CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208056Orig1s000

OTHER REVIEW(S)

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for ***each*** PMR/PMC in the Action Package.

NDA/BLA # 208056
Product Name: Dexilant SoluTab

PMR/PMC Description: Deferred study under PREA to evaluate the pharmacokinetics of dexlansoprazole, maintenance of healing, and symptoms of endoscopy-proven erosive esophagitis (EE) in patients 1 year to 11 years of age.

PMR/PMC Schedule Milestones:

Final Protocol Submission:	10/2020
Study/Trial Completion:	10/2024
Final Report Submission:	10/2025
Other:	

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

   ☐ Unmet need
   ☐ Life-threatening condition
   ☐ Long-term data needed
   ☐ Only feasible to conduct post-approval
   ☐ Prior clinical experience indicates safety
   ☐ Small subpopulation affected
   ☐ Theoretical concern
   ☒ Other

   Pediatric deferral for studies in children was agreed upon by PeRC because adult studies were ready for approval.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

The drug has not been studied in the pediatric population. Pediatric studies are required under PREA. Based on the recommendations from the Gastrointestinal Drug Advisory Committee meeting, held November 5, 2010, it is not clear whether pediatric patients with erosive esophagitis require a maintenance phase of treatment after the erosive esophagitis has been healed. This study will evaluate the need for a maintenance phase of treatment in pediatric patients with EE.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.
   If not a PMR, skip to 4.

   - **Which regulation?**

     ☐ Accelerated Approval (subpart H/E)
     ☐ Animal Efficacy Rule
     ☒ Pediatric Research Equity Act
     ☐ FDAAA required safety study/clinical trial

   - **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

     ☐ Assess a known serious risk related to the use of the drug?
     ☐ Assess signals of serious risk related to the use of the drug?
     ☐ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

   - **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

     ☐ Analysis of spontaneous postmarketing adverse events?
     Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

     ☐ Analysis using pharmacovigilance system?
     Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

     ☐ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
     Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

     ☐ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

A study to evaluate the pharmacokinetics of dexlansoprazole, maintenance of healing, and symptoms of endoscopy-proven erosive esophagitis (EE) in patients 1 year to 11 years of age

Required

☐ Observational pharmacoepidemiologic study
☐ Registry studies
☐ Primary safety study or clinical trial
☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
☐ Thorough Q-T clinical trial
☐ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
☒ Pharmacokinetic studies or clinical trials
☐ Drug interaction or bioavailability studies or clinical trials
☐ Dosing trials

Continuation of Question 4

☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

_____

☐ Meta-analysis or pooled analysis of previous studies/clinical trials
☐ Immunogenicity as a marker of safety
☐ Other (provide explanation)

_____

Agreed upon:

☐ Quality study without a safety endpoint (e.g., manufacturing, stability)
☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
☐ Dose-response study or clinical trial performed for effectiveness
☐ Nonclinical study, not safety-related (specify)

_____

☐ Other

_____

5. Is the PMR/PMC clear, feasible, and appropriate?

☒ Does the study/clinical trial meet criteria for PMRs or PMCs?
☒ Are the objectives clear from the description of the PMR/PMC?
☒ Has the applicant adequately justified the choice of schedule milestone dates?
☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

☐ Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

If so, does the clinical trial meet the following criteria?

☐ There is a significant question about the public health risks of an approved drug
☐ There is not enough existing information to assess these risks
☐ Information cannot be gained through a different kind of investigation
☐ The trial will be appropriately designed to answer question about a drug's efficacy and safety, and
☐ The trial will emphasize risk minimization for participants as the protocol is developed

PMR/PMC Development Coordinator:

☒ *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

_____

(signature line for BLAs)

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for ***each*** PMR/PMC in the Action Package.

NDA/BLA # 208056
Product Name: Dexilant SoluTab

PMR/PMC Description: Deferred study under PREA to evaluate the pharmacokinetics of dexlansoprazole, maintenance of healing, and symptoms of endoscopy-proven erosive esophagitis (EE) in patients 12 years to 17 years of age.

PMR/PMC Schedule Milestones:

Final Protocol Submission:	10/2016
Study/Trial Completion:	10/2018
Final Report Submission:	10/2019
Other:	

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- ☐ Unmet need
- ☐ Life-threatening condition
- ☐ Long-term data needed
- ☐ Only feasible to conduct post-approval
- ☐ Prior clinical experience indicates safety
- ☐ Small subpopulation affected
- ☐ Theoretical concern
- ☒ Other

Pediatric deferral for studies in children was agreed upon by PeRC because adult studies were ready for approval.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

The drug has not been studied in the pediatric population. Pediatric studies are required under PREA. Based on the recommendations from the Gastrointestinal Drug Advisory Committee meeting, held November 5, 2010, it is not clear whether pediatric patients with erosive esophagitis require a maintenance phase of treatment after the erosive esophagitis has been healed. This study will evaluate the need for a maintenance phase of treatment in pediatric patients with EE.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.
If not a PMR, skip to 4.

- **Which regulation?**

☐ Accelerated Approval (subpart H/E)
☐ Animal Efficacy Rule
☒ Pediatric Research Equity Act
☐ FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

☐ Assess a known serious risk related to the use of the drug?
☐ Assess signals of serious risk related to the use of the drug?
☐ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

☐ Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

☐ Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

☐ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

☐ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

A study to evaluate the pharmacokinetics of dexlansoprazole, maintenance of healing, and symptoms of endoscopy-proven erosive esophagitis (EE) in patients 12 years to 17 years of age.

Required

☐ Observational pharmacoepidemiologic study
☐ Registry studies
☐ Primary safety study or clinical trial
☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
☐ Thorough Q-T clinical trial
☐ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
☒ Pharmacokinetic studies or clinical trials
☐ Drug interaction or bioavailability studies or clinical trials
☐ Dosing trials

Continuation of Question 4

☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

_____

☐ Meta-analysis or pooled analysis of previous studies/clinical trials
☐ Immunogenicity as a marker of safety
☐ Other (provide explanation)

_____

Agreed upon:

☐ Quality study without a safety endpoint (e.g., manufacturing, stability)
☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
☐ Dose-response study or clinical trial performed for effectiveness
☐ Nonclinical study, not safety-related (specify)

_____

☐ Other

_____

5. Is the PMR/PMC clear, feasible, and appropriate?

☒ Does the study/clinical trial meet criteria for PMRs or PMCs?
☒ Are the objectives clear from the description of the PMR/PMC?
☒ Has the applicant adequately justified the choice of schedule milestone dates?
☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

☐ Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

If so, does the clinical trial meet the following criteria?

☐ There is a significant question about the public health risks of an approved drug
☐ There is not enough existing information to assess these risks
☐ Information cannot be gained through a different kind of investigation
☐ The trial will be appropriately designed to answer question about a drug's efficacy and safety, and
☐ The trial will emphasize risk minimization for participants as the protocol is developed

PMR/PMC Development Coordinator:

☒ *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

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(signature line for BLAs)

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for ***each*** PMR/PMC in the Action Package.

NDA/BLA # 208056
Product Name: Dexilant SoluTab

PMR/PMC Description: Deferred pediatric study under PREA for treating heartburn associated with non-erosive gastroesophageal reflux disease (GERD) in pediatric patients aged 1 year to 11 years.

PMR/PMC Schedule Milestones:		
	Final Protocol Submission:	10/2020
	Study/Trial Completion:	10/2024
	Final Report Submission:	10/2025
	Other:	

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

   ☐ Unmet need
   ☐ Life-threatening condition
   ☐ Long-term data needed
   ☐ Only feasible to conduct post-approval
   ☐ Prior clinical experience indicates safety
   ☐ Small subpopulation affected
   ☐ Theoretical concern
   ☒ Other

   Pediatric deferral for studies in children was agreed upon by PeRC because adult studies were ready for approval.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

The drug has not been studied in the pediatric population. Pediatric studies are required under PREA.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.
   If not a PMR, skip to 4.

   - **Which regulation?**

     ☐ Accelerated Approval (subpart H/E)
     ☐ Animal Efficacy Rule
     ☒ Pediatric Research Equity Act
     ☐ FDAAA required safety study/clinical trial

   - **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

     ☐ Assess a known serious risk related to the use of the drug?
     ☐ Assess signals of serious risk related to the use of the drug?
     ☐ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

   - **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

     ☐ Analysis of spontaneous postmarketing adverse events?
     Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

     ☐ Analysis using pharmacovigilance system?
     Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

     ☐ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
     Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

     ☐ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

A to evaluate the safety and efficacy for treating heartburn associated with non-erosive gastroesophageal reflux disease (GERD) in pediatric patients 1 year to 11 years of age.

Required

☐ Observational pharmacoepidemiologic study
☐ Registry studies
☐ Primary safety study or clinical trial
☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
☐ Thorough Q-T clinical trial
☐ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
☒ Pharmacokinetic studies or clinical trials
☐ Drug interaction or bioavailability studies or clinical trials
☐ Dosing trials

Continuation of Question 4

☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

_____

☐ Meta-analysis or pooled analysis of previous studies/clinical trials
☐ Immunogenicity as a marker of safety
☐ Other (provide explanation)

_____

Agreed upon:

☐ Quality study without a safety endpoint (e.g., manufacturing, stability)
☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
☐ Dose-response study or clinical trial performed for effectiveness
☐ Nonclinical study, not safety-related (specify)

_____

☐ Other

_____

5. Is the PMR/PMC clear, feasible, and appropriate?

☒ Does the study/clinical trial meet criteria for PMRs or PMCs?
☒ Are the objectives clear from the description of the PMR/PMC?
☒ Has the applicant adequately justified the choice of schedule milestone dates?
☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

☐ Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

If so, does the clinical trial meet the following criteria?

☐ There is a significant question about the public health risks of an approved drug
☐ There is not enough existing information to assess these risks
☐ Information cannot be gained through a different kind of investigation
☐ The trial will be appropriately designed to answer question about a drug's efficacy and safety, and
☐ The trial will emphasize risk minimization for participants as the protocol is developed

PMR/PMC Development Coordinator:

☒ *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

_____

(signature line for BLAs)

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for ***each*** PMR/PMC in the Action Package.

NDA/BLA # 208056
Product Name: Dexilant SoluTab

PMR/PMC Description: Deferred pediatric study under PREA for treating heartburn associated with non-erosive gastroesophageal reflux disease (GERD) in pediatric patients aged 12 year to 17 years.

PMR/PMC Schedule Milestones:		
	Final Protocol Submission:	10/2016
	Study/Trial Completion:	10/2018
	Final Report Submission:	10/2019
	Other:	

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

   - ☐ Unmet need
   - ☐ Life-threatening condition
   - ☐ Long-term data needed
   - ☐ Only feasible to conduct post-approval
   - ☐ Prior clinical experience indicates safety
   - ☐ Small subpopulation affected
   - ☐ Theoretical concern
   - ☒ Other

   Pediatric deferral for studies in children was agreed upon by PeRC because adult studies were ready for approval.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

The drug has not been studied in the pediatric population. Pediatric studies are required under PREA.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.
   If not a PMR, skip to 4.

   - **Which regulation?**

     ☐ Accelerated Approval (subpart H/E)
     ☐ Animal Efficacy Rule
     ☒ Pediatric Research Equity Act
     ☐ FDAAA required safety study/clinical trial

   - **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

     ☐ Assess a known serious risk related to the use of the drug?
     ☐ Assess signals of serious risk related to the use of the drug?
     ☐ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

   - **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

     ☐ Analysis of spontaneous postmarketing adverse events?
     Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

     ☐ Analysis using pharmacovigilance system?
     Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

     ☐ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
     Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

     ☐ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

A to evaluate the safety and efficacy for treating heartburn associated with non-erosive gastroesophageal reflux disease (GERD) in pediatric patients 12 years to 17 years of age.

Required

☐ Observational pharmacoepidemiologic study
☐ Registry studies
☐ Primary safety study or clinical trial
☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
☐ Thorough Q-T clinical trial
☐ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
☒ Pharmacokinetic studies or clinical trials
☐ Drug interaction or bioavailability studies or clinical trials
☐ Dosing trials

Continuation of Question 4

☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

_____

☐ Meta-analysis or pooled analysis of previous studies/clinical trials
☐ Immunogenicity as a marker of safety
☐ Other (provide explanation)

_____

Agreed upon:

☐ Quality study without a safety endpoint (e.g., manufacturing, stability)
☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
☐ Dose-response study or clinical trial performed for effectiveness
☐ Nonclinical study, not safety-related (specify)

_____

☐ Other

_____

5. Is the PMR/PMC clear, feasible, and appropriate?

☒ Does the study/clinical trial meet criteria for PMRs or PMCs?
☒ Are the objectives clear from the description of the PMR/PMC?
☒ Has the applicant adequately justified the choice of schedule milestone dates?
☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

☐ Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

If so, does the clinical trial meet the following criteria?

☐ There is a significant question about the public health risks of an approved drug
☐ There is not enough existing information to assess these risks
☐ Information cannot be gained through a different kind of investigation
☐ The trial will be appropriately designed to answer question about a drug's efficacy and safety, and
☐ The trial will emphasize risk minimization for participants as the protocol is developed

PMR/PMC Development Coordinator:

☒ *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

_____

(signature line for BLAs)

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for ***each*** PMR/PMC in the Action Package.

NDA/BLA # 208056
Product Name: Dexilant SoluTab

PMR/PMC Description: Deferred study under PREA to evaluate the long-term safety of dexlansoprazole for the maintenance of healing of erosive esophagitis (EE) in pediatric patients 1 month through 11 months of age, who require chronic treatment with dexlansoprazole due to underlying conditions that predispose to chronic gastroesophageal reflux disease (GERD) and EE.

PMR/PMC Schedule Milestones:

Final Protocol Submission:	08/2022
Study/Trial Completion:	08/2028
Final Report Submission:	02/2029
Other:	

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- ☐ Unmet need
- ☐ Life-threatening condition
- ☐ Long-term data needed
- ☐ Only feasible to conduct post-approval
- ☐ Prior clinical experience indicates safety
- ☐ Small subpopulation affected
- ☐ Theoretical concern
- ☒ Other

Pediatric deferral for studies in children was agreed upon by PeRC because adult studies were ready for approval.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

The drug has not been studied in the pediatric population. Pediatric studies are required under PREA. The safety of chronic use of acid suppression therapy (e.g., proton pump inhibitors) in children with underlying conditions that predispose to chronic GERD and EE, such as cystic fibrosis, neurological disease, or other conditions has not been well characterized. Therefore, this study will evaluate the long-term safety of dexlansoprazole in this patient population.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.
   If not a PMR, skip to 4.

   - **Which regulation?**

     ☐ Accelerated Approval (subpart H/E)
     ☐ Animal Efficacy Rule
     ☒ Pediatric Research Equity Act
     ☐ FDAAA required safety study/clinical trial

   - **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

     ☐ Assess a known serious risk related to the use of the drug?
     ☐ Assess signals of serious risk related to the use of the drug?
     ☐ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

   - **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

     ☐ Analysis of spontaneous postmarketing adverse events?
     Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

     ☐ Analysis using pharmacovigilance system?
     Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

     ☐ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
     Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

     ☐ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

A study to evaluate the long-term safety of dexlansoprazole for the maintenance of healing of erosive esophagitis (EE) in pediatric patients 1 month through 11 months of age, who require chronic treatment with dexlansoprazole due to underlying conditions that predispose to chronic gastroesophageal reflux disease (GERD) and EE.

Required

☐ Observational pharmacoepidemiologic study
☐ Registry studies
☒ Primary safety study or clinical trial
☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
☐ Thorough Q-T clinical trial
☐ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
☒ Pharmacokinetic studies or clinical trials
☐ Drug interaction or bioavailability studies or clinical trials
☐ Dosing trials

Continuation of Question 4

☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

_____

☐ Meta-analysis or pooled analysis of previous studies/clinical trials
☐ Immunogenicity as a marker of safety
☐ Other (provide explanation)

_____

Agreed upon:

☐ Quality study without a safety endpoint (e.g., manufacturing, stability)
☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
☐ Dose-response study or clinical trial performed for effectiveness
☐ Nonclinical study, not safety-related (specify)

_____

☐ Other

_____

5. Is the PMR/PMC clear, feasible, and appropriate?

☒ Does the study/clinical trial meet criteria for PMRs or PMCs?
☒ Are the objectives clear from the description of the PMR/PMC?
☒ Has the applicant adequately justified the choice of schedule milestone dates?
☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

☐ Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

If so, does the clinical trial meet the following criteria?

☐ There is a significant question about the public health risks of an approved drug
☐ There is not enough existing information to assess these risks
☐ Information cannot be gained through a different kind of investigation
☐ The trial will be appropriately designed to answer question about a drug's efficacy and safety, and
☐ The trial will emphasize risk minimization for participants as the protocol is developed

PMR/PMC Development Coordinator:

☒ *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

_____

(signature line for BLAs)

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for ***each*** PMR/PMC in the Action Package.

NDA/BLA # 208056
Product Name: Dexilant SoluTab

PMR/PMC Description: Deferred study under PREA to evaluate the long-term safety of dexlansoprazole for the maintenance of healing of erosive esophagitis (EE) in pediatric patients 1 year through 17 years of age, who require chronic treatment with dexlansoprazole due to underlying conditions that predispose to chronic gastroesophageal reflux disease (GERD) and EE.

PMR/PMC Schedule Milestones:

Final Protocol Submission:	08/2022
Study/Trial Completion:	08/2028
Final Report Submission:	02/2029
Other:	

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- ☐ Unmet need
- ☐ Life-threatening condition
- ☐ Long-term data needed
- ☐ Only feasible to conduct post-approval
- ☐ Prior clinical experience indicates safety
- ☐ Small subpopulation affected
- ☐ Theoretical concern
- ☒ Other

Pediatric deferral for studies in children was agreed upon by PeRC because adult studies were ready for approval.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

The drug has not been studied in the pediatric population. Pediatric studies are required under PREA. The safety of chronic use of acid suppression therapy (e.g., proton pump inhibitors) in children with underlying conditions that predispose to chronic GERD and EE, such as cystic fibrosis, neurological disease, or other conditions has not been well characterized. Therefore, this study will evaluate the long-term safety of dexlansoprazole in this patient population.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.
   If not a PMR, skip to 4.

   - **Which regulation?**

     ☐ Accelerated Approval (subpart H/E)
     ☐ Animal Efficacy Rule
     ☒ Pediatric Research Equity Act
     ☐ FDAAA required safety study/clinical trial

   - **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

     ☐ Assess a known serious risk related to the use of the drug?
     ☐ Assess signals of serious risk related to the use of the drug?
     ☐ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

   - **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

     ☐ Analysis of spontaneous postmarketing adverse events?
     Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

     ☐ Analysis using pharmacovigilance system?
     Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

     ☐ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
     Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

     ☐ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

A study to evaluate the long-term safety of dexlansoprazole for the maintenance of healing of erosive esophagitis (EE) in pediatric patients 1 year through 17 years of age, who require chronic treatment with dexlansoprazole due to underlying conditions that predispose to chronic gastroesophageal reflux disease (GERD) and EE.

Required

☐ Observational pharmacoepidemiologic study
☐ Registry studies
☒ Primary safety study or clinical trial
☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
☐ Thorough Q-T clinical trial
☐ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
☒ Pharmacokinetic studies or clinical trials
☐ Drug interaction or bioavailability studies or clinical trials
☐ Dosing trials

Continuation of Question 4

☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

_____

☐ Meta-analysis or pooled analysis of previous studies/clinical trials
☐ Immunogenicity as a marker of safety
☐ Other (provide explanation)

_____

Agreed upon:

☐ Quality study without a safety endpoint (e.g., manufacturing, stability)
☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
☐ Dose-response study or clinical trial performed for effectiveness
☐ Nonclinical study, not safety-related (specify)

_____

☐ Other

_____

5. Is the PMR/PMC clear, feasible, and appropriate?

☒ Does the study/clinical trial meet criteria for PMRs or PMCs?
☒ Are the objectives clear from the description of the PMR/PMC?
☒ Has the applicant adequately justified the choice of schedule milestone dates?
☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

☐ Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

If so, does the clinical trial meet the following criteria?

☐ There is a significant question about the public health risks of an approved drug
☐ There is not enough existing information to assess these risks
☐ Information cannot be gained through a different kind of investigation
☐ The trial will be appropriately designed to answer question about a drug's efficacy and safety, and
☐ The trial will emphasize risk minimization for participants as the protocol is developed

PMR/PMC Development Coordinator:

☒ *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

_____

(signature line for BLAs)

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

/s/

MAUREEN D DEWEY
01/20/2016

JULI A TOMAINO
01/20/2016

M E M O R A N D U M

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

DATE: June 12, 2015

TO: Division of Gastroenterology and Inborn Errors Products (DGEIP)

FROM: Division of New Drug Bioequivalence Evaluation (DNDBE)
Office of Study Integrity and Surveillance (OSIS)

SUBJECT: **Recommendation to accept data without an on-site inspection**

RE: NDA 208056

The Division of New Drug Bioequivalence Evaluation (DNDBE) within the Office of Study Integrity and Surveillance (OSIS) recommends accepting data without an on-site inspection. The rationale for this decision is noted below.

OSIS recently inspected the sites listed below. The inspectional outcome from the inspections was classified as No Action Indicated (NAI).

Requested Sites Inspection

Facility Type	Facility Name	Facility Address
Analytical	(b) (4)	
Clinical	Celerion, Inc.	2420 West Baseline Road, Tempe, AZ 85283

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

/s/

SHILA S NKAH
06/12/2015

RPM FILING REVIEW

(Including Memo of Filing Meeting)

To be completed for all new NDAs, BLAs, and Efficacy Supplements [except SE8 (labeling change with clinical data) and SE9 (manufacturing change with clinical data]

Application Information		
NDA # 208056 BLA#	NDA Supplement #: S- BLA Supplement #: S-	Efficacy Supplement Category: ☐ New Indication (SE1) ☐ New Dosing Regimen (SE2) ☐ New Route Of Administration (SE3) ☐ Comparative Efficacy Claim (SE4) ☐ New Patient Population (SE5) ☐ Rx To OTC Switch (SE6) ☐ Accelerated Approval Confirmatory Study (SE7) ☐ Labeling Change With Clinical Data (SE8) ☐ Manufacturing Change With Clinical Data (SE9) ☑ Animal Rule Confirmatory Study (SE10)
Proprietary Name: Dexilant SoluTab (formerly Dexilant (b) (4)) Established/Proper Name: Dexlansoprazole delayed-release orally disintegrating tablets Dosage Form: delayed-release orally disintegrating tablets Strengths: 30 mg		
Applicant: Takeda Pharmaceuticals U.S.A., Inc. Agent for Applicant (if applicable):		
Date of Application: 03/26/2015 Date of Receipt: 03/26/2015 Date clock started after UN:		
PDUFA Goal Date: 01/26/2016	Action Goal Date (if different):	
Filing Date: 05/25/2015	Date of Filing Meeting: 03/07/2015	
Chemical Classification (original NDAs only) : ☐ Type 1- New Molecular Entity (NME); NME and New Combination ☐ Type 2- New Active Ingredient; New Active Ingredient and New Dosage Form; New Active Ingredient and New Combination ☒ Type 3- New Dosage Form; New Dosage Form and New Combination ☐ Type 4- New Combination ☐ Type 5- New Formulation or New Manufacturer ☐ Type 7- Drug Already Marketed without Approved NDA ☐ Type 8- Partial Rx to OTC Switch		
Proposed indications: (b) (4) maintenance of healed EE and relief of heartburn; symptomatic non-erosive GERD		
Type of Original NDA: AND (if applicable) Type of NDA Supplement: ***If 505(b)(2): Draft the "505(b)(2) Assessment" review found at:*** ***http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499.***		☒ 505(b)(1) ☐ 505(b)(2) ☐ 505(b)(1) ☐ 505(b)(2)

Type of BLA ***If 351(k), notify the OND Therapeutic Biologics and Biosimilars Team***	☐ 351(a) ☐ 351(k)
Review Classification: ***The application will be a priority review if:*** • ***A complete response to a pediatric Written Request (WR) was included (a partial response to a WR that is sufficient to change the labeling should also be a priority review – check with DPMH)*** • ***The product is a Qualified Infectious Disease Product (QIDP)*** • ***A Tropical Disease Priority Review Voucher was submitted*** • ***A Pediatric Rare Disease Priority Review Voucher was submitted***	☒ Standard ☐ Priority ☐ Pediatric WR ☐ QIDP ☐ Tropical Disease Priority Review Voucher ☐ Pediatric Rare Disease Priority Review Voucher
Resubmission after withdrawal? ☐	Resubmission after refuse to file? ☐
Part 3 Combination Product? ☐ ***If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults***	☐ Convenience kit/Co-package ☐ Pre-filled drug delivery device/system (syringe, patch, etc.) ☐ Pre-filled biologic delivery device/system (syringe, patch, etc.) ☐ Device coated/impregnated/combined with drug ☐ Device coated/impregnated/combined with biologic ☐ Separate products requiring cross-labeling ☐ Drug/Biologic ☐ Possible combination based on cross-labeling of separate products ☐ Other (drug/device/biological product)

☐ Fast Track Designation ☐ Breakthrough Therapy Designation ***(set the submission property in DARRTS and notify the CDER Breakthrough Therapy Program Manager)*** ☐ Rolling Review ☐ Orphan Designation ☐ Rx-to-OTC switch, Full ☐ Rx-to-OTC switch, Partial ☐ Direct-to-OTC Other:	☐ PMC response ☐ PMR response: ☐ FDAAA [505(o)] ☐ PREA deferred pediatric studies (FDCA Section 505B) ☐ Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) ☐ Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)
Collaborative Review Division (*if OTC product*):	
List referenced IND Number: 106858	

Goal Dates/Product Names/Classification Properties	**YES**	**NO**	**NA**	**Comment**
PDUFA/BsUFA and Action Goal dates correct in tracking system? ***If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.***	☒	☐		
Are the established/proper and applicant names correct in tracking system? ***If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into tracking***	☒	☐		Proprietary Name Proposal Resubmitted 5/01/2015

system.				
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, orphan drug)? ***Check the New Application and New Supplement Notification Checklists for a list of all classifications/properties at:*** ***http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm*** ***If no, ask the document room staff to make the appropriate entries.***	☒	☐	☐	
Application Integrity Policy	**YES**	**NO**	**NA**	**Comment**
Is the application affected by the Application Integrity Policy (AIP)? ***Check the AIP list at:*** ***http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm***	☐	☒		
If yes, explain in comment column.				
If affected by AIP, has OC been notified of the submission? **If yes,** date notified:	☐	☐		
User Fees	**YES**	**NO**	**NA**	**Comment**
Is Form 3397 (User Fee Cover Sheet)/Form 3792 (Biosimilar User Fee Cover Sheet) included with authorized signature?	☒	☐		

User Fee Status ***If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send Unacceptable for Filing (UN) letter and contact user fee staff.***	Payment for this application *(check daily email from UserFeeAR@fda.hhs.gov):* ☒ Paid ☐ Exempt (orphan, government) ☐ Waived (e.g., small business, public health) ☐ Not required
If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.	Payment of other user fees: ☒ Not in arrears ☐ In arrears
User Fee Bundling Policy ***Refer to the guidance for industry, Submitting Separate Marketing Applications and Clinical Data for Purposes of Assessing User Fees at:*** ***http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079320.pdf***	Has the user fee bundling policy been appropriately applied? ***If no, or you are not sure, consult the User Fee Staff.*** ☒ Yes ☐ No

505(b)(2) (NDAs/NDA Efficacy Supplements only)	**YES**	**NO**	**NA**	**Comment**
Is the application a 505(b)(2) NDA? *(Check the 356h form, cover letter, and annotated labeling).* **If yes**, answer the bulleted	☐	☒		

questions below:				
• Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?	☐	☐		
• Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? **[see 21 CFR 314.54(b)(1)].**	☐	☐		
• Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug **[see 21 CFR 314.54(b)(2)]?** ***If you answered yes to any of the above bulleted questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the 505(b)(2) review staff in the Immediate Office of New Drugs for advice.***	☐	☐		
• Is there unexpired exclusivity on another listed drug product containing the same active moiety (e.g., 5-year, 3-year, orphan, or pediatric exclusivity)? ***Check the Electronic Orange Book at:*** ***http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm*** **If yes**, please list below:	☐	☐		

Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration

If there is unexpired, 5-year exclusivity remaining on another listed drug product containing the same active moiety, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 314.108(b)(2). Unexpired, 3-year exclusivity may block the approval but not the submission of a 505(b)(2) application.

Exclusivity	**YES**	**NO**	**NA**	**Comment**
Does another product (same active moiety) have orphan exclusivity for the same indication? ***Check the Orphan Drug Designations and Approvals list at:*** ***http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm***	☐	☒		
If another product has orphan exclusivity, is the product considered to be the same product according to the orphan drug definition of sameness **[see 21 CFR 316.3(b)(13)]**? ***If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy***	☐	☐	☒	
NDAs/NDA efficacy supplements only: Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? **If yes**, # years requested: 3 years ***Note:*** *An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.*	☒	☐	☐	

NDAs only: Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use?	☐	☒	☐	
If yes, did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)? ***If yes, contact the Orange Book Staff (CDER-Orange Book Staff).***	☐	☐	☒	
BLAs only: Has the applicant requested 12-year exclusivity under section 351(k)(7) of the PHS Act? ***If yes, notify Marlene Schultz-DePalo, CDER Purple Book Manager*** ***Note**: Exclusivity requests may be made for an original BLA submitted under Section 351(a) of the PHS Act (i.e., a biological reference product). A request may be located in Module 1.3.5.3 and/or other sections of the BLA and may be included in a supplement (or other correspondence) if exclusivity has not been previously requested in the original 351(a) BLA. An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.*	☐	☐	☒	

Format and Content				
Do not check mixed submission if the only electronic component is the content of labeling (COL).	☐ All paper (except for COL) ☒ All electronic ☐ Mixed (paper/electronic) ☒ CTD ☐ Non-CTD ☐ Mixed (CTD/non-CTD)			
If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?				
Overall Format/Content	**YES**	**NO**	**NA**	**Comment**
If electronic submission, does it follow the eCTD guidance?[1] **If not,** explain (e.g., waiver granted).	☒	☐	☐	
Index: Does the submission contain an accurate comprehensive index?	☒	☐		
Is the submission complete as required under 21 CFR 314.50 (*NDAs/NDA efficacy supplements*) or under 21 CFR 601.2 (*BLAs/BLA efficacy supplements*) including:	☒	☐		

[1] http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf

☒ legible ☒ English (or translated into English) ☒ pagination ☒ navigable hyperlinks (electronic submissions only) **If no**, explain.				
BLAs only: Companion application received if a shared or divided manufacturing arrangement? **If yes**, BLA #	☐	☐	☒	

Forms and Certifications				
Electronic *forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise,* ***paper*** *forms and certifications with hand-written signatures must be included.* ***Forms*** *include: user fee cover sheet (3397/3792), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674);* ***Certifications*** *include: debarment certification, patent certification(s), field copy certification, and pediatric certification.*				
Application Form	**YES**	**NO**	**NA**	**Comment**
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)? ***If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].***	☒	☐		
Are all establishments and their registration numbers listed on the form/attached to the form?	☒	☐	☐	
Patent Information (NDAs/NDA efficacy supplements only)	**YES**	**NO**	**NA**	**Comment**
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?	☒	☐	☐	
Financial Disclosure	**YES**	**NO**	**NA**	**Comment**
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)? ***Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].*** ***Note:*** *Financial disclosure is required for bioequivalence studies that are the basis for approval.*	☒	☐		
Clinical Trials Database	**YES**	**NO**	**NA**	**Comment**
Is form FDA 3674 included with authorized signature? ***If yes, ensure that the application is also coded with the supporting document category, "Form 3674."***	☒	☐		

If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant				
Debarment Certification	**YES**	**NO**	**NA**	**Comment**
Is a correctly worded Debarment Certification included with authorized signature? ***Certification is not required for supplements if submitted in the original application; If foreign applicant, both the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].*** ***Note:*** *Debarment Certification should use wording in FD&C Act Section 306(k)(1) i.e., "[Name of applicant] 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." Applicant may not use wording such as, "To the best of my knowledge…"*	☒	☐	☐	
Field Copy Certification (NDAs/NDA efficacy supplements only)	**YES**	**NO**	**NA**	**Comment**
For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included? ***Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)*** ***If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.***	☒	☐	☐	
Controlled Substance/Product with Abuse Potential	**YES**	**NO**	**NA**	**Comment**
For NMEs: Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)? ***If yes,*** *date consult sent to the Controlled Substance Staff:* For non-NMEs: *Date of consult sent to Controlled Substance Staff*:	☐	☐	☒	
Pediatrics	**YES**	**NO**	**NA**	**Comment**
PREA Does the application trigger PREA? ***If yes, notify PeRC@fda.hhs.gov to schedule required PeRC meeting***[2] ***Note****: NDAs/BLAs/efficacy supplements for new active ingredients (including new fixed combinations), new indications, new dosage*	☒	☐		

[2] http://inside fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/PediatricandMaternalHealthStaff/ucm027829 htm

forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.				
If the application triggers PREA, is there an agreed Initial Pediatric Study Plan (iPSP)? Agreed iPSP December 11, 2014. ***If no, may be an RTF issue - contact DPMH for advice.***	☒	☐	☐	
If required by the agreed iPSP, are the pediatric studies outlined in the agreed iPSP completed and included in the application? Pediatric studies were not required in the agreed iPSP. Waiver Requested: 0-1 month and 1-11 months: all indications Deferral Requested: 1- 11 months old ((b) (4) maintain healing of EE 1-11 years old (all indications) 12-17 years old (all indications) ***If no, may be an RTF issue - contact DPMH for advice.***	☐	☐	☒	
BPCA: Is this submission a complete response to a pediatric Written Request? ***If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)***[3]	☐	☒		
Proprietary Name	**YES**	**NO**	**NA**	**Comment**
Is a proposed proprietary name submitted? ***If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."***	☒	☐	☐	
REMS	**YES**	**NO**	**NA**	**Comment**
Is a REMS submitted? ***If yes, send consult to OSE/DRISK and notify OC/ OSI/DSC/PMSB via the CDER OSI RMP mailbox***	☐	☒	☐	
Prescription Labeling	☐ **Not applicable**			
Check all types of labeling submitted.	☒ Package Insert (PI) ☐ Patient Package Insert (PPI) ☒ Instructions for Use (IFU) ☒ Medication Guide (MedGuide) ☒ Carton labels ☐ Immediate container labels			

[3] http://inside fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/PediatricandMaternalHealthStaff/ucm027837 htm

	☐ Diluent ☒ Other : Sample Blister Packaging			
	YES	**NO**	**NA**	**Comment**
Is Electronic Content of Labeling (COL) submitted in SPL format? ***If no, request applicant to submit SPL before the filing date.***	☒	☐		Resubmitted: 5/1/2015
Is the PI submitted in PLR format?[4]	☒	☐		
If PI not submitted in PLR format, was a waiver or deferral requested before the application was received or in the submission? **If requested before application was submitted**, what is the status of the request? ***If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.***	☐	☐	☒	
For applications submitted on or after June 30, 2015: Is the PI submitted in PLLR format?[5]	☒	☐	☐	
For applications submitted on or after June 30, 2015: If PI not submitted in PLLR format, was a waiver or deferral requested before the application was received or in the submission? **If requested before application was submitted**, what is the status of the request? ***If no waiver or deferral, request applicant to submit labeling in PLR/PLLR format before the filing date.***	☐	☐	☒	
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to OPDP?	☒	☐	☐	
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (*send WORD version if available*)	☒	☐	☐	
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office in OPQ (OBP or ONDP)?	☒	☐	☐	
OTC Labeling	☒ **Not Applicable**			
Check all types of labeling submitted.	☐ Outer carton label ☐ Immediate container label ☐ Blister card ☐ Blister backing label ☐ Consumer Information Leaflet (CIL) ☐ Physician sample ☐ Consumer sample			

[4] http://inside fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/StudyEndpointsandLabelingDevelopmentTeam/ucm025576 htm

[5] http://inside fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/StudyEndpointsandLabelingDevelopmentTeam/ucm025576 htm

	☐ Other (specify)			
	YES	**NO**	**NA**	**Comment**
Is electronic content of labeling (COL) submitted? ***If no, request in 74-day letter.***	☐	☐		
Are annotated specifications submitted for all stock keeping units (SKUs)? ***If no, request in 74-day letter.***	☐	☐	☐	
If representative labeling is submitted, are all represented SKUs defined? ***If no, request in 74-day letter.***	☐	☐	☐	
All labeling/packaging sent to OSE/DMEPA?	☐	☐	☐	
Other Consults	**YES**	**NO**	**NA**	**Comment**
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team) ***If yes, specify consult(s) and date(s) sent:***	☐	☒	☐	
Meeting Minutes/SPAs	**YES**	**NO**	**NA**	**Comment**
End-of Phase 2 meeting(s)? **Date(s):** Type C Preliminary Comments sent on 2/4/2012, Meeting Cancelled by Sponsor ***If yes, distribute minutes before filing meeting***	☐	☒		
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? **Date(s):** 09/03/2014 Type C Written Responses 2/13/2015 ***If yes, distribute minutes before filing meeting***	☒	☐		
Any Special Protocol Assessments (SPAs)? **Date(s):** ***If yes, distribute letter and/or relevant minutes before filing meeting***	☐	☒		

ATTACHMENT

MEMO OF FILING MEETING

DATE: 03/07/2015

BACKGROUND:
Dexlansoprazole is the R-enantiomer of the racemate lansoprazole, which was approved in 1995. The reference product for the subject of this NDA is: Dexilant (dexlansoprazole) Delayed-Release Capsules approved on January 30, 2009.

Takeda submitted a new IND 106858 for dexlansoprazole delayed-release orally disintegrating tablets on June 27, 2011. The formulation consists of dexlansoprazole dual delayed-release microgranules designed to disintegrate in the mouth without chewing or swallowing with water.

Proposed Indications:

(b) (4)

(b) (4) Maintenance of healing of EE and relief of heartburn.
Treating heartburn associated with symptomatic non-erosive gastroesophageal reflux disease (GERD).

FDA issued an acknowledgment to an Agreed initial Pediatric Study Plan (iPSP) on December 11, 2014. Takeda filed the NDA for dexlansoprazole delayed-release orally disintegrating tablets on March 26, 2015.

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Maureen Dewey	Y
	CPMS/TL:	Kevin Bugin/ Brian Strongin	Y Y
Cross-Discipline Team Leader (CDTL)	Juli Tomaino, M.D. (Jessica Lee, M.D.)		Y
Division Director/Deputy	Donna Griebel, M.D.		Y
Office Director/Deputy	Julie Beitz, M.D. Amy Egan, M.D.		Y Y
Clinical	Reviewer:	Juli Tomaino, M.D.	Y
	TL:	Jessica J. Lee, M.D.	Y
Social Scientist Review (*for OTC products*)	Reviewer:		

	TL:		
OTC Labeling Review (*for OTC products*)	Reviewer:		
	TL:		
Clinical Microbiology (*for antimicrobial products*)	Reviewer:		
	TL:		
Clinical Pharmacology	Reviewer:	Dilara Jappar	Y
	TL:	Sue Chih Lee	Y
Biostatistics	Reviewer:	Shahla Farr	Y
	TL:	Yeh Fong Chen	Y

Nonclinical (Pharmacology/Toxicology)	Reviewer:	Ke Zhang	No
	TL:	David Joseph	Y
Statistics (carcinogenicity)	Reviewer:		
	TL:		
Product Quality (CMC) Review Team:	ATL:	Hamid Shafiei	Y
	RBPM:	Kerry Ann Jennings	NO
• Drug Substance	Reviewer:	Ben Stevens	NO
• Drug Product	Reviewer:	Hamid Shafiei	Y
• Process	Reviewer:	Yubing Tang	Y
• Microbiology	Reviewer:	Yubing Tang	Y
• Facility	Reviewer:	Krishna Ghosh	Y
• Biopharmaceutics	Reviewer:	Tien Mien Chen/Peng Duan	Y
• Immunogenicity	Reviewer:		
• ORA	Reviewer:	Paul Perdue, Jr.	Y
• Other (e.g., Branch Chiefs, EA Reviewer)			
OSE/DMEPA (proprietary name, carton/container labels))	Reviewer:	Matt Barlow	N
	TL:	Kendra Worthy	N
OPDP	Reviewer:	Meeta Patel	N
	TL:	Adewale Adeleye	N
DPMH	Reviewer:	Amy Taylor/Miriam Dinatale	Y
	TL:	Hari Sachs/Tamara Johnson	N

Bioresearch Monitoring (OSI)	Reviewer:		
	TL:		
Controlled Substance Staff (CSS)	Reviewer:		
	TL:		
DEPI	Reviewer:	Gabrielle Anic	Y
	TL:	Sukhminder Sandhu	N
Other attendees	Andrew Mulberg, Joyce Korvick, Dragos Roman, Joette Meyer, Mildred Wright, Dina Zand, Lisa Pitt.		

FILING MEETING DISCUSSION:

GENERAL • 505(b)(2) filing issues: ○ Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? ○ Did the applicant provide a scientific "bridge" demonstrating the relationship between the proposed product and the referenced product(s)/published literature? Describe the scientific bridge (e.g., BA/BE studies):	☒ Not Applicable ☐ YES ☐ NO ☐ YES ☐ NO
• Per reviewers, are all parts in English or English translation? **If no**, explain:	☒ YES ☐ NO
• Electronic Submission comments **List comments**:	☒ Not Applicable ☐ No comments
CLINICAL **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• Clinical study site inspections needed? **If no,** explain: This submission contains 7 phase 1	☐ YES ☒ NO

clinical trials evaluating BA/BE of dexlansoprazole orally disintegrating tablets with dexlansoprazole delayed-release capsules, approved January 30, 2009.	
• Advisory Committee Meeting needed? **Comments**: ***If no, for an NME NDA or original BLA, include the reason. For example:*** ○ ***this drug/biologic is not the first in its class*** ○ ***the clinical study design was acceptable*** ○ ***the application did not raise significant safety or efficacy issues*** ○ ***the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease***	☐ YES Date if known: ☒ NO ☐ To be determined Reason: **The application does not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease**
• If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? **Comments**:	☒ Not Applicable ☐ YES ☐ NO
CONTROLLED SUBSTANCE STAFF • Abuse Liability/Potential **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
CLINICAL MICROBIOLOGY **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
CLINICAL PHARMACOLOGY **Comments**: Sponsor submitted the missing raw PK datasets for studies on 5/21/2015.	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter

• Clinical pharmacology study site inspections needed?	☒ YES ☐ NO
BIOSTATISTICS **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
NONCLINICAL (PHARMACOLOGY/TOXICOLOGY) **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter

PRODUCT QUALITY (CMC) **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
<u>New Molecular Entity</u> (NDAs only) • Is the product an NME?	 ☐ YES ☒ NO
<u>Environmental Assessment</u> • Categorical exclusion for environmental assessment (EA) requested? **If no**, was a complete EA submitted? **Comments**:	 ☒ YES ☐ NO ☐ YES ☐ NO
<u>Facility Inspection</u> • Establishment(s) ready for inspection? **Comments**:	☐ Not Applicable ☒ YES ☐ NO

Facility/Microbiology Review (BLAs only) **Comments**:	☐ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
CMC Labeling Review (BLAs only) **Comments**:	☐ Review issues for 74-day letter
APPLICATIONS IN THE PROGRAM (PDUFA V) (NME NDAs/Original BLAs) • Were there agreements made at the application's pre-submission meeting (and documented in the minutes) regarding certain late submission components that could be submitted within 30 days after receipt of the original application? • If so, were the late submission components all submitted within 30 days?	☒ N/A ☐ YES ☐ NO ☐ YES ☐ NO
• What late submission components, if any, arrived after 30 days?	
• Was the application otherwise complete upon submission, including those applications where there were no agreements regarding late submission components?	☐ YES ☐ NO
• Is a comprehensive and readily located list of all clinical sites included or referenced in the application?	☐ YES ☐ NO
• Is a comprehensive and readily located list of all manufacturing facilities included or referenced in the application?	☐ YES ☐ NO
REGULATORY PROJECT MANAGEMENT	
Signatory Authority: Donna Griebel, M.D.	

Date of Mid-Cycle Meeting (for NME NDAs/BLAs in "the Program" PDUFA V):

21st Century Review Milestones (see attached) (listing review milestones in this document is optional):

Comments:

	REGULATORY CONCLUSIONS/DEFICIENCIES
☐	The application is unsuitable for filing. Explain why:
☒	The application, on its face, appears to be suitable for filing. Review Issues: ☒ No review issues have been identified for the 74-day letter. ☐ Review issues have been identified for the 74-day letter. Review Classification: ☒ Standard Review ☐ Priority Review
	ACTION ITEMS
☒	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into the electronic archive (e.g., chemical classification, combination product classification, orphan drug).
☐	If RTF, notify everyone who already received a consult request, OSE PM, and RBPM
☐	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
☐	If priority review, notify applicant in writing by day 60 (see CST for choices)
☒	Send review issues/no review issues by day 74
☒	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
☐	Update the PDUFA V DARRTS page (for applications in the Program)
☐	Other

Annual review of template by OND ADRAs completed: September 2014

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/s/

MAUREEN D DEWEY
06/01/2015

KEVIN B BUGIN
06/02/2015

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy

PATIENT LABELING REVIEW

Date:	December 22, 2015
To:	Donna Griebel, MD Director **Division of Gastroenterology and Inborn Errors Products (DGIEP)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)** Marcia Williams, PhD Team Leader, Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Karen Dowdy, RN, BSN Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Meeta Patel, Pharm.D. Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Medication Guide (MG) and Instructions for Use (IFU)
Drug Name (established name):	DEXILANT SoluTab (dexlansoprazole)
Dosage Form and Route:	delayed-release orally disintegrating tablets, for oral use
Application Type/Number:	NDA 208056
Applicant:	Takeda Development Center Americas, Inc. on behalf of Takeda Pharmaceuticals U.S.A., Inc.

1 INTRODUCTION

On March 26, 2015, Takeda Development Center Americas, Inc. on behalf of Takeda Pharmaceuticals U.S.A., Inc. submitted for the Agency's review original New Drug Application (NDA) 208056 for DEXILANT (b) (4) (dexlansoprazole) delayed-release orally disintegrating tablets. The naming convention for Dexilant (b) (4) (dexlansoprazole) Delayed-release orally disintegrating tablets was revised to DEXILANT SoluTab (dexlansoprazole) delayed-release orally disintegrating tablets during the review process and will be referred to as such throughout the memo.

The proposed indications for Dexilant SoluTab (dexlansoprazole) delayed-release orally disintegrating tablets are as follows:

(b) (4)

- To maintain healing of EE and relief of heartburn for up to six months
- Treatment of heartburn associated with symptomatic non-erosive gastroesophageal reflux disease (GERD) for four weeks

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to requests by the Division of Gastroenterology and Inborn Errors Products (DGIEP) on December 9, 2015, and April 22, 2015, respectively, for DMPP and OPDP to review the Applicant's proposed Medication Guide (MG) and Instructions for Use (IFU) for Dexilant SoluTab (dexlansoprazole) delayed-release orally disintegrating tablets.

2 MATERIAL REVIEWED

- Draft Dexilant SoluTab (dexlansoprazole) delayed-release orally disintegrating tablets MG and IFU received on August 18, 2015, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on December 9, 2015.
- Draft Dexilant SoluTab (dexlansoprazole) delayed-release orally disintegrating tablets Prescribing Information (PI) received on August 18, 2015, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on December 9, 2015.
- Division of Medication Error Prevention and Analysis (DMEPA) Label and Labeling Review for DEXILANT SoluTab (Dexlansoprazole) 30 mg Delayed-release Orally Disintegrating Tablets dated October 15, 2015.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB)

published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss. We have reformatted the MG and IFU documents using the Arial font, size 10.

In our collaborative review of the MG and IFU we have:

- simplified wording and clarified concepts where possible
- ensured that the MG and IFU are consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the MG is free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20
- ensured that the MG and IFU meet the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The MG and IFU are acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the MG and IFU is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the MG or IFU.

Please let us know if you have any questions.

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/s/

KAREN M DOWDY
12/22/2015

MEETA N PATEL
12/22/2015

MARCIA B WILLIAMS
12/22/2015

LASHAWN M GRIFFITHS
12/22/2015

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Office of New Drugs/Office of Drug Evaluation IV
Division of Pediatric and Maternal Health
Silver Spring, MD 20993
Telephone 301-796-2200
FAX 301-796-9855

MEMORANDUM TO FILE

Pediatric Labeling Review

From:	Amy M. Taylor, MD, MHS Medical Officer Division of Pediatric and Maternal Health
Through:	Hari Cheryl Sachs, MD, Team Leader Division of Pediatric and Maternal Health Lynne P. Yao, MD, Director Division of Pediatric and Maternal Health
NDA Number:	208056
Sponsor:	Takeda
Drug:	Dexilant SoluTab® (dexlansoprazole)
Dosage form and route of administration:	delayed release orally disintegrating tablets (ODT) (30 mg)
Additional available dosage form:	Dexilant® delayed-release capsules (30 mg and 60 mg)
Approved indications (capsules):	Adult • Healing of all grades of erosive esophagitis (EE) • Maintain healing of EE and relief of heartburn • Treating heartburn associated with symptomatic non-erosive gastroesophageal reflux disease (GERD) Pediatric • none

Proposed Indications

For SoluTab:

Adult

- Maintaining healing of EE and relief of heartburn
- Treating heartburn associated with symptomatic non-erosive GERD

Pediatric

- none

Consult request: The Division of Gastroenterology and Inborn Errors Products requests DPMH's input on the proposed labeling for Dexilant SoluTab® and assistance preparing for PeRC review.

Background for Dexilant® SoluTab

The sponsor submitted a NDA for a new dexlansoprazole orally disintegrating tablet on January 8, 2015. The application did not include a pediatric assessment.

The sponsor submitted an initial Pediatric Study Plan (iPSP) and FDA confirmed an agreed PSP on December 18, 2014. This agreed PSP includes plans for conducting studies similar to those required under PREA for the capsules (see below) including for the treatment of heartburn associated with non-erosive GERD and the maintenance of healing of EE in pediatric patients 1 to 17 years. The sponsor submitted a deferral request for these studies. The Division acknowledges that the sponsor may, upon review, be able to rely on data from the planned/ongoing safety and efficacy trials of dexlansoprazole capsules in pediatric patients to fulfill the pediatric assessments for dexlansoprazole ODT.

The sponsor submitted a waiver request for pediatric patients 1 to 11 months for the symptomatic non-erosive GERD indication and a waiver for patients 0 to 1 month for all indications.

PeRC review

DPMH assisted DGIEP in preparing for a review of the deferral and waiver request included in the NDA for Dexilant® SoluTab.

Background for Dexilant® delayed-release capsules

PREA requirements

The currently approved NDA for Dexilant (NDA 22287) for oral capsules has the following PMRs under PREA. There are no approved pediatric indications.

Infants Aged 1 to 11 Months

1788-2	Deferred study under PREA to evaluate the PK, PD, and safety profiles of dexlansoprazole inpatients aged 1 to 11 months with endoscopy-proven EE.

1788-4 Deferred study under PREA to evaluate the long-term safety of dexlansoprazole for the healing and maintenance of healing of EE in pediatric patients aged 1 to 11 months who require chronic treatment with dexlansoprazole due to underlying conditions that predispose them to chronic GERD and relapsing EE.

Children Aged 1 to 11 Years

1356-4 Deferred pediatric study under PREA for treating heartburn associated with non-erosive GERD in pediatric patients aged 1 to 11 years.

1788-3 Deferred study under PREA to evaluate the PK, healing, maintenance of healing, and symptoms of endoscopy-proven EE in patients aged 1 to 11 years.

Adolescents Aged 12 to 17 Years

1356-5 Deferred pediatric study under PREA for treating heartburn associated with non-erosive GERD in pediatric patients aged 12 to 17 years.

1788-1 Deferred study under PREA to evaluate the healing, maintenance of healing, and symptoms of endoscopy-proven EE in patients aged 12 to 17 years of age.

Long-Term Safety Study in Pediatric Patients Aged 1 to 17 Years

1788-5 Deferred study under PREA to evaluate the long-term safety of dexlansoprazole for the healing and maintenance of healing of EE in pediatric patients aged 1 to 17 years who require chronic treatment with dexlansoprazole due to underlying conditions that predispose them to chronic GERD and relapsing EE.

Proposed pediatric study request for dexlansoprazole
The sponsor submitted a Proposed Pediatric Study Request (PPSR) on April 3, 2015. The PPSR included proposed studies for:

(b) (4)

- maintenance of healed EE and relief of heartburn in 1 to 11 months of age and 12 to 17 years of age
- treatment of heartburn associated with symptomatic non-erosive GERD in 1 to 17 years of age

The sponsor did not include studies for (b) (4) maintenance of healing of EE in patients 1 to 11 years of age in the PPSR because they did not expect to be able to complete the studies in time to benefit from pediatric exclusivity. Consequently, an Inadequate Study Request letter was issued on July 21, 2015 requesting that the sponsor resubmit the PPSR and include studies in this age group. In addition, the letter

suggested that the PPSR include studies for the treatment of *Helicobacter pylori* in pediatric patients.

Of note, the sponsor submitted studies in adolescents for the treatment of symptomatic nonerosive GERD, (b) (4) maintenance of healing of EE on May 30, 2015. The sponsor was encouraged in the Inadequate Study Request letter to submit these studies even though the WR has not been issued. In the same letter, the sponsor was made aware that the submitted studies will not be a part of the WR. However, there are several studies in other age groups that can be included in the WR. DPMH has been consulted to assist with the review of the adolescent studies.

Sponsor proposed pediatric specific labeling for Dexilant® SoluTab

8.4 Pediatric Use
Safety and effectiveness of DEXILANT (b) (4)

DPMH Recommendations:

DPMH recommends the following changes to subsection 8.4 Pediatric Use.

8.4 Pediatric Use
Safety and effectiveness of DEXILANT have not been established in pediatric patients (b) (4)

Labeling negotiations are ongoing. The final labeling may differ as a result of those negotiations.

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/s/

AMY M TAYLOR
12/18/2015

HARI C SACHS
12/18/2015
I agree with these recommendations.

LYNNE P YAO
12/20/2015

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

Memorandum

****PRE-DECISIONAL AGENCY MEMO****

Date: December 2, 2015

To: Maureen Dewey, MPH
Regulatory Project Manager
Division of Gastroenterology and Inborn Errors Products

From: Meeta Patel, PharmD
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: NDA 208056
OPDP Comments for draft DEXILANT SoluTab (dexlansoprazole) delayed-release orally disintegrating tablets, for oral use PI, MG

OPDP has reviewed the proposed draft PI and MG for DEXILANT SoluTab (dexlansoprazole) delayed-release orally disintegrating tablets, for oral use, retrieved from SharePoint on December 2, 2015, and have the following comments.

Thank you for the opportunity to comment on the proposed PI & MG.

If you have any questions or concerns, please contact Meeta Patel at 301-796-4284 or meeta.patel@fda.hhs.gov.

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/s/

MEETA N PATEL
12/02/2015

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Division of Pediatric and Maternal Health
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Silver Spring, MD 20993
Tel 301-796-2200
FAX 301-796-9744

Division of Pediatric and Maternal Health Memorandum

Date: November 27, 2015 **Dates Consulted:** April 20, 2015, October 8, 2015

From: Miriam Dinatale, D.O., Medical Officer
Division of Pediatric and Maternal Health

Through: Tamara Johnson, MD, MS, Team Leader, Maternal Health
Division of Pediatric and Maternal Health

Lynne P. Yao, MD, Director
Division of Pediatric and Maternal Health

To: Division of Gastroenterology and Inborn Errors Products (DGIEP)

Drug/NDA: 1.) Dexilant SoluTab (dexlansoprazole) delayed-release orally disintegrating tablets, NDA 208056
2.) Dexilant (dexlansoprazole) delayed -release capsules, NDA 22287

Applicant: Takeda Pharmaceuticals U.S.A., Inc.

Subject: Pregnancy and Lactation Labeling

Proposed Indication: [redacted] (b) (4) maintenance of healing of EE and relief of heartburn and treating heartburn associated with symptomatic non-erosive gastroesophageal reflux disease

Materials Reviewed:

- DPMH consult request for NDA 208056, Dexilant SoluTab delayed-release orally disintegrating tablets dated April 20, 2015, DARRTS Reference ID 3737237
- DPMH consult request for NDA 22287, Dexilant delayed- release capsules dated October 8, 2015, DARRTS Reference ID 3830987
- Applicant's submitted background package for NDA 208056, Dexilant SoluTab delayed-release orally disintegrating tablets

- Applicant's submitted background package for NDA 22287, Dexilant delayed- release capsules

Consult Question:
DGIEP requests assistance from DPMH in completing the review of the pregnancy and lactation section of labeling.

INTRODUCTION
The Division of Gastroenterology and Inborn Errors Products (DGEIP) consulted the Division of Pediatric and Maternal Health (DPMH) on April 20, 2015 and on October 8, 2015, to provide input for appropriate labeling for the pregnancy and lactation subsections of Dexilant SoluTab delayed-release orally disintegrating tablets and Dexilant delayed -release capsules.

REGULATORY HISTORY
Dexilant (dexlansoprazole) delayed-release capsules, NDA 22287, is a proton pump inhibitor that was approved in the U.S. on January 30, 2009 for the healing of all grades of erosive esophagitis (EE), maintenance of healing of EE and relief of heartburn and treating heartburn associated with symptomatic non-erosive gastroesophageal reflux disease (GERD). On March 26, 2015, Takeda Pharmaceuticals USA Inc. (Takeda) submitted a 505 (b)(2) New Drug Application for Dexilant SoluTab delayed-release orally disintegrating tablets (NDA 208056) (b) (4) On September 30, 2015, the Takeda submitted a Prior Approval Efficacy Supplement to expand the adult indications for Dexilant delayed-release capsules (NDA 22287) to include pediatric patients aged 12 to 17 and to update the pregnancy and lactation sections of labeling to comply with the Pregnancy and Lactation Labeling Rule.

The two dexlansoprazole oral formulations, Dexilant delayed -release capsules and Dexilant SoluTab delayed-release orally disintegrating tablets, are proposed to be included within one Full Prescribing Information.

BACKGROUND
Dexlansoprazole and Mechanism of Action
Dexlansoprazole is a proton pump inhibitor (PPI) that suppresses gastric acid secretion by specific inhibition of the (H+, K+)-ATPase in the gastric parietal cell. Dexlansoprazole blocks the final step of acid production.

Gastro-esophageal reflux and Pregnancy[1,2]
GERD is seen in about 30-50% of pregnant women and is typically of new onset. The pathogenesis of GERD during pregnancy is controversial. One mechanism by which GERD occurs involves a decrease in the lower esophageal sphincter tone due to the elevated levels of estrogen and progesterone. Other mechanisms by which GERD occurs involve an increase in

[1] Broussard, C. and Richter, Joel. Treating Gastro-Oesphageal Reflux Disease During Pregnancy and Lactation. Drug Safety. 1998; 19 (4): 325-337.
[2] Richter, Joel. Gastroesophageal reflux disease during pregnancy. Gastroenterology Clinics of North America. 2003; 32: 235-261.

abdominal pressure due to the enlarged gravid uterus and a decrease in the gastrointestinal transit time during pregnancy.

Mild cases of GERD can be managed with dietary and lifestyle changes; however moderate to severe cases of GERD may require drug therapy. If lifestyle changes do not work, nonsystemically absorbed medications, such as aluminum-, magnesium-, and calcium –containing antacids or sucralfate are used. If antacids or sucralfate do not work, histamine H2 receptor antagonists (avoiding nizatidine) or prokinetic drugs (metoclopramide, cisapride) are used for patients with more severe symptoms.

Proton pump inhibitors (PPIs) are generally prescribed when other treatments have failed. Safety data on the use of PPIs during pregnancy are limited. Omeprazole demonstrated dose-related embryonic and fetal mortality in pregnant rats and rabbits, but no teratogenicity was observed. Twelve birth defects, including five cases of anencephaly and one case of hydranencephaly, have been seen in infants of women who have taken omeprazole after week 13 of gestation. There have been other case reports and prospective database studies of normal infants born to women who have taken omeprazole throughout pregnancy. Animal reproduction studies with lansoprazole[3] have found no evidence of embryofetal toxicity; in addition, there were no significant fetal effects seen in infants of mothers exposed to lansoprazole during pregnancy. Therefore, if a PPI is required during pregnancy, lansoprazole is recommended. Newer PPIs (rabeprazole, pantoprazole, esomeprazole and dexlansoprazole) have been shown to be safe in animal reproduction studies, but there are no case reports about use during pregnancy for these PPIs.

Pregnancy and Lactation Labeling

On December 4, 2014, the Food and Drug Administration (FDA) announced the publication of the "*Content and Format of Labeling for Human Prescription Drug and Biological Products; Requirements for Pregnancy and Lactation Labeling*,"[4] also known as the Pregnancy and Lactation Labeling Rule (PLLR). The PLLR requirements include a change to the structure and content of labeling for human prescription drug and biologic products with regard to pregnancy and lactation, and create a new subsection for information with regard to females and males of reproductive potential. Specifically, the pregnancy categories (A, B, C, D and X) are removed from all prescription drug and biological product labeling and a new format is required for all products that are subject to the 2006 Physicians Labeling Rule[5] format to include information about the risks and benefits of using these products during pregnancy and lactation.

LITERATURE REVIEW

Dexlansoprazole and Nonclinical Findings

The current dexlansoprazole labeling provided by the applicant includes data from animal reproduction studies that were conducted for the initial approval of dexlansoprazole in 2009. In these animal studies, no fetotoxicity or teratogenicity was observed with oral administration of

[3] Dexlansoprazole is the R-enantiomer of lansoprazole.

[4] *Content and Format of Labeling for Human Prescription Drug and Biological Products, Requirements for Pregnancy and Lactation Labeling* (79 FR 72063, December 4, 2014).

[5] *Requirements on Content and Format of Labeling for Human Prescription Drug and Biological Products*, published in the Federal Register (71 FR 3922; January 24, 2006).

dexlansoprazole in rabbits during organogenesis at doses up to nine times the maximum recommended human dose (MRHD) of dexlansoprazole (60 mg/day). In addition, there was no fetotoxicity or teratogencity with administration of oral lansoprazole (the R-enantiomer of dexlansoprazole) to rabbits and rats during organogenesis at doses up to 16 and 40 times the MRHD, respectively.[6] No additional nonclinical studies were submitted with this NDA.

The carcinogenic potential of dexlansoprazole was assessed using lansoprazole studies. In two 24-month rat carcinogenicity studies, Sprague-Dawley rats were treated with oral lansoprazole at doses 40 times the exposure on a body surface basis (mg/m^2) of a 50kg person of average height ($1.46m^2$ body surface area (BSA)). Lansoprazole was found to produce the following effects: dose-related gastric Enterochromaffin-Like (ECL) cell hyperplasia, ECL cell carcinoids and increased incidence of intestinal metaplasia of the gastric epithelium in both male and female rats and an increase in testicular interstitial cell adenomas in male rats. In a 24-month carcinogenicity study with CD-1 mice treated with oral lansoprazole at doses two to 80 times the recommended human dose based on BSA, lansoprazole produced a dose-related increased incidence of gastric ECL cell hyperplasia, liver tumors (hepatocellular adenoma and carcinoma) in male and female mice and testicular adenoma in male mice.[7] The reader is referred to original nonclinical review[8] and the current review by Ke Zhang, Ph.D. for further details.

Dexlansoprazole and Pregnancy

The applicant performed a search of published literature for available published human pregnancy data for dexlansoprazole using the following databases: OVID, Medline, Embase, PharmaPendium and Pharmacovigilance Insights as well as the Takeda Pharmacovigilance database. The results of the search are presented below.

Although there were no adequate and well-controlled studies that have been conducted in pregnant women taking dexlansoprazole, there were a total of 17 pregnancies that were reported in the dexlansoprazole clinical trial; 12 pregnant subjects were exposed to dexlansoprazole, four pregnant subjects received the placebo; and one pregnant subject received lansoprazole. The following are the outcomes of the 12 women who became pregnant while taking dexlansoprazole:

- Six subjects had elective abortions. The reason for the abortions was not specified.
- Four subjects had live births with normal infants born between 38 and 40 weeks gestation.
- Two subjects had spontaneous abortions (SABs)
    - One subject had been exposed to dexlansoprazole for five days and experienced a SAB. There was no mention of the gestational age of the fetus or if there were any associated fetal malformations. The subject had a prior medical history of SABs, elective abortions and premature births.
    - One subject had been exposed to dexlansoprazole for 126 days and experienced a SAB. There was no mention of the gestational age of the fetus or if there were any associated fetal malformations. The subject had a prior history of a SAB and a full-term stillborn birth.

[6] Yash, Chopra. Pharmacology/Toxicology Review of NDA 21-372 9/26/2002, pg 171-172.
[7] Drugs@FDA: Dexilant (dexlansoprazole) Labeling, Nonclinical Toxicology: section 13.1, accessed 8/28/15
[8] Nonclinical Review. Dexlansoprazole. NDA 22287. Ke Zhang, Ph.D. February 3. 2010

In postmarketing reports, there were 15 cases of pregnant women taking dexlansoprazole.

- There was one case of a serious adverse event of a pregnant woman developing an allergic reaction (pharyngeal edema, dyspnea, swollen tongue and rash) about one hour after taking her first dose of dexlansoprazole. The patient was treated in the emergency department and her symptoms resolved. Dexlansoprazole was discontinued. There was no mention of any effects to the fetus or the pregnancy outcome.
- There were four cases of non-serious adverse events in pregnant woman taking dexlansoprazole
    - One woman reported nausea that resolved without treatment.
    - One woman reported abdominal distension and "feeling gassy" after receiving dexlansoprazole.
    - One woman reported throat tightness (patient had a history of esophageal spasm) that resolved on its own. Treatment with dexlansoprazole continued.
    - One woman reported malaise, chills, fever, diarrhea and upper abdominal pain and decreased weight, but by the time of the report, her symptoms, except for diarrhea and abdominal cramping, had resolved.
- There were ten cases of pregnancy with no outcome data included.

A review of published literature by the applicant and DPMH did not identify data on the use of dexlansoprazole in pregnant women. However, there were studies that evaluated proton pump inhibitors (PPIs) and use in pregnant women. Clinical studies with PPIs, including omeprazole, lansoprazole, and pantoprazole, have demonstrated no association between exposure to these PPIs during the period of organogenesis and increased risk for major malformations, increased risk of spontaneous abortions, decreased birth weight or perinatal complications. [9, 10,11,12,13,14,15]

In an *in vitro* study (Terranova, *et al*.), the muscle relaxant effects of PPIs (omeprazole, esomeprazole, pantoprazole, lansoprazole and rabeprazole) on myometrial tissue samples obtained from pregnant women undergoing caesarian section was studied. The authors found that all PPIs studied reduced the spontaneous contraction of the myometrial smooth muscle and concluded that these data suggest that these drugs can offer new therapeutic strategies for preterm delivery, but further investigations and clinical studies are necessary before adding PPIs to the list of drugs available for the treatment of preterm delivery.[16]

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[9] Matok, et al. The safety of fetal exposure to proton-pump inhibitors during pregnancy. Digestive Diseases & Sciences. 2012. 57 (3): 699-705.

[10] Kallen BA. Use of omeprazole during pregnancy- no hazard demonstrated in 95 infants exposed during pregnancy. Eur J Obstet Gynecol Reprod Biol. 2001; 96: 63-68.

[11] Lalkin et al. The safety of omeprazole during pregnancy: a multicenter prospective controlled study. Am J Obstet Gynecol 1998;179:727–730

[12] Diav-Citrin, et al. The safety of proton pump inhibitors in pregnancy: a multicentre prospective controlled study. Aliment PharmacolTher 2005;21:269–275.

[13] Nielsen, et al. The safety of proton pump inhibitors in pregnancy. Aliment Pharmacol Ther. 1999;13:1085–1089.

[14] Kallen B. Delivery outcome after the use of acid-suppressing drugs in early pregnancy with special reference to omeprazole. Br J Obstet Gynaecol. 1998;105:877–881

[15] Wilton et al. The outcomes of pregnancy in women exposed to newly marketed drugs in general practice in England. Br J Obstet Gynaecol. 1998; 105: 882-889.

[16] Terranova, et al. Relaxant effect of proton pump inhibitors on in vitro myometrium from pregnant women. European Journal of Pharmaceutical Sciences. 2014; 52: 125-131.

DPMH has conducted reviews of other PPIs. In a DPMH review of published literature on Aciphex (rabeprazole), [17,18] the reviewer noted that the information on rabeprazole use in pregnancy is limited and that there is no association between first trimester PPI use and major birth defects. [19]

DPMH also reviewed esomeprazole and omeprazole products and assisted DGIEP in the revision and restructuring of esomeprazole and omeprazole labeling in response to new safety information from pre- and postnatal developmental toxicity studies in pregnant and lactating rats who were administered esomeprazole strontium and demonstrated changes in bone morphology and physeal dysplasia . The reader is referred to the DPMH review by Carrie Ceresa, PharmD for further details.[20]

Discussion

Overall, there is no evidence of embryo-fetotoxicity in animal reproduction studies performed with dexlansoprazole or lansoprazole. Human data on dexlansoprazole use in pregnant women is limited; however, the data on pregnant women taking dexlansoprazole during clinical trials and post-marketing reports do not describe significant fetal or maternal effects. Clinical studies with other PPIs have not shown an association between first trimester exposure to PPIs and increased risk for major malformations or other adverse pregnancy outcomes However, administration of esomeprazole strontium resulted in changes to bone morphology and physeal dysplasia in pre- and postnatal developmental toxicity studies in pregnant rats leading to safety labeling changes for all esomeprazole and omeprazole products. Takeda, the sponsor for both lansoprazole and dexlansoprazole, is currently conducting similar pre- and postnatal developmental toxicity studies to evaluate the safety concern. Once completed, the results of those studies will be included in dexlansoprazole labeling.

Dexlansoprazole and Lactation

The applicant performed a search of published literature for available published human lactation data for dexlansoprazole using the following databases: OVID, Medline, Embase, PharmaPendium and Pharmacovigilance Insights as well as the Takeda Pharmacovigilance database. DPMH also performed a search of the Drugs and Lactation Database (LactMed)[21] and Pubmed. The results of the search are presented below.

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[17] Pasternak, B., Hviid, A. (2010). Use of Proton-Pump Inhibitors in Early Pregnancy and the Risk of Birth Defects. *The New England Journal of Medicine*, 363, 2114-23.

[18] Majithia, R., Johnson, D. (2012). Are Proton Pump Inhibitors Safe during Pregnancy and Lactation? *Drugs*, 72(2), 171-179.

[19] DPMH Review: Aciphex (rabeprazole sodium), NDA 20973/S-033 & 204736/S-003. Carrie Ceresa, PharmD, MPH. April 10, 2014. DARRTS Reference ID 3729478.

[20] DPMH Review: FDAAA Safety Labeling Changes (esomeprazole and omeprazole products) Carrie Ceresa, Pharm D. MPH. November 8, 2013. DARRTS Reference ID 3403670.

[21] http://toxnet nlm nih.gov/cgi-bin/sis/htmlgen?LACT. The LactMed database is a National Library of Medicine (NLM) database with information on drugs and lactation geared toward healthcare practitioners and nursing women. The LactMed database provides information when available on maternal levels in breast milk, infant blood levels, any potential effects in the breastfed infants if known, alternative drugs that can be considered and the American Academy of Pediatrics category indicating the level of compatibility of the drug with breastfeeding.

There was no exposure of dexlansoprazole to infants via breastmilk that was reported during dexlansoprazole clinical trials and no published literature that discussed the use of dexlansoprazole while breastfeeding. In post-marketing reports, there were three cases of dexlansoprazole exposure during breastfeeding that are discussed below:

- In one infant, who had been breastfed for four months, there was no adverse event.
- In the second case, the mother accidentally took two doses of dexlansoprazole in one day; this was considered an overdose. However, there were no reported adverse side effects in the mother or infant due to taking an extra dose, and there was no mention of whether the mother continued to breastfed the infant on that day.
- The third case involved an infant with a medical history of "yellow skin" who experienced worsening of skin discoloration. The infant was breastfed for three months while the mother took dexlansoprazole. There was no reported outcome to this event.

LactMed summarizes available dexlansoprazole lactation data as follows:

> Dexlansoprazole is the R-enantiomer of the protein-pump inhibitor, lansoprazole. No information is available on the use of dexlansoprazole or lansoprazole during breastfeeding. However, lansoprazole has been used safely in newborn infants, so it is unlikely that the amount of dexlansoprazole in breastmilk would be harmful.

In Medications and Mother's Milk[22], Dr. Hale, a breastfeeding expert, notes that dexlansoprazole and lansoprazole have poor stability at an acidic pH, have a short half-life, and would most likely be denatured by the acid in the breastfeeding infant's stomach. Dr. Hale notes that although there are no studies of dexlansoprazole in breastfeeding mothers, transfer of the drug and oral absorption via breast milk are likely to be minimal.

Although there is no information on the presence of dexlansoprazole or lansoprazole in human milk, lansoprazole and its' metabolites are present in rat milk. In an animal lactation study, the administration of [^{14}C] lansoprazole to lactating rats 14 days post-partum, resulted in 2- and 6-fold higher concentrations of radioactivity in milk than plasma.

In addition, in rat carcinogenicity studies with dexlansoprazole and lansoprazole (see "Dexlansoprazole and Nonclinical Findings" above), dose-related increases in gastric ECL cell hyperplasia and ECL cell carcinoid tumors were observed. The dexlansoprazole and lansoprazole labeling has, therefore, discouraged breastfeeding since their initial U.S. approval. Current dexlansoprazole and lansoprazole labeling includes the following Nursing Mothers' regulatory statement:

> Because of the potential for tumorigenicity shown for lansoprazole in rat carcinogenicity studies, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Discussion

Dexlansoprazole is present in rat milk at 2- and 6-fold higher concentrations in maternal milk than plasma. Drug presence and accumulation in breast milk is species specific, and although

[22] Hale, T. Medications and Mother's Milk. Hale Publishing, 2012.

dexlansoprazole has characteristics, such as molecular weight (369.36 Daltons)[23], that suggest the drug is transferred into breast milk, the drug also has characteristics, such as a short half-life (1-2 hours) and high protein binding (96-98.8%), which decrease the presence of the drug in the mother's circulation and may decrease infant exposure to the drug via breast milk.[24]

After discussion with the DGIEP Nonclinical and Clinical teams, DPMH has determined that an update to the language in the lactation section of dexlansoprazole labeling is warranted. It is not known if dexlansoprazole or lansoprazole is present in human milk; however, infants of mothers who have taken lansoprazole while breastfeeding have had no adverse effects. Therefore, although previous approved labeling for Dexilant added warning language in the Nursing Mothers' subsection of labeling based on positive carcinogenicity findings, reassessment of the risk based on the available information brings DPMH to recommend that the Lactation section of Dexilant labeling should state the following:

> The development and health benefits of breastfeeding should be considered along with the mother's clinical need for DEXILANT and any potential adverse effects on the breastfed infant from DEXILANT or from the underlying maternal condition.

Dexlansoprazole and Females and Males of Reproductive Potential

The applicant performed a search of published literature for available published data on dexlansoprazole related effects on fertility and preimplantation loss in humans using the following databases: OVID, Medline, Embase, PharmaPendium and Pharmacovigilance Insights as well as the Takeda Pharmacovigilance database. DPMH also performed a search of Pubmed using the search terms "dexlansoprazole" and "fertility," "sperm," and "reproduction", and searched previous DPMH reviews on other PPIs, and no data were found.

In animal reproduction studies in rabbits given oral dexlansoprazole at doses 9 times the MRHD, there was no evidence of impaired fertility. In addition, in animal reproduction studies in rats and rabbits given 40 and 16 times, respectively, the MRHD of oral lansoprazole, there was no evidence of impaired fertility.[25]

CONCLUSIONS

Dexilant (dexlansoprazole) labeling has been revised to comply with the PLLR. A review of the literature for relevant data revealed no new data with dexlansoprazole use in pregnant or lactating women. DPMH has the following recommendations for the Dexilant labeling:

- **Pregnancy, Section 8.1**
  - The "Pregnancy" subsection of Dexilant labeling was formatted in the PLLR format to include the "Risk Summary" and "Data" subsections[26].

[23] Drugs with molecular weights (MW) greater than 800 Daltons are excluded from the milk compartment more readily than those with MWs less than 800 Daltons

[24] Nice, F and Luo, Amy. Medications and breast-feeding: Current Concepts. Journal of the American Pharmacists Association. 2012; 51 (1): 86-94.

[25] Drugs@FDA. Dexlansoprazole Labeling: Section 13, Nonclinical Toxicology. Accessed 11/9/2015.

[26] Guidance for Industry: Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products-Content and Format. December 2014. Part IV Specific Subsection A-8.1 Pregnancy, 2-Risk Summary.

- **Lactation, Section 8.2**
  - The "Lactation" subsection of Dexilant labeling was formatted in the PLLR format to include the "Risk Summary" and "Data" subsections[27].

RECOMMENDATIONS
DPMH revised subsections 8.1 and 8.2 in Dexilant labeling for compliance with the PLLR (see below). DPMH refers to the final NDA action for final labeling.

DPMH Proposed Dexilant (dexlansoprazole) Pregnancy and Lactation Labeling

FULL PRESCRIBING INFORMATION
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
Risk Summary
There are no studies with dexlansoprazole use in pregnant women to inform a drug-associated risk. In animal reproduction studies, no effects on embryo-fetal development were observed with the administration of oral dexlansoprazole to rabbits during organogenesis at doses up to 9 times the maximum recommended human dose (MRHD) or with administration of oral lansoprazole to rats and rabbits during organogenesis at doses up to 40 and 16 times the MRHD, respectively *[see Data]*.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Data
Animal Data
An embryo-fetal development study conducted in rabbits at oral dexlansoprazole doses up to 30 mg/kg/day (approximately nine times the maximum recommended human dexlansoprazole dose [60 mg/day] based on body surface area) during organogenesis showed no effects on fetuses due to dexlansoprazole. In addition, embryo-fetal development studies performed in rats with oral lansoprazole at doses up to 150 mg/kg/day (40 times the recommended human lansoprazole dose based on body surface area) during organogenesis and in rabbits with oral lansoprazole at doses up to 30 mg/kg/day (16 times the recommended human lansoprazole dose based on body surface area) during organogenesis revealed no effects on fetuses due to lansoprazole.

8.2 Lactation
Risk Summary
There is no information regarding the presence of dexlansoprazole in human milk, the effects on the breastfed infant, or the effects on milk production. However, lansoprazole and its metabolites are present in rat milk *[see Data]*. The development and health benefits of breastfeeding should be considered along with the mother's clinical need for DEXILANT and any potential adverse

[27] Guidance for Industry: Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products-Content and Format. December 2014. Part IV Specific Subsection, B- 8.2 Lactation, 1- Risk Summary.

effects on the breastfed (b) (4) from DEXILANT or from the underlying maternal condition.

Data

When [^{14}C] lansoprazole was administered orally at 2 mg/kg to lactating rats 14 days after parturition, milk collected at 0.5, 2 and 6 hours after the lansoprazole dose, contained 2- to 6-fold higher concentrations of radioactivity than plasma. Almost all of the radioactivity was determined to be from lansoprazole metabolites.

MEDICATION GUIDE

Before you take DEXILANT, tell your doctor if you:

- are pregnant or plan to become pregnant. It is not known if DEXILANT will harm your unborn baby.
- are breastfeeding or plan (b) (4) to breastfeed. It is not known if DEXILANT passes into your breast milk. Talk to your doctor about the best way to feed your baby if you take DEXILANT.

APPENDIX A – Applicant's Proposed Pregnancy and Lactation Labeling

FULL PRESCRIBING INFORMATION
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
Risk Summary
(b) (4)

Data
Animal Data
(b) (4)

8.2 Lactation
Risk Summary
(b) (4) However, lansoprazole and its metabolites are present in rat milk (b) (4)
(b) (4)

Data
Animal Data
When [^{14}C] lansoprazole was administered orally at 2 mg/kg to lactating rats 14 days after parturition, milk collected at 0.5, 2 and 6 hours after the lansoprazole dose contained 2- to 6-fold higher concentrations of radioactivity than plasma. Almost all of the radioactivity was determined to be from lansoprazole metabolites.

MEDICATION GUIDE
Before you take DEXILANT, tell your doctor if you:
- are pregnant or plan to become pregnant. It is not known if DEXILANT will harm your unborn baby.
- are breastfeeding or plan (b) (4) to breastfeed. It is not known if DEXILANT passes into your breast milk. (b) (4) Talk to your doctor about the best way to feed your baby if you take DEXILANT.

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/s/

MIRIAM C DINATALE
11/30/2015

TAMARA N JOHNSON
11/30/2015

LYNNE P YAO
11/30/2015

LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review:	October 15, 2015
Requesting Office or Division:	DGIEP
Application Type and Number:	NDA 208056
Product Name and Strength:	Dexilant SoluTab (Dexlansoprazole) 30 mg Delayed- release Orally Disintegrating Tablets
Product Type:	Single
Rx or OTC:	Rx
Applicant/Sponsor Name:	Takeda Development Center Americas, Inc.
Submission Date:	March 26, 2015
OSE RCM #:	2015-720
DMEPA Primary Reviewer:	Sherly Abraham, R.Ph.
DMEPA Team Leader:	Kendra Worthy, Pharm.D.

1 REASON FOR REVIEW

This review responds to a request from DGIEP to evaluate the proposed prescribing information, carton and container labels, and instructions for use.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Label and Labeling Review

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
Human Factors Study	C-N/A
ISMP Newsletters	D
FDA Adverse Event Reporting System (FAERS)*	E
Other	F-N/A
Labels and Labeling	G

N/A=not applicable for this review
*We do not typically search FAERS for label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

Takeda Development Center Americas, Inc. submitted a NDA to obtain a marketing approval of Dexilant (Dexlansoprazole) SoluTab delayed-release orally disintegrating tablets. Takeda is currently marketing Dexilant delayed-release capsule. We reviewed the proposed prescribing information, carton and container labels, and instructions for use. DMEPA concludes that the proposed label and labeling can be improved to increase the readability and prominence of important information on the label to promote the safe use of the product.

4 CONCLUSION & RECOMMENDATIONS

DMEPA concludes that the proposed label and labeling can be improved to increase the readability and prominence of important information on the label to promote the safe use of the product.

4.1 RECOMMENDATIONS FOR THE DIVISION

Please see the attached minor edits to the prescribing information and instructions for use.

4.2 RECOMMENDATIONS FOR TAKEDA DEVELOPMENT CENTER AMERICAS, INC.

We recommend the following be implemented prior to approval of this NDA:

1. NDC numbers on carton and container for both trade and professional sample are the same. Revise the last two digits of the NDC number so that carton and container labels for trade and professional sample are different.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Dexilant Solutab submitted by Takeda Development Center Americas, Inc. on March 26, 2015.

Products:	**Dexilant SoluTab Proposed**	**Dexilant Capsules Approved January 30, 2009**
Active Ingredient:	Dexlansoprazole	Dexlansoprazole
Indication:	(b) (4) Maintenance of healed EE and relief of heartburn for up to six months. Treatment of heartburn associated with symptomatic non-erasive gastroesophageal reflux disease (GERD) for four weeks.	Healing of all grades of erosive esophagitis (EE) for up to eight weeks. Maintenance of healed EE and relief of heartburn for up to six months. Treatment of heartburn associated with symptomatic non-erasive gastroesophageal reflux disease (GERD) for four weeks.
Route of Admini-stration:	Oral	Oral
Dosage Form:	Orally disintegrating tablets	Delayed-release capsule
Strength:	30 mg	30 mg and 60 mg
Dose and Frequency	Take 1 (b) (4) tablet (b) (4) once daily	Healing of EE: 60 mg once daily up to 8 weeks. Maintenance of healed EE: 30 mg once daily for upto 6

		months. Symptomatic non-erosive GERD: 30 mg once daily for up to 4 weeks.
How Supplied:	Blister packs: Trade unit of 100 (10 packs of 10 tablets) Sample unit of 20 (6 packs of 5 tablets)	Unit dose package of 100, bottle of 30 capsules, bottle of 90 capsules and bottle of 1000.
Storage:	Store at 25°C (77°F); excursions permitted to 15 to 30°C (59 to 86° F)	Store at 25°C (77°F); excursions permitted to 15 to 30°C (59 to 86° F)

APPENDIX B. FDA ADVERSE EVENT REPORTING SYSTEM (FAERS)

B.1 Methods

We searched the FDA Adverse Event Reporting System (FAERS) on October 8, 2015, using the criteria in Table 4, and then individually reviewed each case. We limited our analysis to cases that described errors possibly associated with the label and labeling. We used the NCC MERP Taxonomy of Medication Errors to code the type and factors contributing to the errors when sufficient information was provided by the reporter[1].

Table 4: FAERS Search Strategy	
Date Range	**May 1, 2013 to October 1, 2015**
Product	**Dexilant** [product name]
Event (MedDRA Terms)	**DMEPA Official FBIS Search Terms Event List:** Medication Errors [HLGT] Product Packaging Issues [HLT] Product Label Issues [HLT] Product Adhesion Issue [PT] Product Compounding Quality Issue [PT] Product Difficult to Remove [PT] Product Formulation Issue [PT] Product Substitution Issue [PT] Inadequate Aseptic Technique in Use of Product [PT]

B.2 Results

Our search identified twenty seven cases, of which none described errors relevant for this review.

[1] The National Coordinating Council for Medication Error Reporting and Prevention (NCC MERP) Taxonomy of Medication Errors. Website http://www.nccmerp.org/pdf/taxo2001-07-31.pdf.

APPENDIX C. PREVIOUS DMEPA REVIEWS

C.1 Methods

We searched the L drive on October 8, 2015, using the terms, Dexilant, to identify reviews previously performed by DMEPA.

C.2 Results

Our search identified two previous reviews[2], and we confirmed that our previous recommendations were implemented.

[2] Khosla, Lisa V. Label and Labeling Review for Dexilant (NDA 22287). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2013 06 17. 32 p. OSE RCM No.: 2013-936.

Hamilton-Stokes, Deveonne. Label and Labeling Review for Dexilant(NDA 22287). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2010 03 09. 32 p. OSE RCM No.: 2009-2341.

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APPENDIX E. ISMP NEWSLETTERS

E.1 Methods

We searched the Institute for Safe Medication Practices (ISMP) newsletters on October 8, 2015, using the criteria below, and then individually reviewed each newsletter. We limited our analysis to newsletters that described medication errors or actions possibly associated with the label and labeling.

ISMP Newsletters Search Strategy	
ISMP Newsletter(s)	Acute care, Community, and Nursing
Search Strategy and Terms	Match Exact Word or Phrase: Dexilant

E.2 Results

Our search identified no medication error cases which are relevant for this review.

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[3] along with postmarket medication error data, we reviewed the following Dexilant Solutab labels and labeling submitted by Takeda Development Center Americas, Inc. on March 26, 2015.

- Container label
- Carton labeling
- Professional Sample Blistercards
- Professional Sample Carton Labeling

9 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

[3] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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/s/

SHERLY ABRAHAM
10/15/2015

KENDRA C WORTHY
10/15/2015