CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208056Orig1s000

CHEMISTRY REVIEW(S)

Recommendation: This 505(b)(1) NDA is recommended for **APPROVAL** with the drug product **expiration dating period of 30 months**.

NDA 208056
Review # 1

Drug Name/Dosage Form	Orally Disintegrating Tablet
Strength	30mg
Route of Administration	Oral
Rx/OTC Dispensed	Rx
Applicant	Takeda Pharmaceuticals, U.S.A., Inc.
US agent, if applicable	N/A

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
NDA Original Submission	03/26/2015	All
Amendment	05/15/2015	Drug Product and Biopharmaceutics
Amendment	07/14/2015	Drug Product, Drug Product Process, and Quality Microbiology
Amendment	09/15/2015	Drug Substance, Drug Product, and Drug Product Process
Amendment	09/18/2015	Drug Product
Amendment	10/09/2015	Drug Product, Environmental Assessment
Amendment	10/15/2015	Drug Product Process and Biopharmaceutics
Amendment	11/05/2015	Drug Product Process and Biopharmaceutics

Quality Review Team

DISCIPLINE	REVIEWER	BRANCH/DIVISION
Drug Substance	Benjamin Stevens, Ph. D.	ONDP/DNDAPI Branch II
Drug Product	Hamid Shafiei, Ph. D.	ONDP/Division II/Branch IV
Process	Yubing Tang, Ph. D.	OPF/Division II/Branch V
Microbiology	Yubing Tang, Ph. D.	OPF/Division II/Branch V
Facility	Marisa Heayn/Juandria Williams	OPF/DIA/Branch III
Biopharmaceutics	Peng Duan, Ph. D.	OPQ/DB/Branch II
Regulatory Business Process Manager	Truong Quach, Pharm D.	OPQ/OPRO/Branch I
Application Technical Lead	Hamid Shafiei, Ph. D.	ONDP/Division II/Branch IV
Laboratory (OTR)		
ORA Lead	Paul Perdue	ORA/OO/OMPTO/DMPTPO/MDTP
Environmental Assessment (EA)	Hamid Shafiei, Ph. D.	ONDP/Division II/Branch IV

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Quality Review Data Sheet

1. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	STATUS	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	Type III		(b) (4)	N/A		
	Type III			N/A		
	Type III			N/A		
	Type III			N/A		
	Type III			N/A		
	Type III			N/A		
	Type IV			N/A		
	Type IV			N/A		

1 Adequate, Adequate with Information Request, Deficient, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents: *IND, RLD, or sister applications*

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
NDA	NDA 22287	Dexilant (dexlansoprazole) Delayed-Release Capsules
NDA	NDA 20406	PREVACID (lansoprazole) Delayed-Release Capsules
Type B, Pre-NDA meeting	106858	Discussion of the planned NDA submission

2. CONSULTS:

DISCIPLINE	STATUS	RECOMMENDATION	DATE	REVIEWER
Biostatistics	----------	N/A	---------	----------
Pharmacology/Toxicology	----------	N/A	---------	----------
CDRH	----------	N/A	---------	----------
Clinical	----------	N/A	---------	----------
Other	----------	N/A	---------	----------

Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The applicant of this NDA has provided sufficient CMC information to assure the identity, purity, strength and quality of the drug substance and drug product.

The Office of Process and Facility has issued "Approval" recommendation for all facilities involved in this application.

All labels/labeling issued have been resolved.

Therefore, from the OPQ perspective, this NDA is recommended for approval with the expiration dating period of 30 months.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

N/A

II. Summary of Quality Assessments

Dexilant SoluTab (dexlansoprazole) delayed release orally disintegration (OD) tablets, 30mg for oral use contain the active ingredient, dexlansoprazole, a proton pump inhibitor which is the R-enantiomer of the racemic mix lansoprazole, an approved proton pump inhibitor marketed in the United States for use in adult patients since May 1995. Dexilant SoluTab OD tablets have been developed as an alternative dosage form to Dexilant (dexlansoprazole) delayed release capsules 30mg, and 60mg approved for marketing since January 30, 2009. This new formulation of dexlansoprazole allows for quick disintegration of the tablet in the oral cavity eliminating the need to swallow the tablet and/or drink water.

Dexilant is indicated for healing of all grades of erosive esophagitis (EE), maintaining healing of EE and relief of heartburn, and treatment of heartburn associated with symptomatic non-erosive gastroesophageal reflux disease (GERD).

A. Drug Substance, Dexlansoprazole Quality Summary

Dexlansoprazole,

(1) 1*H*-Benzimidazole, 2-[(*R*)-[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]sulfinyl]-; (2) (+)-2-[(*R*)-{[3-Methyl-4-(2,2,2-trifluoroethoxy)pyridin-2-yl]methyl}sulfinyl]-1*H*-benzimidazole; (3) 2-

[(*R*)-[[3-Methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]sulfinyl]-1*H*-benzimidazole

a proton pump inhibitor is the R-enantiomer of the racemic mix lansoprazole. It is the active ingredient used in the currently approved Dexilant (dexlansoprazole) delayed-release capsules. It is a pale yellowish white crystalline powder with molecular weight of 369.36 (b) (4) (b) (4) This drug substance is classified as BCS Class II (b) (4) This API is very slightly soluble in water with increased solubility at higher pH. This API is soluble in 0.1M sodium hydroxide and acetonitrile, freely soluble in dimethylformamide, methanol, dichloromethane, ethanol, and ethyl acetate, slightly soluble in diethyl ether, and practically insoluble in hexane.

(b) (4) The manufacturing process for dexlansoprazole is well-characterized and includes appropriate control strategy and in-process testing. The detail of the manufacturing process for dexlansoprazole is provided in the referenced Dexilant (dexlansoprazole) delayed-released capsules NDA 22287 (approved on January 30, 2009).

This drug substance is packaged in a (b) (4) (see referenced NDA 22287).

In conclusion, the drug substance, dexlansoprazole is produced by a well-established well-characterized robust manufacturing process with the appropriate control strategy that enables production of API with consistent quality batch to batch. This API is tested and released according to a specification that clearly assures the identity, strength, purity and quality of API at release and throughout the designated retest period. The stability data provided in the referenced NDA 22287 clearly supports the proposed (b) (4) retest date for this drug substance.

B. Drug Product, Dexilant SoluTab (dexlansoprazole) Delayed-Release Orally Disintegrating Tablets Quality Summary

Dexilant SoluTab (dexlansoprazole) delayed-release orally disintegrating (OD) tablets similar to the currently approved Dexilant delayed-release capsules 30mg, and 60mg are indicated for healing of all grades of erosive esophagitis (EE), maintaining healing of EE and relief of heartburn, and

treatment of heartburn associated with symptomatic non-erosive gastroesophageal reflux disease (GERD).

Dexilant SoluTab delayed-Release OD tablet has been formulated to facilitate dosing by quick disintegrating in the oral cavity eliminating the need to swallow the tablet and/or drink water. Dexilant SoluTab delayed-release OD Tablets for commercial use will be packaged (b) (4) in a 100-unite per package configuration.

Dexilant SoluTab delayed-release OD tablets consist of two types of dexlansoprazole enteric coated microgranules (b) (4) (b) (4)

The pharmaceutical development for Dexilant delayed-release OD tablets was targeted toward producing a drug product bioequivalent to the currently marketed Dexilant delayed-release capsules. Formulation development and the selection of components for this drug product were based on the formulation of the currently marketed lansoprazole OD tablets. Therefore, the components used in the composition of Dexilant SoluTab delayed-release OD tablets are similar to the components used in lansoprazole OD tablets.

Each Dexilant SoluTab (dexlansoprazole) delayed-release OD tablet, 30mg contain 30mg of dexlansoprazole as the active ingredient, and lactose monohydrate-microcrystalline cellulose spheres, magnesium carbonate, low-substituted hydroxypropyl cellulose, hydroxypropyl cellulose, hypromellose, talc, titanium dioxide, mannitol, methacrylic acid copolymer, ethyl acrylate methyl methacrylate copolymer, polysorbate 80, glyceryl monostearate, triethyl citrate, anhydrous citric acid, ferric oxide, yellow; polyethylene glycol 8000, methylacrylate methylmethacrylate methacrylic acid copolymer, microcrystalline cellulose, crospovidone, sucralose, strawberry durarome, and magnesium stearate as the excipients. The excipient used in the composition of this drug product are all either compendial, or contain compendial components, and/or tested and release according to the current compendial procedures and requirements.

The drug product specification includes testing and acceptance criteria for appearance, identity (UV spectrum and HPLC retention time), assay (b) (4) %) related substances (NMT (b) (4) % each known impurity, NMT (b) (4) % individual unknown impurity, and NMT (b) (4) % total related substances), Content uniformity (USP <905>), (b) (4) disintegration (b) (4) seconds; USP <701>), dissolution (acid stage: NMT (b) (4) % in 120 minutes; buffer stage: (b) (4) % in 15 minutes and NLT (b) (4) % in 60 minutes; USP <711>), and bioburden. Based on Biopharm, Microbiology, and ONDP

reviewers' assessments, the proposed specification for Dexilant SoluTab delayed-release OD tablets is deemed adequate to assure indent, strength, purity, and quality of the drug product at release and throughout the proposed product shelf-life.

The applicant has provided 6-month accelerated, 12-month intermediates and 24-month long-term stability data from multiple batches of the drug product that clearly support the proposed product expiration dating period of 30 months.

In summary, the applicant has provided sufficient CMC information to illustrate the applicant's capability to routinely manufacture this drug product with adequate quality attributes that will meet the proposed drug product specification. Therefore, from the drug product perspective, this application is recommended for approval.

C. Manufacturing Process

Formulation and process development information provided is found to be based on the attributes/properties of critical materials, especially the drug substance, and demonstrates a robust manufacturing process. The description of manufacturing process provided adequately reflects that of process development and is considered satisfactory. (b) (4) In summary, the applicant has provided sufficient information to show that the manufacturing process is robust and capable for producing the drug product with consistent quality that meet the proposed drug product specification. Therefore, from the manufacturing process perspective, this application is recommended for approval.

D. Biopharmaceutics

Dissolution acceptance criteria in the drug product specification are deemed satisfactory. Significant alcohol dose dumping effect was noticed. OCP will be addressing the potential impacts of alcohol dose dumping.

The justification for ODT designation was found to be appropriate and therefore, ODT designation is accepted. From the biopharm perspective this application is recommended for approval.

E. Facilities

The Office of Process and Facility has issued "Approval" recommendation for all facilities involved in this application.

F. Environmental Assessment

The applicant's request for the categorical exclusion from the environmental assessment analysis is granted.

G. Summary of Drug Product Intended Use

Proprietary Name of the Drug Product	Dexilant SoluTab Delayed-Release Orally Disintegrating Tablets
Non Proprietary Name of the Drug Product	Dexlansoprazole Delayed-Release Orally Disintegrating Tablets
Non Proprietary Name of the Drug Substance	Dexlansoprazole
Proposed Indication(s) including Intended Patient Population	(b) (4) 2) Maintaining healing of EE and relief of heartburn 3) Treatment of heartburn associated with symptomatic non-erosive gastroesophageal reflux disease (GERD)
Duration of Treatment	(b) (4) 6 months, and 4 weeks, respectively
Maximum Daily Dose	30mg
Alternative Methods of Administration	None

OVERALL ASSESSMENT AND SIGNATURES: EXECUTIVE SUMMARY

Application Technical Lead Signature:
Based on the OPQ review team assessment, this application is recommended for approval from the CMC perspective with product expiration dating period of 30 months.

Hamid Shafiei, Ph.D.
Application Technical Lead
ONDP, Branch V, Division II

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ASSESSMENT OF THE BIOPHARMACUETICS

38. Are the in-vitro dissolution test and acceptance criteria adequate for assuring quality control and consistent bioavailability of the drug product?

Applicant's Response:

The Applicant has developed a 30 mg dexlansoprazole delayed-release (DR) orally disintegrating (OD) tablet formulation, which consists of dexlansoprazole dual DR microgranules [redacted] (b) (4) The proposed dissolution method is as shown below:

Stage	Method Parameter	Description
Acid stage	Apparatus	USP Apparatus 1, Basket (Mesh size: 100)
	Agitation	100 rpm
	Dissolution medium	0.1 N HCl
	Medium volume	500 mL (±1%)
	Medium temperature	37°C (±0.5°C)
	Sampling point	120 minutes
	Sampling volume	25 mL
	Deaeration	No
Buffer stage	Apparatus	USP Apparatus 1, Basket (Mesh size: 100)
	Agitation	100 rpm
	Dissolution medium	50 mmol/L phosphate buffer (pH 7.20) containing 5 mmol/L sodium lauryl sulfate (SLS)
	Medium volume	900 mL (±1%)
	Medium temperature	37°C (± 0.5°C)
	Sampling point	5, 10, 15, 20, 30, 45, 60, 75, 90, 120, and 150 minutes *
	Sampling volume	10 mL
	Deaeration	No

*Sampling points used in development

Reviewer's Assessment:

Reviewer's Assessment:

1. Evaluation of dissolution method

Dexlansoprazole was developed as orally disintegrating tablets (ODT) comprising of two kinds of enteric coated microgranules [redacted] (b) (4) as shown in Figure 1. The

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(b) (4)

Overall, the dissolution validation is appropriate and the proposed dissolution method is acceptable.

2. Alcohol dose dumping

Since the proposed drug product is a delayed release ODT tablets, the Applicant conducted in vitro alcohol dose-dumping study to evaluate the drug release in the presence of 0% (baseline), 5%, 10%, 20%, and 40% alcohol.

The Applicant first evaluated the drug release at Acid Stage in the presence of various concentrations of alcohol. After the completion of the acid stage testing, each sample was transferred to the corresponding buffer stage medium containing the same level of ethanol as the Acid Stage. The 40% alcohol is not evaluated in the Buffer Stage because all drugs were released in the Acid Stage in the presence of 40% alcohol. Figure 8a and 8b shows the dissolution profiles of proposed drug products in the presence of various concentrations of alcohol.

As Figure 8a shows, at the Acid Stage, the presence of 20% and 40% of alcohol significantly increase the drug release. Although 40% of alcohol is not evaluated in the Buffer Stage, the drug released in the presence of 20% alcohol is significantly different from the baseline, but with lesser extent as shown in Figure 7b and f2 calculations shown in Table 2. The f2 values (Table 2), although are slightly different as the reviewer's own calculation (55.2, 52.4, and 31.6, respectively), show the dissolution profile of drug release in the presence of 20% alcohol is different as the control (baseline; without alcohol).

Figure 8a. Comparison of dissolution profiles of acid stage media at various concentrations of ethanol (0, 5, 10, 20 and 40%)

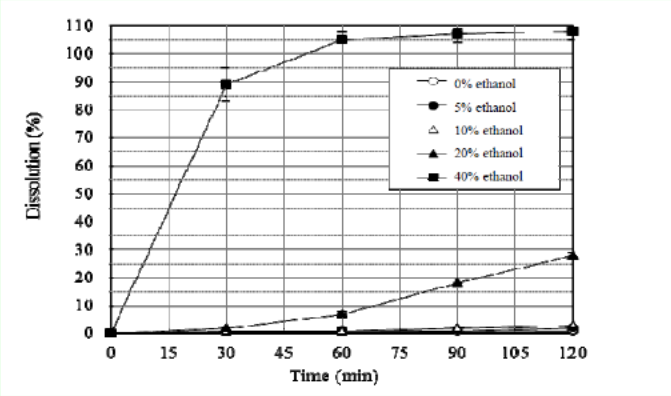


Figure 8b. Comparison of dissolution profiles of buffer stage media at various concentrations of ethanol (0, 5, 10 and 20%)

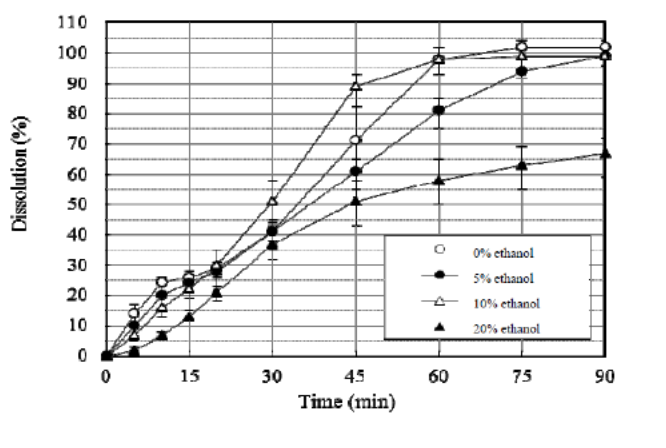


Table 2. The **f2 values of dissolution profiles of buffer stage with ethanol (5, 10 and 20%)**

	Dissolution rate (%)				f2 value
	15 min	30 min	60 min	90 min	
0% ethanol (control)	26%	41%	98%	102%	-
5% ethanol	24%	41%	81%	99%	53
10% ethanol	22%	51%	98%	99%	62
20% ethanol	13%	37%	58%	67%	28

Overall, there is significant potential of alcohol dose-dumping for drug release at the Acid Stage in the presence of 40% alcohol. 90% of drug will be released within 30 min in the presence of 40% alcohol, compared to 1-2% of release at the same time point in the presence of 0%, 5%, and 20% alcohol. The impact of in vitro alcohol dose dumping on drug safety, and the need for conducting in vivo alcohol dose dumping study will be consulted to and to be evaluated by the Office of Clinical Pharmacology.

3. Dissolution acceptance criteria

Figure 9 shows the dissolution profiles of Bio-Batch Z675501, clinical/stability batch Z675502, and stability batches Z675503/Z675504 with the proposed dissolution method. The dissolution acceptance criteria proposed by the Applicant is shown as follows:

15 min: (b) (4)%
60 min: (b) (4)%

Figure 9. Dissolution profiles of Bio-Batch Z675501, clinical/stability batch Z675502, and stability batches Z675503/Z675504 (Red line represents the time point and range proposed by the Applicant)

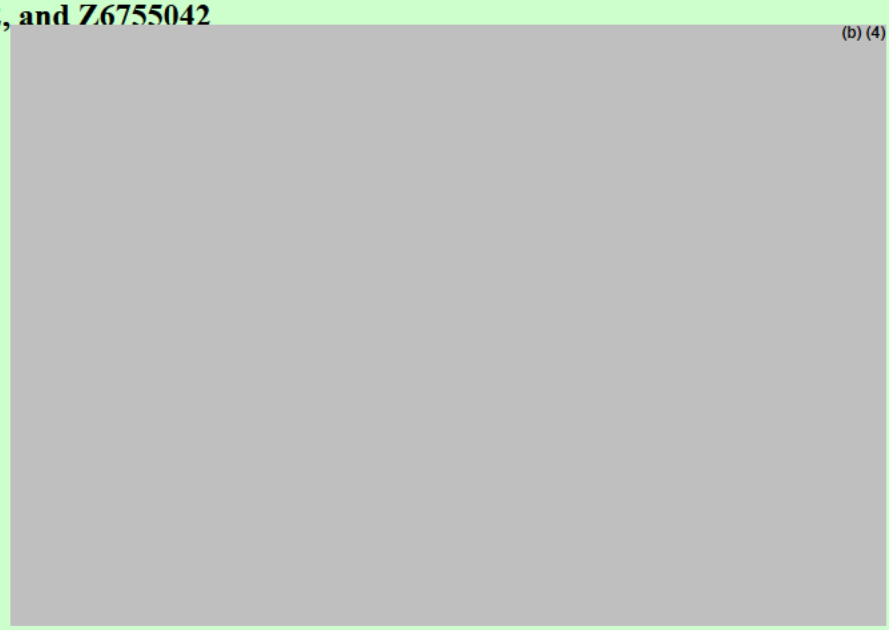
The proposed drug formulation contains (b) (4) granules. The first time point of 15 min will be used to evaluate the drug release from (b) (4) microgranules. The amount of drug released from the (b) (4) granules is about (b) (4)% of the labeled amount of drug (30 mg). Therefore, the proposed acceptance criterion at 15 min is ± (b) (4)% of the

theoretical mean release value and this criterion are supported by the Figure 8 shows and the lower and higher range ((b) (4) %) at this time point for all tested units fall within that criterion.

To ensure the complete release of the (b) (4) microgranules accounting around (b) (4) % of the labeled amount of drug, a specification at 60 min is also set based on the dissolution profile of bio-batch Z675501, and it is supported by the batches tested in Figure 9. The mean drug release at 60 min for all units from each batch tested ranges from (b) (4) %.

Figure 10 shows the stability tests conducted at 15 min and 60 min time points for three stability batches under room temperature and accelerated storage conditions. The points represent the lower and higher release in all units tested from each batch. The blue dash line represents the (b) (4) % specification at 15 min, while the red dash line represents the NLT (b) (4) % at 60 min. Although the specification will not be set based on the drug release of the accelerate storage condition, we can see from the Figure 9, the drug release in all stability testing including both room temperature and accelerated conditions meets the dissolution acceptance criteria. Therefore, the proposed dissolution acceptance criteria are acceptable.

Figure 10 Drug release in stability test for three stability batches Z675502, Z6755032, and Z6755042



4. Justification of ODT Designation

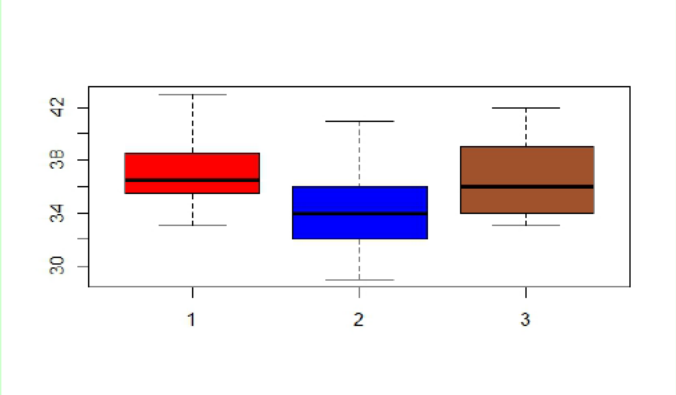
Dexlansoprazole Delayed-Release Orally Disintegrating Tablets (ODT) (30 mg) (Dexlansoprazole OD tablet) formulation is designed to disintegrate quickly on the tongue without water. The Applicant conducted both in vivo and in vitro studies to determine the characteristics of ODT. In the in vivo study TAK-390MR (OD) 107, 8 subjects tested in vivo disintegration time of ODT tablet by mouth and each subject performed the test in triplicate. Figure 11 shows the boxplots of the disintegration time of

ODT tablet in 8 subjects for each of the test. During the test, each subject sipped and swallowed 20 mL of spring water 30 sec prior to tablet administration (for rinsing purpose) and 30 sec after the water was consumed; the ODT was placed on the tongue and gently rolled against the roof of the mouth with the tongue until the tablet disintegrated into small granules.

In the Guidance for Industry: Orally Disintegrating Tablets, ODT tablet is defined as: *A solid dosage form containing medicinal substances, which disintegrates rapidly, usually within a matter of seconds, when placed upon the tongue.* In order to distinguish ODT with other oral dosage forms, such as chewable tablets, ODT tablet should exhibit rapid oral disintegration in saliva without assistance of chewing or drinking liquids to help ***ingest*** these products. In this Guidance, however, there are no detailed requirements on how an *in vivo* disintegration study should be conducted.

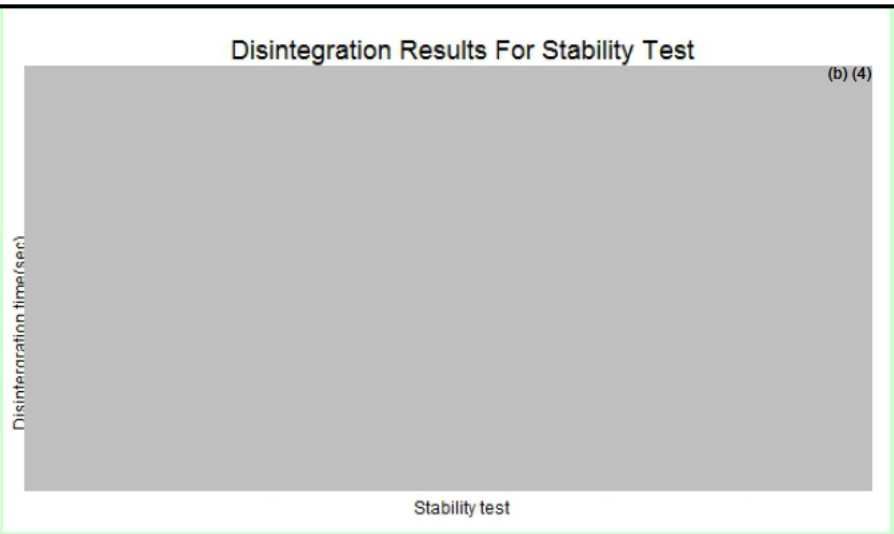
Wetting the tongue with water only but not administrated/ingested with water, will help provide a similar tongue moisture baseline for each subject, and thus reducing the intrasubject variability on the tongue moisture (e.g. avoid the effect of dry mouth might exist in some subjects). Therefore, this test approach is acceptable from the perspectives of Biopharmaceutics. The mean in vivo disintegration time is 36 sec, with 95% confidence interval of 34.6~37.4 sec. Each subject was tested the disintegration time three times, and the overall disintegration time measured was consistent (Figure 11).

Figure 11. Reviewer's own Boxplot of in vivo disintegration time results of 8 subjects in three replicated tests (Test 1- Test 3)



The Applicant also measured the in vitro disintegration time at each test interval in the primary stability studies (Figure 12).

Figure 12. Reviewer's own plot of Mean disintegration (sec) results for dexlansoprazole ODT stability(Red dash line represents the mean of all measured disintegration time, blue dash line represents the 30s criterion described in ODT Guidance)



The mean *in vitro* disintegration time measured in stability test up to 24 months is (b) (4) sec with 95% CI of (b) (4) sec, which showed consistent results.

Overall, the disintegration times measured in vitro and in vivo are similar and consistent. Per the *Guidance for Industry: Orally Disintegrating Tablets*, ODTs be considered solid oral preparations that disintegrate rapidly in the oral cavity, with an in vitro disintegration time of approximately 30 sec or less (represented as blue dash line in Figure 12). Therefore, the disintegration time of the proposed drug product is slightly above this range. However, the value of 30 sec is not intended to represent an arbitrary distinction between an ODT and other tablet form per guidance stated. The appropriate characteristics for a disintegrating tablet mean that ODT is to be taken without chewing or liquids. It is should be noted that the proposed OD tablet weights is about (b) (4) mg per tablet, which is heavier than what the guidance generally recommended, 500 mg. For tablet exceeding 500 mg, its ability to perform effectively as an ODT should be justified based on product performance.

To assess the performance and acceptability of dexlansoprazole OD tablet in human subjects, a survey was conducted in conjunction with study TAK-390MR (OD) _103 titled "Phase 1 TAK-390MR ODT Food Effect Study". The subjects in the study were asked to describe the ease of administration (place the tablet on tongue without water or chewing) of the tablet. The responses are summarized in following Table (Adapted Table 3 from the study report TAK-390MRODT-10673).

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Table 3 **Descriptive Statistics of the Taste Questionnaire for Dexlansoprazole Delayed-Release 30 mg OD Tablet Administered Without Water**

	Flavor	Texture	Overall Taste	Ease of Administration*
N	68	68	68	68
Mean (score)	4.4	3.9	4.3	4.4
Range (score)	3-5	2-5	3-5	3-5

*The question was "On a scale of 1 to 5 (with 5 being the easiest), please rate how easy it would be to take this formulation daily without water for 4 to 8 weeks."

The score for the ease of administration ranges from 3-5 and with a mean score of 4.4, which suggested that majority of subjects regarded the proposed ODT tablet to be easily taken without water for 4 to 8 weeks.

Another survey was conducted in clinical study TAK-390MR (OD) 106 with the purpose of assessing the amount of reside left on tongue after the administration of tablet to human subjects without water. The results are summarized in following Table 3.

Table 3. Descriptive Statistics of the Residue Questionnaire for Dexlansoprazole Delayed-Release 30 mg OD Tablet Administered Without Water

Question	Response
Was there tablet residue? (N=70)	Response: yes n=45 (60%)
	Response: no n=35 (40%)
If residue remained, amount of water needed to rinse? (N=70)	Response: no water n=9, (20%)
	Response: a sip of water n=33, (73%)
	Response: ½ glass of water n=3 (7%)

Forty% of subjects will not feel any residue on tongue after administration of ODT tablet without water. Sixty% of the surveyed subjects feel residue remained on tongue, 73% of them responded that only a sip of water rather than a large amount of water is needed to rinse the residues down the passage.

Overall, although the weight of the tablet is over 500 mg, the mean in vivo and in vitro disintegration time is consistent and slightly over 30 sec, surveyed subjects can easily take this ODT formulation without water for 4 to 8 weeks. From the perspectives of Biopharmaceutics, the orally disintegrating tablet designation is acceptable.

39. Are the changes in the formulation, manufacturing process, manufacturing sites during the development appropriately bridged to the commercial product?

Applicant's Response:
The Applicant developed a couple of pilot formulations. The bioavailability (BA) of 2 developmental formulations (A and B) of 30 mg dexlansoprazole OD tablets was evaluated in study (TAK-390MR(OD)_101), and failed the bioequivalence. Later on, the Applicant developed another three 3 new 30 mg dexlansoprazole OD tablet formulations (X, Y, Z) (Table 2) to evaluate the BA relative the a single dose of 30 mg dexlansoprazole capsules in pilot study TAK-390MR (OD)_102. Based on results, formulation Z is selected as the final commercial formulation and further clinical evaluation (Table 3). In the clinical study TAK-390MR(OD)_105, the bioequivalence of the final formulation relative to the 30 mg capsule was established. Subsequent studies assessed the effect of food and water on the BA of dexlansoprazole from the OD tablet (TAK-390MR(OD)_103), and the effect of alternative administration approaches (swallowed intact or mixed with water and administrated via oral syringe or nasogastric (NG) tube) on the BA of dexlansoprazole from the 30 mg OD tablet (TAK-390MR(OD)_104). The multiple-dose PKPD response to the administration of one 30 mg dexlansoprazole OD tablet (TAK-390MR (OD)_105) or two 30 mg OD tablets (TAK-390MR(OD)_104) were also assessed. The acceptability of the final formulation was assessed in TAK-390-MR(OD)_103 and TAK-390MR(OD)_106 via subject questionnaires. The in vivo disintegration time of OD tablets was evaluated in vivo study (TAK-390MR(OD)_107).

Table 2. Formulation of Dexlansoprazole OD Tablets (30 mg)

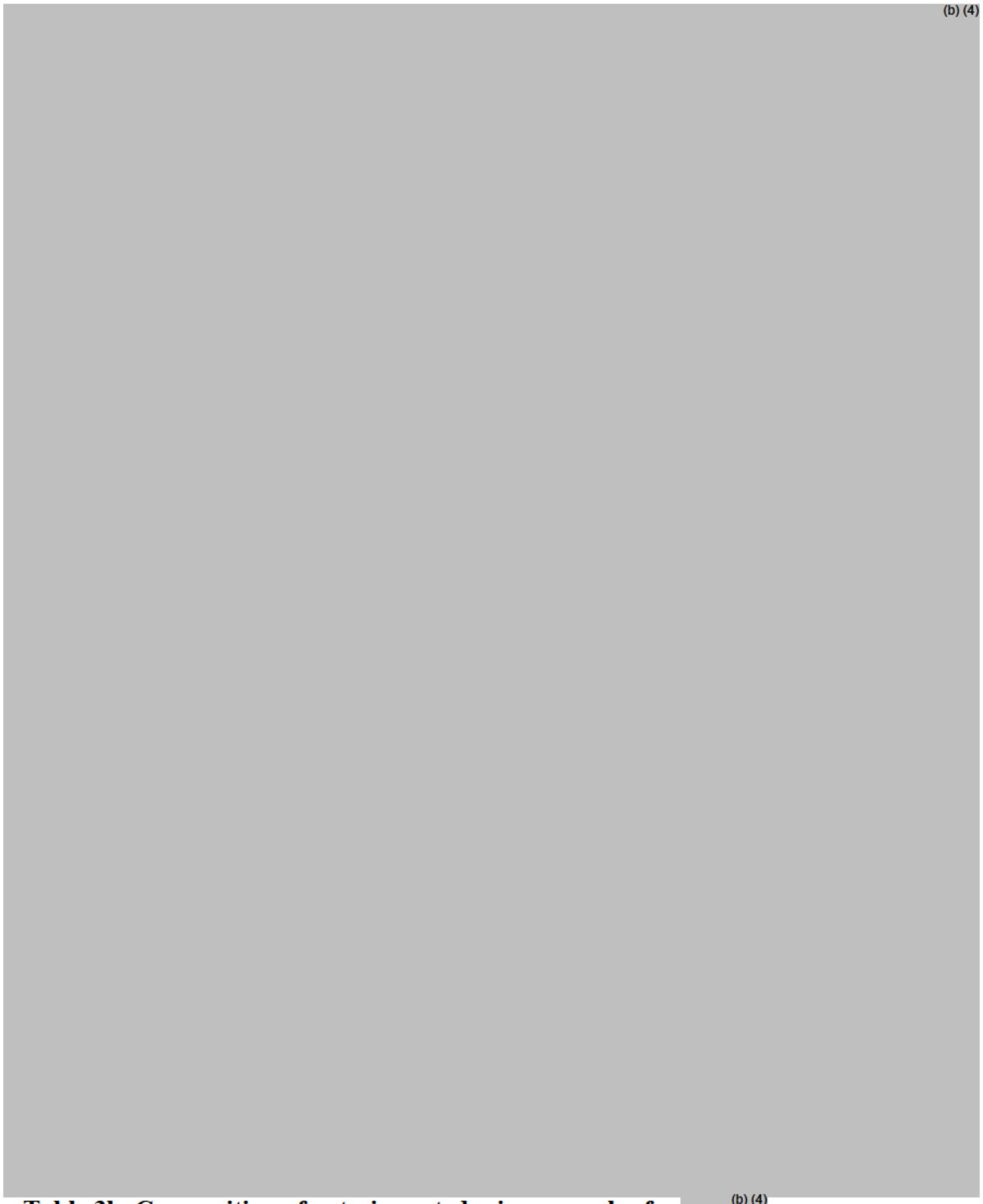


Table 3b. Composition of enteric coated microgranules for (b) (4)

(b) (4)

Reviewer's Assessment:

The to-be-market formulation is bioequivalent to the 30 mg capsule in the multiple-dose PKPD study (TAK-390MR (OD) 105). Furthermore, the PK results after the administration of two 30 mg dexlansoprazole OD tablets from the final formulation are comparable to that of a 60 mg capsule in multiple PKPD study (TAK-390MR (OD)_104). The detailed review of these BA/BE studies will be conducted by the Office of Clinical Pharmacology. The-to-be market formulation is also used in alcohol dose dumping study, dissolution method development, in vivo disintegration time evaluation, and stability test. Therefore, the to-be-market formulation is properly bridged.

OVERALL ASSESSMENT AND SIGNATURES: BIOPHARMACUETICS

Reviewer's Assessment and Signature:

1. The following proposed dissolution method (following table) and dissolution acceptance criteria are reviewed and found acceptable.

Dissolution Method Parameters

Stage	Method Parameter	Description
Acid stage	Apparatus	USP Apparatus 1, Basket (Mesh size: 100)
	Agitation	100 rpm
	Dissolution medium	0.1 N HCl
	Medium volume	500 mL (±1%)
	Medium temperature	37°C (±0.5°C)
	Sampling point	120 minutes
	Sampling volume	25 mL
	Deaeration	No
Buffer stage	Apparatus	USP Apparatus 1, Basket (Mesh size: 100)
	Agitation	100 rpm
	Dissolution medium	50 mmol/L phosphate buffer (pH 7.20) containing 5 mmol/L sodium lauryl sulfate (SLS)
	Medium volume	900 mL (±1%)
	Medium temperature	37°C (± 0.5°C)
	Sampling point	5, 10, 15, 20, 30, 45, 60, 75, 90, 120, and 150 minutes *
	Sampling volume	10 mL
	Deaeration	No

*Sampling points used in development

Dissolution acceptance criteria: 15 min: (b) (4)%; 60 min: (b) (4)% are acceptable.

2. Significant alcohol dose dumping effect was found and OCP has been consulted. OCP will evaluate its impact on drug safety.

3. The justification for ODT designation is appropriate and therefore, acceptable.

From the Biopharmaceutics perspectives, NDA 208056 is recommended for approval.

Vincent (Peng) Duan, Ph.D.
Biopharmaceutics Primary Reviewer
OPQ/DB/Branch II
11/19/2015

<u>Secondary Review Comments and Concurrence</u>:

I concur.
Tien Mien Chen, Ph. D. 2nd Reviewer, OPQ/DB/Branch II
11/19/15

ASSESSMENT OF MICROBIOLOGY

40. Are the tests and proposed acceptance criteria for microbial burden adequate for assuring the microbial quality of the drug product?

Applicant's Response:
In original submission, the applicant stated that as all the components of the drug product are controlled with microbial limit tests and all isolated intermediates at each process step are controlled at low moisture levels, no microbial tests should be necessary for release and stability (section 3.2.P.2.5.). Microbial test data at T=0 for all the stability registration batches are provided in section P.8 to confirm the rationale. Results are found adequate.

Reviewer's Assessment: Adequate as Amended
The initial proposal not to conduct microbial limit test (MLT) is not acceptable per 21 CFR 211.188.

The deficiency was sent to the applicant via IR on 05/20/2015. The applicant responded on 07/14/2015 and agreed to list MLT in the specification for release; however, proposed to only conduct (b)(4) batches per year of production if the results of at least the first 10 commercial batches conform to the criteria and there are no anomalies. No MLT was proposed for stability.

The response proposed skip lot testing for MLT; however this is not allowed per 21 CFR 211.165 (a) and (b). The applicant then agreed to conduct MLT for all product release and for stability (in Amendment on 09/15/2015).

Specification in section P.5.4 and Post-approval stability protocol in P.8.2 are revised accordingly.

MLT test methods and specification limits are in compliance with USP <61>, <62> and <1111>. In section P.8.3, suitability study of the USP methods is provided and the results are found adequate.

2.3.P.7 Container/Closure System

41. Is the proposed container/closure system for the drug product validated to function as a barrier to microbial ingress? What is the container/closure design space and change control program in terms of validation?

Applicant's Response:

Reviewer's Assessment: N/A

A APPENDICES

A.2 Adventitious Agents Safety Evaluation

42. Are any materials used for the manufacture of the drug substance or drug product of biological origin or derived from biological sources? If the drug product contains material sourced from animals, what documentation is provided to assure a low risk of virus or prion contamination (causative agent of TSE)?

Applicant's Response:

The following is provided in P.4.5.

The drug substance is chemically synthesized and no material of animal origin is used in the drug substance synthesis.

For the drug product, three excipients in Dexlansoprazole (TAK-390) Delayed-Release Orally Disintegrating Tablets (30 mg) that could potentially be of animal origin are lactose monohydrate-microcrystalline cellulose spheres, polysorbate 80 and magnesium stearate. Takeda certifies these excipients used in the manufacture of the Dexlansoprazole OD Tablets are of vegetable origin only.

Statements from the current suppliers are provided in Module 3.2.A.2 Adventitious Agents Safety Evaluation. These statements are provided as representative of the quality of the current suppliers, however, alternate suppliers may be substituted as long as the quality of the materials is assured to be equivalent.

In Module 3.2.A.2, it is indicated that three components: lactose monohydrate-microcrystalline cellulose spheres, polysorbate 80 and magnesium stearate will be of plant and animal origins and could be of a risk of contamination with or transmission of adventitious agents including Transmissible Spongiform Encephalopathy (TSE). The applicant then provided declaration of TSE/BSE certificates from the suppliers for these components.

Reviewer's Assessment: Adequate

43. If any of the materials used for the manufacture of the drug substance or drug product are of biological origin or derived from biological sources, what drug substance/drug product processing steps assure microbiological (viral) safety of the component(s) and how are the viral inactivation/clearance capacity of these processes validated?

Applicant's Response:

Reviewer's Assessment: N/A

OVERALL ASSESSMENT AND SIGNATURES: MICROBIOLOGY

Reviewer's Assessment and Signature:
The applicant accepted the Agency's requests and agreed to conduct microbial tests per USP <1111> for product release and for stability, therefore the information is adequate.

Yubing Tang, Ph.D., Primary Reviewer, Branch V/DPQAII/OPF, 11/01/2015

Secondary Review Comments and Concurrence:
I concur, microbiology overall assessment recommendation is acceptable.
Celia Cruz, Ph.D., Branch Chief, Branch V/DPQAII/OPF, 11/09/2015

ASSESSMENT OF ENVIRONMENTAL ANALYSIS

44. Is the applicant's claim for categorical exclusion acceptable?

Applicant's Response:

The applicant has requested categorical exclusion from the preparation of the environmental assessment analysis according to 21 CFR 25.31(b). Based anticipated production of Dexilant SoluTab (dexlansoprazole) Delayed-Release Orally Disintegrating tablets, the applicant has provided 5-year projection for the amount of the active moiety produced each year. The projected amount of active moiety includes all related application in which this active moiety will be used. The Table below provides the 5-year projection for this active moiety.

	2016	2017	2018	2019	2020
API for TAK-390 (kg)					(b) (4)

API=active pharmaceutical ingredient.

Based on the maximum of (b) (4) kg the moiety projected for the first year, the calculated EIC is (b) (4) ppb which approximately (b) (4) fold below 1ppb, the threshold for the preparation of environmental assessment analysis. The applicant has also confirmed to their knowledge no extraordinary circumstances exist to suggest that the requested action for approval might significantly affect the quality of the human environment.

Reviewer's Assessment:

The calculated EIC based the projected amount active produced each year is ≥ (b) (4) ppb. EIC below 1ppb does not require preparation of the environmental assessment analysis. Therefore, the applicant requested for categorical exclusion from the preparation of the environmental assessment analysis is considered appropriate.

OVERALL ASSESSMENT AND SIGNATURES: ENVIRONMENTAL

Reviewer's Assessment and Signature:

The categorical exclusion from the preparation of the environmental assessment analysis is **granted**

Hamid Shafiei, Ph.D.
Application Technical Lead
ONDP, Branch V, Division II

Secondary Review Comments and Concurrence:

I concur with Dr. Shafiei's assessment.

Moo-Jhong Rhee, Ph.D.
Chief, Branch V/DNDP II
ONDP/OPQ

I. Review of Common Technical Document-Quality (Ctd-Q) Module 1

Labeling & Package Insert

For ANDA only

A. Labeling & Package Insert

a) DESCRIPTION section

i) Is the information accurate? ☐ Yes ☐ No

If "No," explain.

ii) Is the drug product subject of a USP monograph? ☐ Yes ☐ No

If "Yes," state if labeling needs a special USP statement in the Description. (e.g., USP test pending. Meets USP assay test 2. Meets USP organic impurities test 3.)

Note: If there is a potential that USP statement needs to be added or modified in the Description, alert the labeling reviewer.

Reviewer's Assessment:

b) HOW SUPPLIED section

i) Is the information accurate? ☐ Yes ☐ No
If "No," explain.

ii) Are the storage conditions acceptable? ☐ Yes ☐ No
If "No," explain.

Reviewer's Assessment:

c) DOSAGE AND ADMINISTRATION section, for injectables, and where applicable:

Did the applicant provide quality data to support in-use conditions (e.g. diluent compatibility studies)? ☐ Yes ☐ No ☐ N/A
If "No," explain.

Reviewer's Assessment:

d) For OTC Drugs and Controlled Substances:

Is tamper evident feature provided in the container/closure? ☐ Yes ☐ No
If "No," explain.

Reviewer's Assessment:

e) For solid oral drug products, only: drug product length(s) of commercial batch(es):

ANDA Strength	Length (mm)	Imprint Code

f) Describe issue(s) sent to and/or received from the OGD Labeling Reviewer:

Reviewer's Assessment:

For NDA only

1. Package Insert

(a) "Highlights" Section (21CFR 201.57(a))

DEXILANT (dexlansoprazole) delayed-release capsules, for oral use.
DEXILANT SoluTab (dexlansoprazole) delayed-release orally disintegrating tablets, for oral use.
Initial U.S. Approval: 1995 (lansoprazole)

Delayed-Release capsules: 30 mg and 60 mg.
Delayed-release orally disintegrating tablets: 30 mg.

Item	Information Provided in NDA	Reviewer's Assessment
Product title, Drug name (201.57(a)(2))		
Proprietary name and established name	DEXILANT (dexlansoprazole) DEXILANT SoluTab (dexlansoprazole)	Proprietary name and established name is provided. **Satisfactory**
Dosage form, route of administration	Delayed-release capsules, for oral use Delayed-release orally disintegrating tablets, for oral use	Dosage form, route of administration provided. **Satisfactory**
Controlled drug substance symbol (if applicable)	Not applicable	Not applicable
Dosage Forms and Strengths (201.57(a)(8))		
A concise summary of dosage forms and strengths	Delayed-Release capsules: 30 mg and 60 mg Delayed-release orally disintegrating tablets: 30 mg	The dosage forms and strengths are described correctly. **Satisfactory**

Conclusion:
The highlights section of the PI is adequate.

(b) "Full Prescribing Information" Section

 # 3: Dosage Forms and Strengths (21CFR 201.57(c)(4))

- 30 mg delayed-release capsules are opaque, blue and gray with TAP and "30" imprinted on the capsule.
- 60 mg delayed-release capsules are opaque, blue with TAP and "60" imprinted on the capsule.
- 30 mg delayed-release orally disintegrating tablets are white to yellowish-white, round, tablets containing orange to dark brown speckles, with "D30" debossed on one side.

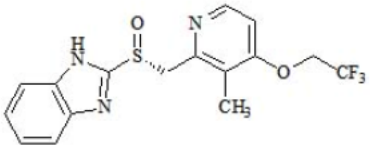
Item	Information Provided in NDA	Reviewer's Assessment
Available dosage forms	delayed-release capsules delayed-release orally disintegrating tablets	**Satisfactory**
Strengths: in metric system	30 mg and 60 mg delayed-release capsules 30 mg delayed-release orally disintegrating tablets	**Satisfactory**
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting, when applicable.	DEXILANT delayed-release capsules • 30 mg delayed-release capsules are opaque, blue and gray with TAP and "30" imprinted on the capsule. • 60 mg delayed-release capsules are opaque, blue with TAP and "60" imprinted on the capsule. • 30 mg delayed-release orally disintegrating tablets are white to yellowish-white, round, tablets containing orange to dark brown speckles, with "D30" debossed on one side.	**Satisfactory**

Conclusion:
The Dosage Forms and Strengths Section of the PI is Adequate.

#11: Description (21CFR 201.57(c)(12))

The active ingredient in DEXILANT (dexlansoprazole) delayed-release capsules, and DEXILANT SoluTab (dexlansoprazole) delayed-release orally disintegrating tablets, a proton pump inhibitor, is (+)-2-[(*R*)-{[3-methyl-4-(2,2,2-trifluoroethoxy)pyridin-2-yl] methyl} sulfinyl]-*1H*-

benzimidazole, a compound that inhibits gastric acid secretion. Dexlansoprazole is the *R*-enantiomer of lansoprazole (a racemic mixture of the *R*- and *S*- enantiomers). Its empirical formula is: $C_{16}H_{14}F_3N_3O_2S$, with a molecular weight of 369.36. Dexlansoprazole has the following chemical structure: The structural formula is:



Dexlansoprazole is a white to nearly white crystalline powder which melts with decomposition at 140°C. Dexlansoprazole is freely soluble in dimethylformamide, methanol, dichloromethane, ethanol, and ethyl acetate; and soluble in acetonitrile; slightly soluble in ether; and very slightly soluble in water; and practically insoluble in hexane.

Dexlansoprazole is stable when exposed to light. Dexlansoprazole is more stable in neutral and alkaline conditions than acidic conditions.

Dexlansoprazole is supplied for oral administration as dual delayed-release formulations in capsules and orally disintegrating tablets. The capsules and tablets contain dexlansoprazole in a mixture of two types of enteric-coated granules with different pH-dependent dissolution profiles *[see Clinical Pharmacology (12.3)]*.

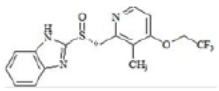
DEXILANT delayed-release capsules are available in two dosage strengths: 30 mg and 60 mg, per capsule. Each capsule contains enteric-coated granules consisting of dexlansoprazole (active ingredient) and the following inactive ingredients: sugar spheres, magnesium carbonate, sucrose, low-substituted hydroxypropyl cellulose, titanium dioxide, hydroxypropyl cellulose, hypromellose 2910, talc, methacrylic acid copolymers, polyethylene glycol 8000, triethyl citrate, polysorbate 80, and colloidal silicon dioxide. The components of the capsule shell include the following inactive ingredients: hypromellose, carrageenan and potassium chloride. Based on the capsule shell color, blue contains FD&C Blue No. 2 aluminum lake; gray contains black ferric oxide; and both contain titanium dioxide.

DEXILANT SoluTab delayed-release orally disintegrating tablets are available as 30 mg tablets. Each tablet contains enteric-coated microgranules. The tablet consists of dexlansoprazole (active ingredient) and the following inactive ingredients: lactose monohydrate-microcrystalline cellulose spheres, magnesium carbonate, low-substituted hydroxypropyl cellulose, hydroxypropyl cellulose, hypromellose, talc, titanium dioxide, mannitol, methacrylic acid copolymer, ethyl acrylate

methyl methacrylate copolymer, polysorbate 80, glyceryl monostearate, triethyl citrate, anhydrous citric acid, ferric oxide, red; ferric oxide, yellow; polyethylene glycol 8000, methylacrylate methylmethacrylate methacrylic acid copolymer, microcrystalline cellulose, crospovidone, sucralose, strawberry durarome, and magnesium stearate.

(b) (4)

Item	Information Provided in NDA	Reviewer's Assessment
Proprietary name and established name	DEXILANT (dexlansoprazole)	Proprietary name and established name is described correctly. **Satisfactory**
Dosage form and route of administration	DEXILANT delayed-release capsules DEXILANT SoluTab delayed-release orally disintegrating tablets for oral administration	**Satisfactory**
Active moiety expression of strength with equivalence statement for salt (if applicable)	Not applicable	Not applicable
Inactive ingredient information (quantitative, if injectables 21CFR201.100(b)(5)(iii)), listed by USP/NF names.	Capsules: Sugar spheres, magnesium carbonate, sucrose, low-substituted hydroxypropyl cellulose, titanium dioxide, hydroxypropyl cellulose, hypromellose 2910, talc, methacrylic acid copolymers, polyethylene glycol 8000, triethyl citrate, polysorbate 80, and colloidal silicon dioxide. The components of the capsule shell include the following inactive ingredients: hypromellose, carrageenan and potassium chloride. Based on the capsule shell color, blue contains FD&C Blue No. 2 aluminum lake; gray contains black ferric oxide; and both contain titanium dioxide Tablets: lactose monohydrate-microcrystalline cellulose spheres, magnesium carbonate, low-substituted hydroxypropyl cellulose, hydroxypropyl cellulose, hypromellose, talc, titanium dioxide, mannitol, methacrylic acid copolymer, ethyl acrylate methyl methacrylate copolymer, polysorbate 80, glyceryl monostearate, triethyl citrate, anhydrous citric acid, ferric oxide, red; ferric oxide, yellow; polyethylene glycol 8000, methylacrylate methylmethacrylate methacrylic acid copolymer, microcrystalline cellulose, crospovidone, sucralose, strawberry durarome, and magnesium stearate	Inactive ingredients of capsules and tablets are appropriately provided. **Satisfactory**
Statement of being sterile (if	Not applicable	Not applicable

applicable)		
Pharmacological/ therapeutic class	A proton pump inhibitor , a compound that inhibits gastric acid secretion	**Satisfactory**
Chemical name, structural formula, molecular weight	Chemical Name: (+)-2-[(R)-{[3-methyl-4-(2,2,2-trifluoroethoxy)pyridin-2-yl] methyl} sulfinyl]-1H-benzimidazole Structural formula:  Molecular weight: 369.36 Empirical formula: $C_{16}H_{14}F_3N_3O_2S$	All necessary information provided. **Satisfactory**
If radioactive, statement of important nuclear characteristics.	Not applicable	Not applicable
Other important chemical or physical properties (such as pKa, solubility, or pH)	Dexlansoprazole is a white to nearly white crystalline powder which melts with decomposition at 140°C. Dexlansoprazole is freely soluble in dimethylformamide, methanol, dichloromethane, ethanol, and ethyl acetate; and soluble in acetonitrile; slightly soluble in ether; and very slightly soluble in water; and practically insoluble in hexane.	Provided. **Satisfactory**

Conclusion:
The information provided in the description section of PI is adequate.

#16: How Supplied/Storage and Handling (21CFR 201.57(c)(17))

DEXILANT delayed-release capsules, 30 mg, are opaque, blue and gray with TAP and "30" imprinted on the capsule and supplied as:

NDC Number	Size
64764-171-11	Unit dose package of 100
64764-171-30	Bottle of 30
64764-171-90	Bottle of 90
64764-171-19	Bottle of 1000

DEXILANT delayed-release capsules, 60 mg, are opaque, blue with TAP and "60" imprinted on the capsule and supplied as:

NDC Number	Size
64764-175-11	Unit dose package of 100
64764-175-30	Bottle of 30
64764-175-90	Bottle of 90
64764-175-19	Bottle of 1000

DEXILANT SoluTab delayed-release orally disintegrating tablets, 30 mg, are white to yellowish-white, round, tablets containing orange to dark brown speckles, with "D30" debossed on one side and supplied as:

NDC Number	Size
64764-177-11	Unit dose package of 100

Store at 20 to 25°C (68 to 77°F); excursions permitted to 15 to 30°C (59 to 86°F) [see USP Controlled Room Temperature].

Item	Information Provided in NDA	Reviewer's Assessment
Strength of dosage form	30mg and 60mg capsules 30mg orally disintegrating tablets	**Satisfactory**
Available units (e.g., bottles of 100 tablets)	30mg and 60mg capsules: Unit dose package of 100, bottle of 30, bottle of 90, and bottle of 1000 OD tablets: Unit dose package of 100	**Satisfactory**
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	30mg capsules: 64764-171-11, 64764-171-30, 64764-171-90, and 64764-171-19 60mg capsules: 64764-175-11, 64764-175-30, 64764-175-90, and 64764-175-19 OD Tablets: 64764-177-11	**Satisfactory**
Special handling (e.g., protect from light, do not freeze)	Not applicable	Not applicable
Storage conditions	Store at temperature, 25°C (77°F); excursions permitted to 15° to 30 °C (59° to 86°F) [see USP Controlled Room Temperature]	**Satisfactory**

Manufacturer/distributor name listed at the end of PI, following Section #17

Item	Information Provided in NDA	Reviewer's Assessment
Manufacturer/distributor name (21 CFR 201.1)	Distributed by: Takeda Pharmaceuticals America, Inc. Deerfield, IL 60015	**Satisfactory**

Conclusion:
The information provided in sections 16 and 17 of the PI is adequate.

2. Container and Carton Labeling

1) Immediate Container Label

Although the immediate container labels for both physician sample and commercial product are provided in the figure above, only the immediate container label for the commercial product (10-count blister) will be reviewed.

Reviewer's Assessment:

Item	Comments on the Information Provided in NDA	Conclusions
Proprietary name, established name (font size and prominence (21 CFR 201.10(g)(2))	Proprietary name, established name are provided with appropriate font size and prominence that satisfies 21 CFR 201.10(g)(2).	**Satisfactory**
Strength (21CFR 201.10(d)(1); 21.CFR 201.100(b)(4))	The following strengths are provided on sachets (packets) are consistent with requirements in 21CFR 201.10(d)(1); 21.CFR 201.100(b)(4). 30mg orally disintegrating tablet	**Satisfactory**
Net contents (21 CFR 201.51(a))	Not applicable	**N/A**
Lot number per 21 CFR 201.18	The location on the immediate container label where the lot number will be displayed is provided. Satisfies 21 CFR 201.18.	**Satisfactory**
Expiration date per 21 CFR 201.17	The location on the immediate container label where the expiration date will be displayed is provided. Satisfies 21 CFR 201.17.	**Satisfactory**
"Rx only" statement per 21 CFR 201.100(b)(1)	"Rx only" is displayed. Satisfies 21 CFR 201.100(b)(1).	**Satisfactory**
Storage (not required)	Storage condition is not provided on the blister packaging but provided on the product	**Not required**
NDC number (per 21 CFR 201.2) (requested, but not required for all labels or labeling), also see 21 CFR 207.35(b)(3)	Provided.	**Satisfactory**
Bar Code per 21 CFR 201.25(c)(2)**	Provided.	**Satisfactory**
Name of manufacturer/distributor	Name of manufacturer/distributor is appropriately displayed.	**Satisfactory**
Others	Not applicable.	**N/A**

*21 CFR 201.51(h) A drug shall be exempt from compliance with the net quantity declaration required by this section if it is an ointment labeled ''sample'', ''physician's sample'', or a substantially similar statement and the contents of the package do not exceed 8 grams.
**For solid oral dosage forms, CDER policy provides for exclusion of "oral" from the container label

**Not required for Physician's samples. The bar code requirement does not apply to prescription drugs sold by a manufacturer, repacker, relabeler, or private label distributor directly to patients, but versions of the same drug product that are sold to or used in hospitals are subject to the bar code requirements.

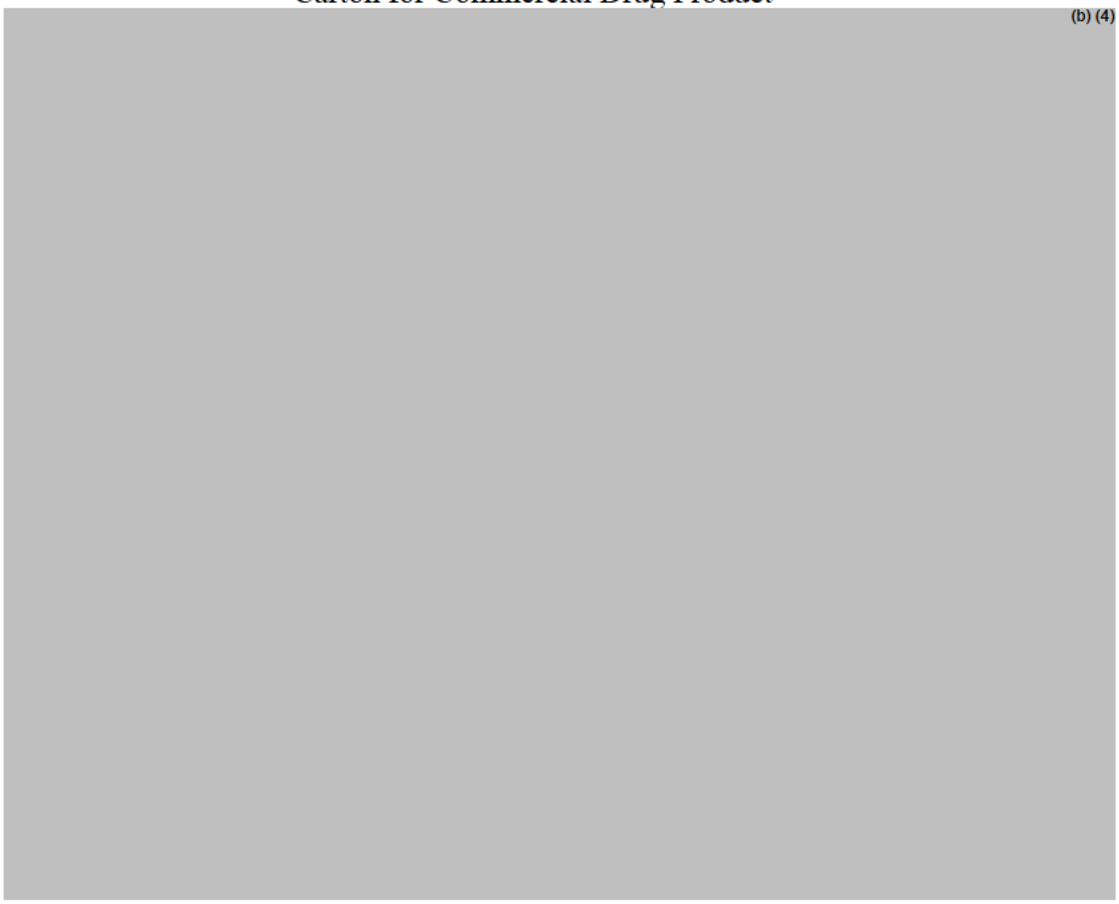
Conclusion:
The proposed immediate container (blister) label for the commercial product is satisfactory.

2) Carton Labeling

Carton for Health Professional Use Samples (Physician Samples; not for Sale or Commercial Use)

Carton for Commercial Drug Product

(b) (4)



Although carton labels for both physician sample and commercial product are provided in the figures above, only the carton label for the commercial product (10 packs of 10 tablets each) will be reviewed.

Item	Comments on the Information Provided in NDA	Conclusions
Proprietary name, established name (font size and prominence (FD&C Act 502(e)(1)(A)(i), FD&C Act 502(e)(1)(B), 21 CFR 201.10(g)(2))	Proprietary name, established name are provided with appropriate font size and prominence that satisfies FD&C Act 502(e)(1)(A)(i), FD&C Act 502(e)(1)(B), 21 CFR 201.10(g)(2).	**Satisfactory**
Strength (21CFR 201.10(d)(1); 21.CFR 201.100(b)(4))	The following strengths are provided on sachets (packets) are consistent with requirements in 21CFR 201.10(d)(1); 21.CFR 201.100(b)(4). 30mg Delayed-Release Orally Disintegrating Tablets	**Satisfactory**
Net contents (21 CFR 201.51(a))	10 Packs of 10 Tablets Each	**Satisfactory**
Lot number per 21 CFR 201.18	The location on the carton where the lot number will be displayed is provided. Satisfies 21 CFR 201.18.	**Satisfactory**
Expiration date per 21 CFR 201.17	The location on the carton where the expiration date will be displayed is provided. Satisfies 21 CFR 201.17.	**Satisfactory**
Name of all inactive ingredients (except for oral drugs); Quantitative ingredient information is required for injectables)[201.10(a),	Not applicable	**N/A**
Sterility Information (if applicable)	Not applicable	**N/A**
"Rx only" statement per 21 CFR 201.100(b)(1)	Appropriately displayed. Satisfies 21 CFR 201.100(b)(1).	**Satisfactory**
Storage Conditions	Store at 25°C (77°F); excursions permitted to 15°C to 30°C (59°F to 86°F).	**Satisfactory**
NDC number (per 21 CFR 201.2) (requested, but not required for all labels or labeling), also see 21 CFR	Appropriately displayed. Satisfies 21 CFR 201.2.	**Satisfactory**
Bar Code per 21 CFR 201.25(c)(2)**	Appropriately displayed. Satisfies 21 CFR 201.25(c)(2).	**Satisfactory**
Name of manufacturer/distributor	Distributed by: Takeda Pharmaceuticals America, Inc. Deerfield, IL 60015	**Satisfactory**

"See package insert for dosage information" (21 CFR 201.55)	Appropriately displayed. Satisfies 21 CFR 201.55.	**Satisfactory**
"Keep out of reach of children" (optional for Rx, required for OTC)	The statement is optional for Rx. However, the following statement is displayed on the carton label: "PACKAGE NOT CHILD-RESISTANT Dispense in a child-resistant container-closure package."	**Satisfactory**
Route of Administration (not required for oral, 21 CFR 201.100(b)(3))	Route of administration is provided as oral	**Satisfactory**

Conclusion:
The proposed carton label for the commercial product is satisfactory.

OVERALL ASSESSMENT AND SIGNATURES: LABELING

Reviewer's Assessment and Signature:

The label and labeling for this drug product are deemed **satisfactory**.

Hamid Shafiei, Ph.D.
Application Technical Lead
ONDP, Branch V, Division II

Secondary Review Comments and Concurrence:
I concur with Dr. Shafiei's assessment.

Moo-Jhong Rhee, Ph.D.
Chief, Branch V/DNDP II
ONDP/OPQ

II. List of Deficiencies To Be Communicated

None

III. Attachments

A. Lifecycle Knowledge Management

a) Drug Product

From Initial Risk Identification			Review Assessment		
Attribute/ CQA	**Factors that can impact the CQA**	**Initial Risk Ranking**	**Risk Mitigation Approach**	**Final Risk Evaluation**	**Lifecycle Considerations/ Comments**
Assay	Formulation Process Scale	L	Sensitive validated analytical method for determination of assay	L	None
Degradation Product	Formulation Process Scale	L	Sensitive validated analytical method for determination of impurities	L	None

B. Facility Report

(b) (4)

(b) (4)