. 202
Boulder, CO 80301

Dear Dr. Rohrschneider:

Please refer to your pre-investigational new drug application (PIND) file for esomeprazole delayed-release orally disintegrating tablet, 20 mg.

We also refer to the meeting between representatives of your firm and the FDA on October 31, 2019. The purpose of the meeting was to discuss the format and content of an NDA for a new delayed-release orally disintegrating tablet dosage form of esomeprazole.

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 any questions, call Helen Lee, Regulatory Project Manager at 301-796-6848.

Sincerely,

{See appended electronic signature page}

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

Enclosure:

- Meeting Minutes

MEMORANDUM OF MEETING MINUTES

Meeting Type:	B
Meeting Category:	Pre-NDA
Meeting Date and Time:	October 31, 2019; 1:30 – 2:30 PM (ET)
Meeting Location:	10903 New Hampshire Avenue White Oak Building 22, Conference Room: 1309 Silver Spring, Maryland 20903
Application Number:	PIND 129881
Product Name:	esomeprazole delayed-release orally disintegrating tablet
Indication:	Treatment of frequent heartburn (occurs 2 or more days a week) in adults (18 years of age and older)
Sponsor Name:	Dexcel Pharma Technologies Ltd.
Meeting Chair:	Karen Murry Mahoney, MD, FACE, Deputy Director
Meeting Recorder:	Helen Lee, PharmD, Regulatory Project Manager

FDA ATTENDEES

Office of New Drugs (OND)/Office of Drug Evaluation IV/Division of Nonprescription Drug Products (DNDP)
Karen Murry Mahoney, MD, FACE, Deputy Director
Jenny Kelty, MD, Clinical Team Leader
Teresa Podruchny, MD, Clinical Reviewer
Jane Sohn, PhD, Pharmacology/Toxicology Team Leader
Donald Charles Thompson, RPh, PhD, Pharmacology/Toxicology Reviewer
Kevin Lorick, PhD, Interdisciplinary Scientist Team Leader
Lori Parsons, PhD, Interdisciplinary Scientist
Dan Brum, PharmD, MBA, BCPS, RAC, Chief, Project Management Staff
Helen Lee, PharmD, Regulatory Project Manager

OND/Office of Drug Evaluation III/Office of Division of Dermatology and Dental Products (DDDP)
Fred Hyman, DDS, MPH, Clinical Reviewer

Office of Pharmaceutical Quality/Office of New Drug Products
Swapan De, PhD, Team Lead

Office of Translational Sciences/Office of Clinical Pharmacology
Sojeong Yi, PhD, Clinical Pharmacology Reviewer

Office of Pharmaceutical Quality/Division of Biopharmaceutics
Hansong Chen, PharmD, PhD, Biopharmaceutics Reviewer

SPONSOR ATTENDEES
Dexcel Pharma Technologies Ltd.
Tomer Gold, BSc, MSc, Vice President, Research and Development
Keren Agmon Mogle, BPharm, MBA, Head of Research and Development Regulatory Affairs
Sigalit Melcer, MSc, Manager, Clinical Trials Department
Valery Azulay, Head of Research and Development Chemistry, Manufacturing, and Controls
Liora Gerad, Team Manager, Regulatory Affairs
Michal Keisar, Analytical Research and Development Manager

CBR International Corp.
Jeanne M. Novak, PhD, CEO and Principal Consultant
Monica Rohrschneider, PhD, Managing Consultant – Regulatory Affairs
Leah Jimmerson, PhD, Acting Managing Consultant

1.0 BACKGROUND

On June 14, 2019, Dexcel Pharma Technologies (DPT) submitted a meeting request to discuss the format and content that will be included in a planned NDA submission for esomeprazole delayed-release (DR) orally disintegrating tablet (ODT).

On April 4, 2019, DPT submitted an initial Pediatric Study Plan (iPSP) with a full waiver request because esomeprazole delayed-release orally disintegrating tablets would be unsafe in all pediatric age groups, similar to the justification accepted for currently approved over-the-counter (OTC) proton pump inhibitor products. The FDA provided a written response on July 3, 2019. Subsequently, the Sponsor submitted an "Agreed iPSP" on August 28, 2019.

FDA met with DPT on May 23, 2016, to discuss the Sponsor's clinical development program and specific issues related to chemistry, manufacturing and controls (CMC). DPT intends to submit a 505(b)(2) New Drug Application (NDA) and intends to rely on FDA's findings of safety and efficacy of Nexium 24HR (esomeprazole magnesium) capsules approved under NDA 204655.

In response to the information and questions posed in the meeting package, FDA sent Preliminary Comments to the Sponsor on October 23, 2019.

2.0 DISCUSSION

The Sponsor's questions are **bolded**, FDA's preliminary responses are *italicized*, the Sponsor's postmeeting clarifying question to FDA's preliminary response is in ***bold italics***, and the meeting discussion and FDA's postmeeting response are in regular nonitalicized font.

Regulatory

Question 1:

Does the Agency agree that reliance on FDA's findings of safety and effectiveness for Nexium 24HR capsules (NDA 204655) is appropriate as part of the support for the approval of the proposed 505(b)(2) NDA?

FDA Response to Question 1:

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, in part, on Nexium 24HR capsules (NDA 204655) appears acceptable.

Clinical Pharmacology

Question 2:

Does the Agency agree that based on the demonstration of bioequivalence with Nexium 24HR capsules, the scientific bridge has been established and the Sponsor can rely on data and information in NDA 204655 for purposes of supporting the approval of the proposed Esomeprazole DR ODT drug product?

FDA Response to Question 2:

The summarized PK results of study 190030 in the meeting package appear acceptable to support an establishment of the scientific bridge. However, the final decision will be determined after review of the full clinical study report along with other information including the validation of the bioanalytical assay used for the PK study.

Question 3:

Does the Agency agree that the bioequivalence study using Nexium 24HR capsules as a reference drug, along with the bioavailability (food effect) study could be sufficient for gaining an approval of the 505 (b)(2) NDA?

FDA Response to Question 3:

The bioequivalence study and the food effect study appear sufficient to file your 505(b)(2) NDA. Whether the data of these studies would support an approval is a review issue and will be determined after the full review of your application.

Question 4:

Does the Agency agree with the proposed direction: "Place the tablet on tongue; tablet disintegrates, with or without water. The tablets can also be swallowed whole with water."?

FDA Response to Question 4:
Although the proposed direction of use may be reasonable based on the summarized PK results of study 190030, we do not agree upon the proposed labeling until we complete the full review of your NDA application.

Question 5:
Does the Agency agree with the proposed directions: "Take 1 tablet before eating in the morning"?

FDA Response to Question 5:
Although the proposed direction of use may be reasonable based on the summarized PK results of study 190031, we do not agree upon the proposed labeling until we complete the full review of your NDA application.

Clinical
Question 6:
Does the Agency agree that, based on demonstration of bioequivalence with Nexium 24HR capsules, the oropharyngeal examination, and FDA's determination of safety and efficacy for Nexium 24HR, no additional clinical studies are required to support the safety and efficacy of the proposed product?

FDA Response to Question 6:
During your May 23, 2016 meeting with the Agency, your plan to conduct oropharyngeal examinations was noted and you were advised that "No additional safety studies will be required if all ingredients are adequately qualified and there are no safety concerns that arise from the oropharyngeal examinations in your bioavailability investigations." The Agency further stated during that meeting that "Safety information in your NDA must support repeated use of your ODT formulation for the duration of treatment (14 days) in the OTC setting. Whether the product is safe for use during the 14-day treatment period is a matter for review."

Consistent with the May 23, 2016 response, we will evaluate the methodology of your completed oral safety evaluations and the safety results data as part of the formal NDA review process. We are unable to agree at this time that no additional clinical studies are required to support the safety and efficacy of the proposed product until our actual review is completed.

Question 7:
Does the Agency agree that the proposed sources as well as the proposed targeted time windows are sufficient to support the safety portion of the NDA?

FDA Response to Question 7:
In addition to the safety data from your PK studies, include a comprehensive literature review of the molecule with the initial NDA submission that contains a synthesized discussion of the findings with summary conclusions. Assess and discuss your findings as to whether there are differences or suggestions of differences in any part of the

safety profile between the immediate and delayed formulations. Discuss the strengths and weaknesses of each publication. Include a list of references. Full articles should be available upon request. Alternatively, the full publication can be hyperlinked to a corresponding listing. For critical safety references, include the full hyperlinked publication. Include as a safety issue the high incidence of dysgeusia reported in your studies.

For the FAERS, WHO, National Poison Data System (NPDS) and other databases, provide analysis and discussion by formulation and strength. Topics of interest include but are not limited to, acute and chronic kidney injury, cardiovascular events, hypocalcemia, acute generalized exanthematous pustulosis (AGEP), acute and chronic pancreatitis, hepatic encephalopathy and spontaneous bacterial peritonitis, all-cause mortality, and misuse (use greater than 14 days or three 14-day courses in one year).

Provide a list of countries in which the product is marketed OTC vs. Rx. As applicable, submit foreign language labels with English translation.

The 120-day safety update is an update of all of the sources of safety data that are included in the initial NDA.

Meeting Discussion (Question 7):
Dexcel agreed to submit data from FAERS and WHO. Dexcel stated it does not intend to submit data from NPDS and asked FDA whether that would be acceptable.

FDA stated that Dexcel's approach sounded reasonable on-face; however, Dexcel would need to submit a rationale with the NDA for review and determination. FDA clarified that all the source data listed in the preliminary comments must be included in the initial NDA submission (the 4-month safety update will include updates from the agreed-upon sources).

Postmeeting Comment (Question 7):
When you submit the NDA, include all requested safety information, with a cut-off date of 6 months prior to the NDA submission date (i.e. if the NDA is submitted January 1, 2020, the cutoff for safety information included would be no earlier than July 1, 2019). Include data up until at least the NDA submission date in the 4-month safety update.

Question 8:
Does the Agency agree with the Sponsor's approach for submitting the content of the Integrated Summary of Safety (ISS) in Module 2.7.4 only?

FDA Response to Question 8:
This appears reasonable assuming it meets criteria outlined in the guidance for industry Integrated Summaries of Effectiveness and Safety: Location Within the Common Technical Document (April 2009).

Nonclinical
Question 9:
Does the Agency agree that the levels of ascorbic acid, benzyl alcohol, triacetin, and modified starch in the proposed product can be considered qualified based on their presence in approved oral solutions/suspensions/syrups/chewable tablets described in the IID at concentrations higher than in the proposed product, and that no additional nonclinical studies are required to support the proposed product?

FDA Response to Question 9:
No, we do not agree. The safety of your proposed excipients will be reviewed at the time of your NDA submission. In general, justification based on concentrations/potencies of excipients is not sufficient to support safety, as explained below.

Ensure that you provide adequate justification for each proposed excipient in your NDA. Qualify each proposed excipient exceeding levels in currently approved oral products for safety as described in the FDA guidance for industry Nonclinical Studies for the Safety Evaluation of Pharmaceutical Excipients (May 2005).

If you intend to use an FDA-approved product to justify your proposed level for a specific excipient, note that information from the Inactive Ingredient Database (IID) alone may not provide sufficient information to provide an adequate justification because the IID focuses on potency. Adequate justification of proposed excipient levels addresses the route of administration, maximum daily dose (MDD), duration of use, the intended consumer population/indication of your proposed product.

We suggest that you provide a table in your NDA submission summarizing the information to support your proposed excipients. If you choose to rely upon animal data, instead of an approved product, state how the studies address the recommendations for chronic use (long-term), oral products as described in the guidance for industry Nonclinical Studies for the Safety Evaluation of Pharmaceutical Excipients (May 2005). Refer to the table below for an example of how you could present your information.

		Comparable Product				Level Supported from Appropriate Nonclinical Studies	
Excipient Name	Proposed Product Maximum Daily Dose (mg)	Maximum Daily Dose (mg)	Target Population and Indication	Route	Duration of Use	Maximum Daily Dose (mg)	Justification
Excipient X	5 mg	15 mg	Nonprescription cough/cold	Oral	Chronic (lifetime)	N/A	N/A
Excipient Y	10 mg	N/A	N/A	N/A	N/A	1000 mg	Genetic toxicology battery, chronic general toxicology studies in two species, carcinogenicity assessment, developmental and reproductive battery. See description of studies in Section Z, and Letter of Authorization to Drug Master File containing studies.

Additional Comments:
Provide structures of any impurities and degradants of the drug substance and drug product in your NDA. Monitor impurities and degradation products of all active ingredients and refer to ICH guidances for industry Q3A(R2) Impurities in New Drug Substances (June 2008) and Q3B(R2) Impurities in New Drug Products (July 2006) for possible qualification requirements. Impurities or degradants of active ingredients that are identified as having mutagenic structural alerts need to be at or below acceptable qualification thresholds to support an IND submission and NDA as described in the ICH guidance for industry M7 Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk (March 2018). To facilitate the review of impurities, report the total daily intake (TDI) of each impurity as determined by the proposed use of your product.

Meeting Discussion (Question 9):
Dexcel stated it will submit all relevant information from the IID and supporting information from its comparable approved products.

FDA recommended that Dexcel estimate and submit the total patient dose per day of each component in explicit detail based on the recommended dosing regimen in the proposed labeling. FDA stated that Dexcel will need to provide a letter of authorization from the drug master file (DMF) holder for the proposed flavoring ingredient that was referred to in the briefing package. FDA noted that if supporting information for the

flavor constituents is not provided individually, then Dexcel will need to ensure that the DMF holder is aware of what safety information will be available to FDA in the DMF.

Dexcel noted that the drug will have a once daily dosing regimen and asked if the information from the IID would be sufficient. FDA stated that if the IID reports the excipient potency on a mg-per-tablet basis, then it would likely be acceptable.

FDA stated that potency in the IID is usually listed as a concentration and does not provide information on the total daily intake (mg/day) that an individual was exposed to in the approved reference drug product. In addition, the indication for the approved excipient use may not necessarily be appropriate for OTC use. FDA recommended that Dexcel calculate and tabularize the maximum daily dose for each of the excipients proposed for use in the finished drug product formulation. FDA emphasized that maximum daily dose should be the focus and not potency.

Dexcel stated it will submit the data using the table provided, but for the products that rely on the IID, the database does not have all the necessary information such as duration of use. Dexcel stated it will do its best to provide the requested data within those limitations.

FDA stated that they are aware of the limitations of the IID, but it is still Dexcel's responsibility to submit adequate safety justification for each proposed excipient, and the corresponding use level thereof, regardless of the publicly available information in the IID.

CMC
Question 10:
Does the Agency agree with the Sponsor's proposal to include 9 months of stability data in the application, followed by submission of 12 months of stability data within 60 calendar days after NDA submission?

FDA Response to Question 10:
Yes, the proposed submission of 12 months stability data within 60 calendar days after the NDA submission appears acceptable.

Question 11:
Does the Agency agree that the data included to support the selected dissolution method is acceptable?

FDA Response to Question 11:
No, we do not agree that the dissolution method, as proposed in the briefing package, is adequate. In the gastric resistance method described in the briefing document, provide details on preparation of samples and the quantitation of esomeprazole in the acid stage.

Considering that esomeprazole is not stable at pH below 4, FDA recommends use of an indirect method (i.e., % dissolved at acid stage = the amount of esomeprazole from the

assay – the amount of esomeprazole remained after acid stage) in the determination of esomeprazole dissolved in the acid stage. In addition, clarify the proposed rotation speed in the acid stage. On Page 50 of the meeting package, you propose (b) (4) rpm as the agitation speed; however, on Pages 51 and 52, you indicated (b) (4) rpm.

The dissolution conditions for the buffer stage appear reasonable. However, the data provided indicate that the method has no meaningful discriminatory power.

Additionally, the proposed drug product is an orally disintegrating tablet; therefore, we recommend a disintegration test and acceptance criterion to be proposed in the future NDA.

We also have the following additional comments regarding dissolution data and dissolution acceptance criteria:

(b) (4)

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3.0 OTHER IMPORTANT INFORMATION

PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), 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 (iPSP) within 60 days of an End-of-Phase-2 (EOP2) meeting. In the absence of an EOP2 meeting, refer to the draft guidance below. The iPSP 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 iPSP should be submitted in PDF and Word format. Failure to include an Agreed iPSP with a marketing application could result in a refuse to file action.

For additional guidance on the timing, content, and submission of the iPSP, including an iPSP 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*.[1] In addition, you may contact the Division of Pediatric and Maternal Health at 301-796-2200 or email Pedsdrugs@fda.hhs.gov. For further guidance on pediatric product development, please refer to FDA.gov.[2]

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).[3] 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 Regulations.gov.[4]

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

[1] When final, this guidance will represent the FDA's current thinking on this topic. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.
[2] https://www.fda.gov/drugs/development-resources/pediatric-and-maternal-health-product-development
[3] We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.
[4] http://www.regulations.gov

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. by 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 FDA has approved one or more pharmaceutically equivalent products in one or more NDA(s) before the date of submission of the original 505(b)(2) application, you must identify one such pharmaceutically equivalent product as a listed drug (or an additional listed drug) relied upon (see 21 CFR 314.50(i)(1)(i)(C), 314.54, and 314.125(b)(19); see also 21 CFR 314.101(d)(9)). If you identify a listed drug solely to comply with this regulatory requirement, you must provide an appropriate patent certification or statement for any patents that are listed in the Orange Book for the pharmaceutically equivalent product, but you are not required to establish a "bridge" to justify the scientific appropriateness of reliance on the pharmaceutically equivalent product if it is scientifically unnecessary to support approval.

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 is supported by reliance on FDA's finding of safety and/or effectiveness for a listed drug(s) or on published literature (see table below). 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 the source of supporting information in your annotated labeling,

we encourage you to include in your marketing application a summary of the information that supports the 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 effectiveness 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 A*
(3) Example: NDA YYYYYY "TRADENAME"	*Previous finding of safety for Carcinogenicity, labeling section B*
(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 ISSUES REQUIRING FURTHER DISCUSSION

No issues requiring further discussion.

5.0 ACTION ITEMS

No action items.

6.0 ATTACHMENTS AND HANDOUTS

No attachments or handouts.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

KAREN M MAHONEY
11/22/2019 08:38:42 AM