

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**125513Orig1s000**

**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.

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BLA # 125513  
Product Name: Strensiq (asfotatse alfa)

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PMR/PMC Description: A prospective, long-term, observational study in patients with perinatal/infantile-onset and juvenile-onset hypophosphatasia (HPP) from ages birth and older. The purpose of the study is to assess the long term safety of treatment with STRENSIQ (asfotase alfa) with respect to incidence rates of severe allergic reactions (including anaphylaxis), systemic immune complex-mediated reactions and ectopic calcification events. Specify case definitions and validation methods and procedures for all outcomes. Enroll adequate number of patients, including both infantile-onset and juvenile-onset-patients, and follow for a minimum of 5 years from the time of enrollment or until death, whichever comes first.

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PMR/PMC Schedule Milestones:	Final Protocol Submission:	<u>07/2016</u>
	Study Completion:	<u>10/2022</u>
	Final Report Submission:	<u>06/2013</u>

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

STRENSIQ (asfotase alfa) is being developed for the treatment of patients with infantile-onset and juvenile-onset hypophosphatasia (HPP), a serious and potentially life-threatening condition. Clinical features in patients with infantile-onset HPP, a severe form of the disease, include respiratory failure, craniosynostosis, and increased intracranial pressure. Clinical features common to both infantile-onset and juvenile-onset HPP include growth failure, motor delays, nephrocalcinosis, and pathological fractures. Currently, there are no approved therapies for this condition.

STRENSIQ is a recombinant form of tissue-nonspecific alkaline phosphatase, an enzyme involved in bone mineralization. The mechanism of action is not fully understood. However, enzymatic activity results in increased concentrations of inorganic phosphate, which subsequently precipitates with calcium to form calcium phosphate which is transformed into hydroxyapatite crystals, which provide the structural matrix for bones and teeth.

The efficacy and short-term safety of STRENSIQ have been established. However, data are needed on the long-term safety of the product, including the immunogenic profile of the drug and the potential risk of deposition of hydroxyapatite crystals outside of bones and teeth (ectopic calcification).

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 goal of the study is to evaluate the long-term safety of STRENSIQ in patients with infantile-onset and juvenile-onset HPP, including assessing the known serious risk of severe hypersensitivity reactions (including anaphylaxis) and to identify an unexpected serious risk of systemic immune complex-mediated reactions.

In addition, reported adverse reactions include ectopic calcifications of the eye and nephrocalcinosis. Another goal of the study will be to assess a signal of a serious risk of ectopic calcification events.

An analysis of spontaneous postmarketing adverse events will not be sufficient to assess risk for these adverse reactions.

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.

This will be a prospective observational study.

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

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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

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**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)



Strensiq is a fusion protein that consists of human tissue non-specific alkaline phosphatase, human IgG1 Fc domain, and a decamer aspartate peptide used as a bone targeting domain. The Fc part appears to be derived from unmodified IgG1 and is N-glycosylated. Strensiq is likely to bind to Fc-receptors and complement components, because it contains all the IgG1 protein elements necessary for such interactions, including the hinge and the N-linked glycan. Interaction of Strensiq with Fc- and complement receptors expressed on dendritic cells could enhance the uptake and antigen processing of Strensiq, and thus the immunogenicity of the product. A further concern is potential complement activation by Strensiq.

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)**

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- Assess signals of serious risk related to the use of the drug?
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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.

The sponsor will develop an assay to compare the complement activation potential of Strensiq to that of human IgG1. If Strensiq activates complement more strongly than human IgG1, further studies might be necessary.

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)  
Complement activation as a marker of safety
- 

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?
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- Has the applicant adequately justified the choice of schedule milestone dates?
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***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

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**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.

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NDA/BLA # 125513  
Product Name: STRENSIQ (asfotase alfa)

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PMR/PMC Description: Develop a validated cross-reactive immunologic material (CRIM) assay for patients with hypophosphatasia (HPP) and test patient samples in a cohort of untreated patients. Results should be correlated with antibody response (binding and neutralizing), genetic mutations, enzyme activity level and clinical outcome in patients who are receiving Asfotase alfa treatment.

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PMR/PMC Schedule Milestones: Final Report Submission: 06/2016

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

Strensiq (asfotase alfa) will be used to treat a rare disease, hypophosphatasia (HPP). Disease severity is generally inversely related to the age of onset and mortality in newborn patients with perinatal HPP is considered to be 100%. There is currently no treatment for HPP. More data are needed to characterize patients who are at risk of experiencing diminished efficacy to better inform the prescribers and patients through labeling.

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.”

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.

The PMR study will develop a validated cross-reactive immunologic material (CRIM) assay for patients with HPP and test patient samples in a cohort of untreated patients. Results will be correlated with antibody response (binding and neutralizing), genetic mutations, enzyme activity level, and clinical outcome in patients who are receiving STRENSIQ treatment (b) (4)

(b) (4) The study is open to all HPP patients.

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)
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- 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  
Develop a validated cross-reactive immunologic material (CRIM) assay
- 

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?
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- 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

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**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: Product Quality (CMC)

This template should be completed by the review chemist (ONDQA) or biologist (OBP) and included for *each* type of CMC PMR/PMC in the Action Package. See #4 for a list of CMC PMR/PMC types

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BLA # 125513 Strensiq (asfotase alfa)  
Product Name:

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PMC #1 Description: Evaluate the asfotase alfa manufacturing process and develop a control strategy (b) (4)  
Provide detailed summaries of all data utilized to propose the revised control strategy (b) (4)

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PMC Schedule Milestones: Final Report Submission: 11/2016

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- **ADD MORE AS NEEDED USING THE SAME TABULAR FORMAT FOR EACH PMC.**
- **INCLUDE DESCRIPTIONS AND MILESTONES IN THE TABLE ABOVE FOR ALL CMC/OBP NON-REPORTABLE PMCS FOR WHICH THE FOLLOWING ANSWERS WILL BE IDENTICAL. USE A SEPARATE TEMPLATE FOR EACH PMR/PMC FOR WHICH THE ANSWERS TO THE FOLLOWING QUESTIONS DIFFER.**
- **DO NOT USE THIS FORM IF ANY STUDIES WILL BE REQUIRED UNDER FDAAA OR WILL BE PUBLICALLY REPORTABLE**

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

- Need for drug (unmet need/life-threatening condition)
- Long-term data needed (e.g., stability data)
- Only feasible to conduct post-approval
- Improvements to methods
- Theoretical concern
- Manufacturing process analysis
- Other

The current drug substance process has been validated to support BLA approval. The validated process produces asfotase alfa (b) (4)  
Further evaluation of the drug substance manufacturing process is needed (b) (4)

2. Describe the particular review issue and the goal of the study.

Analysis of the population PK analysis by the clinical pharmacology team indicated a (b) (4) process is (b) (4). At this time the manufacturing process is (b) (4). In order to ensure consistency with patient exposure to asfotase alfa over the course of treatment, the ultimate goal would be for Alexion to consistently manufacture asfotase alfa (b) (4)

3. [OMIT – for PMRs only]

4. What type of study is agreed upon (describe and check type below)?

Select only one. Fill out a new sheet for each type of PMR/PMC study.

- Dissolution testing
- Assay
- Sterility
- Potency
- Product delivery
- Drug substance characterization
- Intermediates characterization
- Impurity characterization
- Reformulation
- Manufacturing process issues
- Other

Describe the agreed-upon study:

(b) (4)

5. To be completed by ONDQA/OBP Manager:

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

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**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 only)

## PMR/PMC Development Template: Product Quality (CMC)

This template should be completed by the review chemist (ONDQA) or biologist (OBP) and included for *each* type of CMC PMR/PMC in the Action Package. See #4 for a list of CMC PMR/PMC types

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BLA # 125513 Strensiq (asfotase alfa)  
Product Name:

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PMC #5 Description: To re-evaluate the (b) (4) endotoxin limits for the (b) (4) after data from thirty batches is available (b) (4) to reflect manufacturing process capability.

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PMC Schedule Milestones: Final Report Submission: 12/2017

- **ADD MORE AS NEEDED USING THE SAME TABULAR FORMAT FOR EACH PMC.**
- **INCLUDE DESCRIPTIONS AND MILESTONES IN THE TABLE ABOVE FOR ALL CMC/OBP NON-REPORTABLE PMCS FOR WHICH THE FOLLOWING ANSWERS WILL BE IDENTICAL. USE A SEPARATE TEMPLATE FOR EACH PMR/PMC FOR WHICH THE ANSWERS TO THE FOLLOWING QUESTIONS DIFFER.**
- **DO NOT USE THIS FORM IF ANY STUDIES WILL BE REQUIRED UNDER FDAAA OR WILL BE PUBLICALLY REPORTABLE**

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

- Need for drug (unmet need/life-threatening condition)
- Long-term data needed (e.g., stability data)
- Only feasible to conduct post-approval
- Improvements to methods
- Theoretical concern
- Manufacturing process analysis
- Other

The (b) (4) endotoxin limits are too wide for the (b) (4). The limits should be set to reflect manufacturing process capability. The sponsor has agreed to re-evaluate these limits and (b) (4) them after thirty batches have been manufactured which cannot be completed during the review cycle due to the manufacturing schedule. Adequate microbial controls are in place, therefore this is not an approvability issue.

2. Describe the particular review issue and the goal of the study.

The (b) (4) endotoxin limits for the (b) (4) are high and improved product quality can be ensured by (b) (4) the (b) (4) limits for endotoxin.

3. [OMIT – for PMRs only]

4. What type of study is agreed upon (describe and check type below)?

Select only one. Fill out a new sheet for each type of PMR/PMC study.

- Dissolution testing
- Assay
- Sterility
- Potency
- Product delivery
- Drug substance characterization
- Intermediates characterization
- Impurity characterization
- Reformulation
- Manufacturing process issues
- Other

Describe the agreed-upon study:

The sponsor will re-evaluate the (b) (4) endotoxin limits after thirty batches have been manufactured and (b) (4) them based on the manufacturing capability.

5. To be completed by ONDQA/OBP Manager:

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

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**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 only)

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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LISA N PITT  
10/23/2015

AMY G EGAN  
10/23/2015



Department of Health and Human Services  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Biotechnology Products

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**FINAL LABEL AND LABELING REVIEW**

Date:	October 8 2015
Reviewer:	Jibril Abdus-Samad, PharmD Office of Biotechnology Products  Jibril Abdus-samad -S <small>Digitally signed by Jibril Abdus samad -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, o.9.2342.19200300.100.1.1=1300433429, cn=Jibril Abdus samad -S Date: 2015.10.08 21:36:07 -0400</small>
Through:	Gunther Boekhoudt, Ph.D., Quality Reviewer Division of Biotechnology Review and Research IV  Gunther H. Boekhoudt -S <small>Digitally signed by Gunther H. Boekhoudt -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, o.9.2342.19200300.100.1.1=2000605472, cn=Gunther H. Boekhoudt -S Date: 2015.10.09 07:48:46 -0400</small>
Application:	125513/0
Product:	Strensiq™ (asfotase alfa)
Applicant:	Alexion Pharmaceuticals, Inc.
Submission Dates:	December 23 2014; May 7; September 21; October 2 2015

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**Executive Summary:**

The container labels and carton labeling for Strensiq™ (asfotase alfa) were reviewed and found to comply with the following regulations: 21 CFR 610.60 through 21 CFR 610.67; 21 CFR 201.2 through 21 CFR 201.25; 21 CFR 201.50 through 21 CFR 201.57, 21 CFR 201.100 and United States Pharmacopeia (USP), USP 38/NF 33[August 1 2015 to November 30 2015]. Labeling deficiencies were identified and resolved. The container labels submitted on September 21 2015 and carton labeling submitted on October 2 2015 are acceptable.

**Background and Summary Description:**

The Applicant submitted BLA Strensiq™ (asfotase alfa) on March 31 2014 as rolling submission. Table 1 lists the proposed characteristics of Strensiq™ (asfotase alfa).

**Table 1:** Proposed Product Characteristics of Strensiq™ (asfotase alfa).

<b>Proprietary Name:</b>	Strensiq™
<b>Proper Name:</b>	asfotase alfa
<b>Indication:</b>	(b) (4) in patients with perinatal/infantile- and juvenile-onset hypophosphatasia (HPP)
<b>Dose:</b>	2 mg/kg subcutaneously three times per week, or 1 mg/kg six times per week. The maximum volume of subcutaneous injection is 1 mL per injection
<b>Route of Administration:</b>	Subcutaneous
<b>Dosage Form:</b>	Injection
<b>Strength and Container-Closure:</b>	(b) (4) 18 mg/0.45 mL, 28 mg/0.7 mL, and 40 mg/1 mL, or 80 mg/0.8 mL
<b>Storage and Handling:</b>	stored in the original carton until the time of use under refrigerated conditions at 2-8°C (36-46°F) and protected from light. DO NOT FREEZE OR SHAKE.

(b) (4)

**Materials Reviewed:**

Container Label  
Carton Labeling

(b) (4)

**Subpart G-Labeling Standards**  
**Subpart A-General Labeling Provisions**

**I. Container**

A. 21 CFR 610.60 Container Label

(a) Full label. The following items shall appear on the label affixed to each container of a product capable of bearing a full label; *not applicable. The vial container label is a partial label.*

(b) Package label information. If the container is not enclosed in a package, all the items required for a package label shall appear on the container label. *Not applicable.*

(c) Partial label. If the container is capable of bearing only a partial label, the container shall show as a minimum the name (expressed either as the proper or common name), the lot number or other lot identification and the name of the manufacturer; in addition, for multiple dose containers, the recommended individual dose. Containers bearing partial labels shall be placed in a package which bears all the items required for a package label; *does not conform.*

OBP Requests:

Relocate the proper name to appear under the proprietary name. *Applicant revised as requested.*

Delete (b) (4) Consider abbreviating the manufacturer information to "Mfd by: Alexion", or "Alexion Pharm. Inc". *Applicant revised as requested.*

(d) No container label. If the container is incapable of bearing any label, the items required for a container label may be omitted, provided the container is placed in a package which bears all the items required for a package label; *not applicable.*

(e) Visual inspection. When the label has been affixed to the container, a sufficient area of the container shall remain uncovered for its full length or circumference to permit inspection of the contents; *does not conform.*

OBP Request: Indicate how the label is affixed to the vial and where the visual area of inspection is located per 21 CFR 610.60(e). *Applicant's response is acceptable.*

- B. 21 CFR 201.2 Drugs and devices; National Drug Code numbers – The National Drug Code (NDC) number is located at the top of the label. [See 21 CFR 207.35]; *not applicable. The container label is partial/small label and therefore NDC is not required.*
- C. 21 CFR 201.5 Drugs; adequate directions for use; *not applicable. The container label is partial/small label and therefore not required.*
- D. 21 CFR 201.6 Drugs; misleading statements; *conforms.*
- E. 21CFR 201.10 Drugs; statement of ingredients; placement and prominence; *conforms.*
- F. 21 CFR 201.15 Drugs; prominence of required label statements. *conforms. We consider the vial container label a partial label due to its small size per 21 CFR 610.60(c). Therefore we provided recommendations to preserve the required and recommended information on the label and remove less important information to provide more white space and improve readability.*
- G. 21 CFR 201.17 Drugs; location of expiration date; *conforms.*
- H. 21 CFR 201.25 Bar code; *conforms.*
- I. 21 CFR 201.50 Statement of identity; *conforms.*
- J. 21 CFR 201.51 Declaration of net quantity of contents; *conforms.*
- K. 21 CFR 201.55 Statement of dosage; *not applicable. The container label is partial/small label and therefore not required.*
- L. 21 CFR 201.100 Prescription drugs for human use; *conforms. Although this label is a partial label, there is space to add the route of administration.*

OBP Requests:

Delete (b) (4) *Applicant revised as requested.*

Delete the (b) (4) *Applicant revised as requested.*

Delete (b) (4) Consider abbreviating the manufacturer information to "Mfd by: Alexion", or "Alexion Pharm. Inc". *Applicant revised as requested.*

## II. Carton

### A. 21 CFR 610.61 Package Label:

- a) The proper name of the product [see 21 CFR 600.3 (k) and section 351 of the PHS Act]; *conforms*.
- b) The name, addresses, and license number of manufacturer; *does not conform*.

OBP Request: Alexion Pharmaceuticals Inc, appears on the 356h form as the Applicant/Licensee for your proposed product Strensiq (asfotase alfa). Therefore Alexion Pharmaceuticals, Inc. is considered the licensed manufacturer for purposes of fulfilling 21 CFR 600.3(t), 21 CFR 610.60 (a)(2), and 21 CFR 610.61. Therefore, revise the manufacturer information on the labeling from (b) (4) to "Manufactured by". For example:

Manufactured by:  
Alexion Pharmaceuticals, Inc.  
Cheshire, CT 06410 USA  
U.S. License No 1743

*Applicant revised as requested.*

- c) The lot number or other lot identification; *conforms*.
- d) The expiration date; *conforms*.
- e) The preservative used and its concentration, if no preservative is used and the absence of a preservative is a safety factor, the words "no preservative"; *conforms*.
- f) The number of containers, if more than one; *conforms*.
- g) The amount of product in the container expressed as (1) the number of doses, (2) the volume, (3) units of potency, (4) weight, (5) equivalent volume (for dried product to be reconstituted), or (6) such combination of the foregoing as needed for an accurate description of the contents, whichever is applicable; *does not conform*.

OBP Request: Remove the (b) (4) Containers holding a volume of less than 1 mL the strength per fraction of a mL should be the only expression of strength as per USP General Chapters <1> Injections, Labels and Labeling, Strength and Total Volume for Single- and Multiple-Dose Injectable Drug Products. For example the 80 mg vial strength should appear as "80 mg/0.8 mL". *Applicant revised as requested.*

h) The recommended storage temperature; *conforms. However we recommend adding the units of measure.*

OBP Requests: Include "C" and "F" in the temperature ranges to read as "Store in refrigerator at 2°C to 8°C (36°F to 46°F)". *Applicant revised as requested.*

i) The words "Do not Freeze" or the equivalent, as well as other instructions, when indicated by the character of the product; *conforms.*

j) The recommended individual dose if the enclosed container(s) is a multiple-dose container; *conforms.*

k) The route of administration recommended, or reference to such directions in and enclosed circular; *conforms.*

l) Known sensitizing substances, or reference to enclosed circular containing appropriate information; *not applicable.*

m) The type and calculated amount of antibiotics added during manufacture; *not applicable.*

n) The inactive ingredients when a safety factor, or reference to enclosed circular containing appropriate information; *not applicable.*

o) The adjuvant, if present; *not applicable.*

p) The source of the product when a factor in safe administration; *not applicable.*

q) The identity of each microorganism used in manufacture, and, where applicable, the production medium and the method of inactivation, or reference to an enclosed circular containing appropriate information; *not applicable*.

r) Minimum potency of product expressed in terms of official standard of potency or, if potency is a factor and no U.S. standard of potency has been prescribed, the words "No U.S. standard of potency"; *does not conform*.

OBP Request: Add the statement "No U.S. standard of potency." *Applicant revised as requested*.

s) The statement "Rx only" for prescription biologicals. *conforms*.

- Note: If product has a medication guide, a statement is required on the package label if it is not on the container label (see above). It is recommended on both labels.

B. 21 CFR 610.62 Proper name; package label; legible type [Note: Per 21 CFR 601.2(c)(1), certain regulation including 21 CFR 610.62 do not apply to the four categories of "specified" biological products listed in 21 CFR 601.2(a)]. *Strensiq (asfotase alfa) is a therapeutic recombinant DNA-derived product, therefore exempt*.

C. 21 CFR 610.63 Divided manufacturing responsibility to be shown; *not applicable*.

D. 21 CFR 610.64 Name and address of distributor; *not applicable*.

E. 21 CFR 610.67 Bar code label requirements: *conforms*.

Biological products must comply with the bar code requirements at §201.25 of this chapter;

F. 21 CFR 201.2 Drugs and devices; National Drug Code numbers – The National Drug Code (NDC) number is located on top of the label. [See 21 CFR 207.35] *does not conform*.

OBP Request: Add the NDC number to the principal display panel (PDP) in the upper top portion per 21 CFR 201.2 and 21 CFR 207.35. *Applicant revised as requested*.

Applicant's September 22, 2015 emailed response: On Panel 3, the primary display panel (PDP) for all single vial cartons, the NDC number and "Rx only" statement were moved as close to the top as possible. There is a 10 mm by 36 mm box above the NDC and "Rx only" for placement of the tamper evident seals where text cannot be placed. *Applicant's response is acceptable.*

We concur with DMEPA's request to revise the product code (middle 3 digits) to ensure they are not sequential. *Applicant revised as requested.*

G. 21 CFR 201.5 Drugs; adequate directions for use; *does not conform.*

See 21 CFR 201.15 Drugs; prominence of required label statements for discussion of 80 mg/0.8 mL vial warning.

OBP Requests:

Bold the following statements to improve prominence: "For Subcutaneous Use Only" and "Single-Use Only. Discard Unused Portion". *Applicant revised as requested.*

H. 21 CFR 201.6 Drugs; misleading statements; *conforms.*

I. 21 CFR 201.10 Drugs; statement of ingredients; [Placement and Prominence] *conforms.*

J. 21 CFR 201.15 Drugs; prominence of required label statements; *does not conform.*

OBP Requests:

For the 1-count carton, consider making third panel the PDP. It appears as if the top panel is the PDP. Relocate the information on the third panel from the lower half of the PDP to the upper half. *Applicant revised as requested.*

Remove the background coloring from the net quantity statements and relocate these background colors to the strength statements to improve strength differentiation, similar to the container labels. *Applicant revised as requested.*

Relocate "For subcutaneous use only" to appear under the strength statement. *Applicant revised as requested.*

Relocate "Single-Use Only. Discard Unused Portion" to appear under "For Subcutaneous Use Only." *Applicant revised as requested.*

Add "Do not mix or dilute with any solutions" to appear under "Single-Use Only. Discard Unused Portions." *Applicant revised as requested.*

Decrease the prominence of net quantity statements by removing the background colors. *Applicant revised as requested.*

Bold the following statements to improve prominence: "For Subcutaneous Use Only" and "Single-Use Only. Discard Unused Portion". *Applicant revised as requested.*

For the 80 mg/0.8 mL carton, add the statement "For patients 40 kg and greater", bold it, and relocate it under "For Subcutaneous Use Only" to improve prominence. *Applicant revised as requested.*

For the 12-count carton, relocate the net quantity statement to the bottom of the PDP. *Applicant revised as requested.*

- K. 21 CFR 201.17 Drugs; location of expiration date; *conforms.*
- L. 21 CFR 201.25 Bar code label requirements; *conforms.*
- M. 21 CFR 201.50 Statement of identity; *conforms.*
- N. 21 CFR 201.51 Declaration of net quantity of contents; *conforms.*
- O. 21 CFR 201.55 Statement of dosage; *conforms.*
- P. 21 CFR 201.100 Prescription drugs for human use; *conforms.*  
*However, we recommend revising to comply with USP <1051> Labeling of Inactive Ingredients.*

OBP Request: Revise the list of ingredients on the side panel to comply with USP General Chapters <1051> Labeling of Inactive Ingredients. For example: Each (b) (4) vial contains (b) (4) asfotase alfa, dibasic sodium phosphate (x mg), monobasic sodium phosphate, monohydrate (x mg), sodium chloride (x mg), and water for injection. *Applicant revised as requested.*

## **CDER Labeling Recommendations**

This section describes additional container label and carton labeling recommendations provided to the Applicant that address CDER Labeling preferences. The Applicant's response to these recommendations is acceptable.

### **A. General Comments**

1. Confirm there is no text on the ferrule and cap overseal of the vials to comply with USP General Chapters: <7> Labeling, Labels and Labeling for Injectable Products, Ferrules and Cap Overseals.

### **B. Carton Labeling**

1. Revise the finished dosage from (b) (4) to "Injection". "Injection" is the correct finished dosage form for this product per USP General Chapters <1> Injections. (b) (4) is reserved for products that require reconstitution prior to injection such as lyophilized powders.
2. Delete the (b) (4) on the side panel.

## **Review Issues**

This section describes additional labeling issues.

### **80 mg/0.8 mL vial Warning Statement**

Administration of the 80 mg/0.8 mL vial (higher concentration) results in lower absorbed asfotase alfa dose when compared to the other strength vials (lower concentration). For this reason, the Clinical and Clinical Pharmacology Teams concluded the 80 mg/0.8 mL vial should not be used in patients with perinatal/infantile-onset HPP. This warning was added to the prescribing information (PI) in section 2 – DOSAGE AND ADMINISTRATION.

We find this warning should be placed on the carton labeling so that healthcare practitioners (HCP) that dispense, prepare, and administer (e.g. pharmacists and nurses) Strensiq are aware and can easily determine the appropriateness of the selected vial strength. However as currently proposed (b) (4) only prescribers would be able to easily determine the diagnosis of the patient. Furthermore, it will be challenging for pharmacists and nurses to determine if a patient was diagnosed with perinatal/infantile HPP vs. juvenile-onset HPP. Subsequent to our request to improve the warning statement to allow for HCPs to easily determine the appropriateness of the selected vial strength, the Clinical Team recommended revising the warning to limit the 80 mg/0.8 mL vial to patients 40 kg and greater.

Therefore, the Team agreed to revise the PI to include the revised warning in section 2 – DOSAGE AND ADMINISTRATION and section 16 – HOW SUPPLIED/STORAGE AND HANDLING. Additionally, we recommended this adding this statement to the PDP of the carton labeling. DMEPA concurs with this labeling statement and placement. The Applicant agreed to the labeling revisions.

### **Conclusions**

The container labels and carton labeling for Strensiq™ (asfotase alfa) were reviewed and found to comply with the following regulations: 21 CFR 610.60 through 21 CFR 610.67; 21 CFR 201.2 through 21 CFR 201.25; 21 CFR 201.50 through 21 CFR 201.57, 21 CFR 201.100 and United States Pharmacopeia (USP), USP 38/NF 33 [August 1 2015 to November 30 2015]. Labeling deficiencies were identified and resolved. The container labels submitted on September 21 2015 and carton labeling submitted on October 2 2015 are acceptable (see below).

Container Labels

(b) (4)



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**Department of Health and Human Services  
Public Health Service  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Surveillance and Epidemiology (OSE)  
Office of Pharmacovigilance and Epidemiology (OPE)**

**Epidemiology: Review of Study Protocol**

Date: 10/02/2015

Reviewer(s): Joel L. Weissfeld, MD MPH  
Division of Epidemiology I

Team Leader: Sukhminder K. Sandhu, PhD MPH MS  
Division of Epidemiology I

Director: Cunlin Wang, MD, PhD  
Division of Epidemiology I

Drug Name(s): asfotase alfa (Strensiq)

Subject: A Review of a Draft Protocol, ALX-HPP-501,  
(Amendment 2, 03 September 2015), An Observational,  
Longitudinal, Prospective, Long-Term Registry of Patients  
With Hypophosphatasia (HPP)

Application Type/Number: BLA 125513

Applicant/sponsor: Alexion Pharmaceuticals, Inc.

OSE RCM #: 2015-1909

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JOEL L WEISSFELD  
10/02/2015

SUKHMINDER K SANDHU  
10/02/2015

CUNLIN WANG  
10/02/2015

**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: September 11, 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: Shawna Hutchins, MPH, BSN, RN  
Senior Patient Labeling Reviewer  
**Division of Medical Policy Programs (DMPP)**  
Adewale Adeleye, Pharm.D., MBA  
Regulatory Review Officer  
**Office of Prescription Drug Promotion (OPDP)**

Subject: Review of Patient Labeling: Patient Package Insert (PPI) and  
Instructions for Use (IFU)

Drug Name (established name): STRENSIQ (asfotase alfa)

Dosage Form and Route: Injection, for subcutaneous use

Application Type/Number: BLA 125513

Applicant: Alexion Pharmaceuticals Inc.

## 1 INTRODUCTION

On December 23, 2014, Alexion Pharmaceuticals Inc., submitted for the Agency's review a new Biologics License Application (BLA-125513) for STRENSIQ (asfotase alfa) injection, for subcutaneous use, indicated for the treatment of patients with perinatal/infantile and juvenile-onset hypophosphatasia (HPP).

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Gastroenterology and Inborn Errors Products (DGIEP) on February 09, 2015, and February 10, 2015, respectively, for DMPP and OPDP to review the Applicant's proposed Patient Package Insert (PPI) and Instructions for Use (IFU) for STRENSIQ (asfotase alfa) injection, for subcutaneous use.

## 2 MATERIAL REVIEWED

- Draft STRENSIQ (asfotase alfa) PPI and IFU received on December 23, 2014, revised by the Review Division throughout the review cycle, and received by DMPP on September 09, 2015.
- Draft STRENSIQ (asfotase alfa) PPI and IFU received on December 23, 2014, revised by the Review Division throughout the review cycle, and received by OPDP on September 09, 2015.
- Draft STRENSIQ (asfotase alfa) Prescribing Information (PI) received on December 23, 2014, revised by the Review Division throughout the review cycle, and received by DMPP on September 09, 2015.
- Draft STRENSIQ (asfotase alfa) Prescribing Information (PI) received on December 23, 2014, revised by the Review Division throughout the review cycle, and received by OPDP on July 28, 2015.

## 3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6<sup>th</sup> to 8<sup>th</sup> grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8<sup>th</sup> grade reading level. In our review of the PPI and IFU the target reading level is at or below an 8<sup>th</sup> grade 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 reformatted the PPI document using the Arial font, size 10 and the IFU document using the Arial font, size 11.

In our review of the PPI and IFU we:

- simplified wording and clarified concepts where possible

- ensured that the PPI and IFU are consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the PPI and IFU are free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the PPI and IFU meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

#### **4 CONCLUSIONS**

The PPI 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 PPI and IFU are 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 PPI and IFU.

Please let us know if you have any questions.

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SHAWNA L HUTCHINS  
09/11/2015

ADEWALE A ADELEYE  
09/11/2015

MARCIA B WILLIAMS  
09/11/2015



**DEPARTMENT OF HEALTH & HUMAN SERVICES**    Public Health Service

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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 Review**

**Date:** August 6, 2015

**From:** Carrie Ceresa, Pharm D, MPH  
Clinical Analyst, Maternal Health Team  
Pediatric and Maternal Health Staff

**Through:** Tamara Johnson, M.D., M.S.  
Acting Team Leader, Maternal Health Team  
Division of Pediatric and Maternal Health

Lynne P. Yao, M.D., Acting Division Director,  
Division of Pediatric and Maternal Health

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

**Drug:** STRENSIQ (asfotase alfa)

**BLA:** 125513

**Subject:** Maternal Health Labeling Recommendations

**Applicant:** Alexion Pharmaceuticals, Inc.

**Materials Reviewed:**

- Alexion submission dated 12/23/2014

**Consult Question:** DGIEP requests assistance with review of maternal health labeling subsections 8.1 and 8.2.

## INTRODUCTION

On December 23, 2014, Alexion Pharmaceuticals, Inc., submitted BLA 125513 for STRENSIQ (asfotase alfa) for the treatment of (b) (4) patients with infantile- and juvenile-onset hypophosphatasia (HPP).

Asfotase alfa was granted Orphan Drug Designation on September 12, 2008, for the treatment of hypophosphatasia. HPP is a rare genetic disorder that affects the development of bones and teeth. The disease is classified by patient age at first onset of symptoms (perinatal, infantile, childhood, adult HPP).<sup>1</sup> Most severe forms of HPP affect approximately 1 in 100,000 newborns.<sup>2</sup> Less severe cases usually appear in childhood or adulthood. HPP symptoms include a weakening and softening of bones, rickets, short limbs, abnormal shaped chest, soft skull, poor feeding in infants and failure to gain weight, respiratory problems, and hypercalcemia.<sup>2</sup> Treatment to date, has primarily been symptomatic management.

DGIEP consulted DPMH to review and update the subsections related to Pregnancy and Lactation (8.1-8.2).

## BACKGROUND

### Product Background

Asfotase alfa is a recombinant fusion protein of tissue-nonspecific alkaline phosphatase-Fc-deca-aspartate (TNSALP). Asfotase acts as an enzyme replacement therapy by targeting the bone by addressing the deficiency of TNSALP activity which causes HPP. Asfotase alfa is a subcutaneous injection given 6 times per week and is dosed by body weight.

### Pregnancy and Lactation Labeling Rule (PLLR)

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*,”<sup>3</sup> 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) will be removed from all prescription drug and biological product labeling and a new format will be required for all products that are subject to the 2006 Physicians Labeling Rule<sup>4</sup> format to include information about the risks and benefits of using these products during pregnancy and lactation. The recommendations in this review are consistent with the PLLR format.

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<sup>1</sup> Millan, J., Plotkin, H. (2012). Hypophosphatasia – pathophysiology and treatment. *Actual osteol*, 8(3), 164-182.

<sup>2</sup> Hypophosphatasia. Genetics Home Reference. U.S. National Library of Medicine. web accessed 7 July 2015. <http://ghr.nlm.nih.gov/condition/hypophosphatasia>.

<sup>3</sup> *Content and Format of Labeling for Human Prescription Drug and Biological Products, Requirements for Pregnancy and Lactation Labeling* (79 FR 72063, December 4, 2014).

<sup>4</sup> *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).

## **DISCUSSION**

### **Review of Data & Labeling recommendations**

#### **Pregnancy**

A search of published literature was performed on the use of asfotase alfa during pregnancy and no information was found; therefore, there is no safety information in humans to inform the drug associated risk with use during pregnancy

In animal reproduction studies, asfotase alfa administered intravenously to pregnant rats and rabbits during the period of organogenesis showed no evidence of fetotoxicity, embryoletality or teratogenicity at doses causing plasma exposures up to 1539 and 3310 times, respectively, the exposure at the recommended human dose.

#### **Lactation**

The Drugs and Lactation Database (LactMed)<sup>5</sup> was searched for available lactation data with the use of asfotase alfa, and no information was located. 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 any available information on maternal levels in breast milk, infant blood levels, any potential effects in the breastfed infants, if known, as well as alternative drugs that can be considered. The database also includes the American Academy of Pediatrics category indicating the level of compatibility of the drug with breastfeeding.

There is no animal data with respect to lactation.

Therefore, because there is no current safety information to recommend against breastfeeding, the following regulatory statement has been added to subsection 8.2 Lactation as required by the PLLR:

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

(b) (4)

## **CONCLUSION**

The Pregnancy and Lactation subsections of labeling were structured to be consistent with the PLLR. DPMH refers to the NDA action for final labeling. The applicant's draft labeling recommendation can be found in Appendix A.

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<sup>5</sup> United States National Library of Medicine. TOXNET Toxicology Data Network. *Drugs and Lactation Database (LactMed)*. <http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?LACT>

## DPMH LABELING RECOMMENDATIONS

### 8 USE IN SPECIFIC POPULATIONS

#### 8.1 Pregnancy

##### Risk Summary

There are no available human data on STRENSIQ use in pregnant women to inform a drug associated risk. In animal reproduction studies, asfotase alfa administered intravenously to pregnant rats and rabbits during the period of organogenesis showed no evidence of fetotoxicity, embryoletality or teratogenicity at doses causing plasma exposures up to 1539 and 3310 times, respectively, the exposure at the recommended human dose [see Data].

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*

Asfotase alfa administered during the period of organogenesis to rats (from gestation Day 6 to Day (b) (4) post-partum) and rabbits (on gestation days 7 to 19) at intravenous doses up to 50 mg/kg/day, (approximately (b) (4) and (b) (4) times the human AUC of (b) (4) ng.h/mL at 2 mg/kg dose administered three times weekly, respectively) did not cause any adverse effects on embryofetal development. A pre- and postnatal development study in rats showed no evidence of adverse effects on pre- and postnatal development at intravenous doses (from Day 6 of gestation to Day (b) (4) postpartum) of asfotase alfa up to 50 mg/kg/day (approximately (b) (4) times the human AUC of (b) (4) ng.h/mL at 2 mg/kg dose administered three times weekly).

#### 8.2 Lactation

##### Risk Summary

There are no data on the presence of asfotase alfa in human milk, the effects on the breastfed infant, or the effects on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for asfotase alfa and any potential adverse effects on the breastfed infant from asfotase alfa or from the underlying maternal condition.

## APPENDIX A - Applicant's Labeling Recommendations

### 8 USE IN SPECIFIC POPULATIONS

#### 8.1 Pregnancy

##### Risk Summary

(b) (4)

##### Data

(b) (4)

##### *Animal Data*

(b) (4)

#### 8.2 Lactation

##### Risk Summary

(b) (4)

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

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CARRIE M CERESA  
08/06/2015

TAMARA N JOHNSON  
08/06/2015

LYNNE P YAO  
08/06/2015

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### **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\*\*\***

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**Date of This Review:** August 3, 2015

**Requesting Office or Division:** Division of Gastroenterology & Inborn Error Products (DGIEP)

**Application Type and Number:** BLA 125513

**Product Name and Strength:** Strensiq (asfotase alfa) Injection (b) (4), 18 mg/0.45 mL, 28 mg/0.7 mL, 40 mg/mL, and 80 mg/0.8 mL

**Product Type:** Single Ingredient

**Rx or OTC:** Rx

**Applicant/Sponsor Name:** Alexion Pharmaceuticals

**Submission Dates:** December 23, 2014, March 13, 2015, and May 7, 2015

**OSE RCM #:** 2015-22

**DMEPA Primary Reviewer:** Matthew Barlow, RN, BSN

**DMEPA Team Leader:** Kendra Worthy, PharmD

---

## 1 REASON FOR REVIEW

This review is in response to DGIEP's request to review the labels and labeling for any areas that may lead to medication errors. Alexion Pharmaceuticals initially submitted the proposed carton/container labels and the prescribing information on December 23, 2014. Additionally, the applicant submitted revised prescribing information and container labels on March 13, 2015 and May 7, 2015.

## 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.

<b>Material Reviewed</b>	<b>Appendix Section (for Methods and Results)</b>
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
Human Factors Study	C-N/A
ISMP Newsletters	D-N/A
FDA Adverse Event Reporting System (FAERS)*	E-N/A
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 post market safety surveillance

## 3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

This product is a NME, and the applicant submitted the label and labeling for this product on December 23, 2014. The applicant submitted revised prescribing information and container labels on March 13, 2015 and May 7, 2015, respectively. We performed a risk assessment of the carton/container labels along with the prescribing information (PI) for any areas that may lead to medication errors. We have found certain aspects of the label, labeling, and prescribing information that could be revised to increase clarity and organization of these labels, thus promoting safe use of this product. We provide recommendations to the Division and Alexion Pharmaceuticals in sections 4.1 and 4.2.

## 4 CONCLUSION & RECOMMENDATIONS

We recommend changes to the submitted labels, labeling, and packaging to improve clarity and understanding for safe use of this product.

#### 4.1 RECOMMENDATIONS FOR THE DIVISION

This includes the recommended revisions within the PI, presented to the division.

### 2.2 Preparation

STRENSIQ is for subcutaneous injection only.

The maximum volume of subcutaneous injection is 1 mL per injection.

1. Determine the volume needed for the prescribed dosage based on the patient's weight and recommended dosage of 2 mg/kg administered three times a week. Alternatively, the dosage may be 1 mg/kg administered six times a week to avoid multiple injections administered on the same day.
2. Inspect the solution in the vial(s) for particular matter and discoloration. The solution should be clear to slightly opalescent. Discard any vials(s) if particular matter or discoloration is observed.
3. Assemble injection supplies. Administer STRENSIQ using sterile disposable syringes and injection needles. (b) (4)  
 Always use a new syringe and needle.
4. Remove vial cap, aseptically prepare the vial and insert the syringe into the vial to withdraw the prescribed dose for administration.
5. Remove any air bubbles in the syringe and verify the correct dose.

### 2.3 Administration

1. Administer STRENSIQ within 1 hour upon removal from refrigeration.
2. Determine the injection site from the following: abdominal area (or I could say "quadrants"), thigh, or deltoid and clean the chosen site.
  - a) Rotate injection sites from one injection to the next to reduce the risk of lipodystrophy [See Adverse Reactions (6.1)].
3. Inject STRENSIQ, subcutaneously, into the determined site and properly dispose of the needle.
  - a) Do NOT administer injections in areas that are reddened, inflamed, or swollen.

#### 4.2 RECOMMENDATIONS FOR ALEXION PHARMACEUTICALS

##### 1. Carton Labels:

- a. We recommend revising the statement  (b) (4) to "Injection" as this product does not require any reconstitution.
- b. We recommend shifting the strength up so it would be directly below "Injection." Additionally, we recommend placing the statement "For subcutaneous use only" where the strength used to be, followed by the

statement “Do not mix or dilute with any solutions.” These revisions allow for the emphasis of proper preparation and administration of this product.

- c. We recommend placing the statement “Must be refrigerated” on the Principal Display Panel (PDP), possibly where the statement “For subcutaneous use only” was originally.
- d. We emphasize the need for the cartons containing multiple vials to have a different NDC number than the cartons containing a single vial.
- e. We recommend highlighting the strengths on all the carton labels instead of the text below the strength to provide further emphasis of this information.

**2. Container Labels:**

- a. We recommend adding the statement(s) “Single Use Vial” and “For subcutaneous use only” to the container labels to provide emphasis on the proper administration of this product.

## APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

### APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Strensiq that Alexion Pharmaceuticals submitted on December 23, 2014 [also March 13, 2015 and May 7, 2015].

Table 2. Relevant Product Information for Strensiq	
Initial Approval Date	N/A
Active Ingredient	Asfotase Alfa
Indication	Indicated for the (b) (4) treatment of patients with infantile- and juvenile-onset hypophosphatasia (HPP).
Route of Administration	Subcutaneous Injection
Dosage Form	Injectable
Strength	(b) (4) 18 mg/0.45 mL, 28 mg/0.7 mL, 40 mg/mL, and 80 mg/0.8 mL.
Dose and Frequency	Based on the patient's weight and recommended dosage of 2 mg/kg administered three times a week or 1 mg/kg administered six times a week.
How Supplied	Supplied as a sterile, non-pyrogenic, preservative free solution in a single-use vial as a clear, colorless to slightly yellow aqueous solution at a concentration of either 40 mg/mL or 100 mg/mL in a carton of one (1) or twelve (12) vials at the above mentioned strengths.
Storage	Vials must be stored in the original carton until the time of use under refrigerated conditions at 2°C -to 8°C (36°F- to 46°F) and protected from light.
Container Closure	See "How Supplied."

## **APPENDIX B. PREVIOUS DMEPA REVIEWS**

### **B.1 Methods**

On February 15, 2015, we searched the L:drive and AIMS using the terms, Strensiq to identify reviews previously performed by DMEPA.

### **B.2 Results**

Our search identified no previous label and labeling reviews, only one proprietary name review.

**APPENDIX C. HUMAN FACTORS STUDY**

**C.1 Study Design**

N/A

**C.2 Results**

N/A

**APPENDIX D. ISMP NEWSLETTERS**

**D.1 Methods**

N/A

**D.2 Results**

N/A

**APPENDIX E. FDA ADVERSE EVENT REPORTING SYSTEM (FAERS)**

**E.1 Methods**

N/A

**E.2 Results**

N/A

**E.3 List of FAERS Case Numbers**

N/A

**APPENDIX F.**

**F.1 Methods**

N/A

**F.2 Results**

N/A

## **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,<sup>1</sup> along with post market medication error data, we reviewed the following Strensiq labels and labeling submitted by Alexion Pharmaceuticals on December 23, 2014, March 13, 2015, and May 7, 2015.

- Container label
- Carton labeling
- Prescribing Information
- Instructions for Use
- Medication Guide

### **G.2 Label and Labeling Images**

#### **A. Multi-Vial Carton Labels**



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<sup>1</sup> Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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/s/  
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MATTHEW J BARLOW  
08/03/2015

KENDRA C WORTHY  
08/03/2015

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

**\*\*\*\*Pre-decisional Agency Information\*\*\*\***

## Memorandum

**Date:** August 3, 2015

**To:** Lisa Pitt, Pharm.D., MSJ, Senior Regulatory Project Manager  
Division of Gastroenterology and Inborn Errors Products (DGIEP)

**From:** Adewale Adeleye, Pharm.D., MBA, Regulatory Review Officer,  
Office of Prescription Drug Promotion (OPDP)

**Subject:** BLA # 125513 - STRENSIQ (asfotase alfa) injection, for  
subcutaneous use

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Reference is made to DGIEP's consult request dated February 10, 2015, requesting review of the proposed Package Insert (PI), Patient Package Insert (PPI), and Carton/Container Labeling for STRENSIQ (asfotase alfa) injection, for subcutaneous use (Strensiq).

OPDP has reviewed the proposed PI entitled, "SN 0015\_strensiq-pi-mg-final-13 Mar 2015-plr-format\_in TC.docx" that was available in SharePoint on July 28, 2015. OPDP's comments on the proposed PI are provided directly on the attached copy of the labeling (see below).

OPDP has also reviewed the proposed Carton/Container labeling entitled:

- (b) (4)
- "Vial label 18mg\_0.45 mL (18 mg\_mL) - ALXN2015038.pdf"
  - "Vial Label 28mg\_0.7mL (28 mg\_mL) - ALXN2015036.pdf"
  - "Vial Label 40mg\_1mL (40 mg\_mL) - ALXN2015039.pdf"
  - "Vial Label 80mg\_0.8mL (80 mg\_mL) - ALXN2015040.pdf"

that was sent from DGIEP to OPDP on July 30, 2015. OPDP has no comments at this time on the proposed Carton/Container labeling.

Please note that comments on the proposed PPI will be provided under separate cover as a collaborative review between OPDP and the Division of Medical Policy Programs (DMPP).

Thank you for your consult. If you have any questions please contact me at (240) 402-5039 or [adewale.adeleye@fda.hhs.gov](mailto:adewale.adeleye@fda.hhs.gov)

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ADEWALE A ADELEYE  
08/03/2015

MEMORANDUM

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

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**CLINICAL INSPECTION SUMMARY**

DATE: July 30, 2015

TO: Lisa Pitt, Regulatory Project Manager  
Carla Epps, M.D., Medical Officer  
Division of Gastroenterology and Inborn Errors Products

FROM: Susan Leibenhaut, M.D.  
Medical Officer  
Good Clinical Practice Assessment Branch  
Division of Clinical Compliance Evaluation  
Office of Scientific Investigations

THROUGH: Susan D. Thompson, M.D.  
Team Leader  
Good Clinical Practice Assessment Branch  
Division of Clinical Compliance Evaluation  
Office of Scientific Investigations

THROUGH: Kassa Ayalew, M.D., M.P.H  
Branch Chief  
Good Clinical Practice Assessment Branch  
Division of Clinical Compliance Evaluation  
Office of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections

BLA 125513  
APPLICANT: Alexion Pharmaceuticals  
BIOLOGIC: asfotase alfa  
NME: Yes  
THERAPEUTIC CLASSIFICATION: Priority

INDICATION: (b) (4) patients with infantile- and  
juvenile-onset hypophosphatasia

CONSULTATION REQUEST DATE: December 1, 2015  
INSPECTION SUMMARY GOAL DATE: July 31, 2015  
DIVISION ACTION GOAL DATE: October 23, 2015  
PDUFA DATE: November 23, 2015

## I. BACKGROUND:

Alexion Pharmaceuticals submitted this BLA for asfotase alfa for the indication of (b) (4) in patients with infantile- and juvenile-onset hypophosphatasia (HPP). Hypophosphatasia (HPP) is a rare, serious, and potentially fatal, genetic disorder caused by loss-of-function mutations(s) in the gene encoding Tissue Non-Specific Alkaline Phosphatase (TNSALP). Asfotase alfa is a bone-targeted enzyme replacement therapy designed to address the underlying cause of HPP, a deficiency of TNSALP activity, by replacing the defective enzyme and preventing or reversing the mineralization defects of the skeleton, thereby preventing morbidities, risk of ventilator dependence, and premature death.

The review division requested inspection of two interventional protocols and three observational (natural history) studies that are planned to be the basis for the approval of the product. Sites were chosen for inspection based on participation in more than one study and high enrollment. A sponsor inspection was conducted as per OSI procedures because the product is a new molecular entity. For Study ENB-006-09, verification of bone biopsy readings conducted centrally in an unblinded manner by (b) (6) were able to be verified at the sites by comparing the reports located at the sites with the line listings of results submitted by the sponsor to the BLA.

### Studies of asfotase alfa (investigational product administered)

1. Protocol ENB-006-09 entitled “A Randomized, Open-Label, Multicenter, Multinational, Dose-Ranging, Historical Control Study of the Safety, Efficacy, Pharmacokinetics, and Pharmacodynamics of ENB-0040 (Human Recombinant Tissue-Nonspecific Alkaline Phosphatase Fusion Protein) in Children with Hypophosphatasia (HPP) and Protocol ENB-008-10 entitled “Extension Study of Protocol ENB-006-09 Evaluating the Long-Term Safety and Efficacy of ENB-0040 (Human Recombinant Tissue-Nonspecific Alkaline Phosphatase Fusion Protein) in Children with Hypophosphatasia (HPP)”

This study was a 24-week, randomized, international, multicenter, dose-ranging, open-label study to assess the safety, efficacy, PK, and PD of asfotase alfa in patients 5 to 12 years of age with infantile- or juvenile-onset HPP conducted from September 2009 to April 2010 by the original sponsor Enobia. A total of 13 subjects were randomized at 2 sites. Protocol ENB-008-10 is an ongoing, open-label extension study of asfotase alfa in 12 patients who previously received treatment under clinical study ENB-006-09 and completed the study. The extension study began in July 2010 with a data analysis cutoff of January 22, 2013.

2. Protocol ENB-002-08 entitled “Compassionate Use Protocol to Provide Access to ENB-0040 (human recombinant tissue nonspecific alkaline phosphatase fusion protein) in up to 6 Severely Affected Infants with Hypophosphatasia (HPP)” and ENB-003-08 extension study

This study was a six-month, multicenter, open-label study to assess the safety and efficacy of ENB-0040 in infants with severe HPP and a grave prognosis. The study was conducted from October 2008 to May 2010 with an extension study conducted from April 2009 to November 2012. A total of 11 subjects were enrolled at 9 sites (highest enrolling site had 2 subjects).

Natural history studies (no investigational product administered)

3. Protocol ENB-011-10 entitled “A Retrospective, Non-Interventional Epidemiologic Study of the Natural History of Patients with Severe Perinatal and Infantile Hypophosphatasia (HPP)”

This study was a multicenter, multinational, retrospective chart review study of the natural history of patients with perinatal/infantile onset HPP where signs of the disease are present before 6 months of age. A total of 48 subject records were reviewed at 12 sites in 7 countries, and the data was abstracted between September 2012 and April 2013.

4. Protocol ALX-HPP-502 entitled “A Retrospective, Non-interventional, Epidemiologic Study of the Natural History of Patients with Juvenile-onset Hypophosphatasia (HPP)”

This study was a multicenter, multinational, retrospective chart review study of the natural history of patients with Juvenile-onset HPP. A total of 32 subject records were abstracted at 9 sites from June 2014 to September 2014.

5. Protocol ALX-HPP-502s entitled “A Single-Center, Noninterventional Substudy of ALX-HPP-502 to Assess Functional Natural History Data of Patients With Juvenile-Onset HPP who Served as Historical Controls in ENB-006-09”

This study was conducted only at the Whyte site where videotapes of subjects whose data had been extracted in Protocol ALX-HPP-502 were available for analysis and submission to the BLA. Data were abstracted from six subject records at this clinical site from June 2014 to September 2014.

## II. RESULTS (by Site):

Type of Inspected Entity, Name and Address	Protocol #, Site #, and # of Subjects	Inspection Date	Final Classification*
CI: Michael P. Whyte, M.D. Shriner's Hospitals for Children-St. Louis St. Louis, MO 63131-3597	ENB-006-09/ ENB-008-10 (extension study)/Site 1/ 9 subjects  ENB-011-10 (Natural history study)/ Site 7/ 12 subjects  ALX-HPP-502/ (Natural history study)/ Site 257/ 22 subjects  ALX-HPP-502s (Natural history study)/ 6 subjects	March 2 to 11, 2015	VAI
CI: Cheryl Rockman-Greenberg, M.D. University of Manitoba Health Sciences Centre 849 Sherbrook Street, Winnipeg Manitoba, CANADA R3A 1S1	ENB-006-09/ ENB-008-10 (extension study)/site 2/ 4 subjects  ENB-002-08 ENB-008-10 (extension study)/site 1/ 1 subject	April 20 to 24, 2015	NAI
Sponsor : Alexion Pharmaceuticals 352 Knotter Dr. Cheshire, CT 06410	All protocols noted above	June 6 to June 17, 2015	Pending NAI

### Key to Classifications

NAI = No deviation from regulations.

VAI = Deviation(s) from regulations.

OAI = Significant deviations from regulations.

Pending = Complete review of EIR is pending.

### 1. Michael P. Whyte, MD

**Shriner's Hospitals for Children-St. Louis, St. Louis, MO 63131-3597**

- a. **What was inspected:** At this site, for Protocol ENB-006-09 and the extension study Protocol ENB-008-10, there were nine subjects who were screened, enrolled, and completed the study. All nine subjects' records were reviewed. These were the only studies at this site in which test article was administered

and the Form FDA 483 observations below apply to these studies.

Protocol ENB-011-10, Protocol ALX-HPP-502, and Protocol ALX-HPP-502s were observational studies and no test article was administered. These studies each had an associated informed consent document and IRB review. There was a prospectively written protocol for data extraction from the records and evaluation of videotapes. For Protocol ENB-011-10 there were 14 subjects screened and 12 subjects were enrolled. Records of all screened subjects were reviewed. For Protocol ALX-HPP-502, there were 27 subject records screened, 22 subject records met the review criteria, and data was captured for all time points. Records for all 27 subjects were reviewed. For Protocol ALX-HPP-502s, there were six subject records screened and these met the review criteria.

The inspection included review of informed consent documents (ICDs), source documents, institutional review board (IRB) correspondence and approvals, sponsor correspondence, investigator agreements (1572s), financial disclosure, adverse event reports, and case report forms (CRFs).

- b. **General Observations/Commentary:** There was no evidence of under-reporting of adverse events. The bone biopsy results were able to be compared with the reports from the central reader and there were no discrepancies. There was one discrepancy between the data submitted in the NDA and the source data. This was a discrepancy between the line listing and the source document for the Week 120 six minute walk test (6MWT) for Subject 01-07 in Protocol ENB-008-10. This value was noted to be incorrectly calculated on the source worksheet as 920 (13 hash marks X 40m=520), but was correctly entered as 520 in the CRF, and incorrectly reported on the line listings as 920.

*Reviewer note: This is discussed further in the sponsor inspection below.*

A two item FDA-483 was issued at the conclusion of this inspection citing the following deficiencies:

1. Failure to properly dispose of unused investigational drugs. Specifically, when subjects returned unused temperature sensitive study drug, the site returned it back into the general drug inventory and re-dispensed it to study subjects.

*Reviewer note: The dispensing of vials was of concern to the FDA investigator because of the requirement for refrigeration of the drug and the potential for dispensing unstable product to subjects. However, after discussions with the product reviewers for this BLA, it was determined that the drug was stable under the conditions of storage and handling at the site so that refrigeration would have been ideal, but not required for product stability.*

2. CI did not ensure study personnel were delegated to perform study related activities. The pharmacist who is employed by Shriners Hospital was not on the delegation log. There was no delegation to a physical therapist of certain duties required in the protocol to be conducted by a physical therapist.

*Reviewer note: This observation is not a protocol violation. The protocol required a licensed physical therapist, and this individual was supplied by the sponsor. In addition,*

*the study was conducted in an unblinded fashion, so whether employed by the sponsor or the clinical site, bias could be introduced. The review division was made aware of this finding. The finding is discussed further in Item #3, sponsor inspection.*

Inspection of the observational studies noted that the protocols were followed and that there were no discrepancies between source data and the data submitted to the NDA by the sponsor and provided to the FDA field investigator.

The clinical investigator acknowledged the observations and responded to the inspection findings in written communication on March 24, 2015.

- c. **Assessment of data integrity:** The observations noted on the Form FDA 483 are not considered serious violations. The discrepancy noted above is discussed further in Item #3 of the Alexion Inspection. The studies appear to have been conducted adequately, and the data generated by this site may be used in support of the respective indication.

**2. Cheryl Rockman-Greenberg, MD**  
**University of Manitoba Health Sciences Centre, Winnipeg Manitoba, Canada**

- a. **What was inspected:** At this site, for Protocol ENB-006-09 and the extension study Protocol ENB-008-10, there were four subjects who were screened and enrolled. A total of three subjects completed the study. All four subjects' records were reviewed. At this site, for Protocol ENB-002-08 and the extension study Protocol ENB-003-08, there was one subject who was screened and enrolled who later transferred to a site in Ireland. This subject record was reviewed. The review included protocol adherence and data verification for endpoints including six minute walk test and bone biopsy as well as drug accountability.
- b. **General observations/commentary:** There was no evidence of under-reporting of adverse events. There were no discrepancies between the data submitted in the NDA and the source data for either the six minute walk test or the measured values for the bone biopsy. Data discrepancies were noted in the following listings:
1. Although the line listings contained a column for the lot number of the drug taken associated with a specific day, this information was not available at the clinical site. Families were provided with product for the intervals between visits and completed diaries recording test article administration. The diaries had no listing for specific lot number administered, and because product from two different lots may have been dispensed to the family, it was not documented which lot was administered on a specific day. The line listing in the BLA contains lot numbers for specific days as though it was known which lot had been

administered.

*Reviewer note: Because this was considered a sponsor responsibility, the CI was not cited for this item. It is discussed further in the sponsor inspection Item #3. The issues concerning the lot numbers were reported to the review team on June 24, 2015 and are discussed further in the sponsor inspection below.*

2. Although the bone biopsy values for the individual subjects were consistent with the data reported to the BLA, the derived data in the column “% of healthy subjects” could not be verified at the site. This derived value was not on the source document. In attempting to calculate the value the FDA investigator noted the following:
  - i. Some of the derived values were similar but not the same as what was listed. For example, for Subject 02-03, the trabecular number 1.9 divided by 1.7 was calculated to be 111.8, but the line listing states 114.5. This may be a mathematical error or may be due to the fact that the values for controls consist of a range, so the divisor is actually  $1.7 \pm 0.2$ , and the calculated value may be in the range from 100.0 to 126.7.
  - ii. For patient 02-04, the control values that were used to calculate the “% normal” were not listed on the source document.

*Reviewer comment: The issues concerning the lack of ability to verify the % of normal was conveyed to the medical reviewer on July 20, 2015. Because the actual values for the readings of the bone biopsies could be verified at both sites, this is not considered a significant issue of compliance. The determination of whether appropriate control values were used for the calculations is deferred to the review team.*

- c. **Assessment of data integrity:** The data generated for the studies conducted at this site are considered reliable. The determinations of the significance of the issues noted above are deferred to the review team.

### **3. Alexion Pharmaceuticals, Inc. 352 Knotter Dr. Cheshire, CT 06410**

**Note:** Observations below for this sponsor inspection are based on preliminary review of the Establishment Inspection Report (EIR). An inspection summary addendum will be issued if conclusions change upon final review of the EIR.

- a. **What was inspected:** The inspection covered sponsor responsibilities for two prospective studies and the extensions, ENB-002-08 and extension 003-08 and ENB 006-09 and extension 008-10 and well as the three retrospective non-interventional studies ENB 011-10 and ALX-HPP-502, and 502s. Conduct of the studies at two clinical sites, in Manitoba, Canada and St. Louis, Missouri were covered as well as the contracts and arrangements for the bone biopsy readings for ENB 006-09.

- b. **General Observations/Commentary:** Sponsorship of IND 100619 was transferred from Enobia to Alexion on July 25, 2012. No significant regulatory violations were noted, and no Form FDA 483 was issued. The following items were noted during inspection and conveyed to the review division:
1. The data discrepancy noted at the Whyte site concerning the 6MWT in Subject 01-07 in Study ENB-008-10 was further investigated during the sponsor inspection. When Alexion acquired the product from Enobia in 2012, Alexion conducted more frequent and targeted monitoring regarding issues noted from audits for studies ENB-006-09 and 008-10. During inspection, the sponsor could not provide data concerning which values had been changed during remonitoring. This issue was raised during the mid-cycle meeting with an information request. The sponsor replied adequately in a submission to FDA dated July 24, 2015 providing details concerning the review of 6MWT worksheets, noting that the value for this subject was the only value that had been changed during the remonitoring.

*Reviewer comment: From a compliance standpoint, the sponsor responded adequately to this request.*

2. It was determined that the lot numbers per dose data in the CSR for studies ENB 006 and 008 are not accurate. During the sponsor inspection, the sponsor stated that they assigned the lots to each dose retrospectively using their best guess, because the lot numbers were not being captured contemporaneously when the subjects were dosed at home. Because parents were usually provided with product from two different lots for administration to subjects in the intervals between clinic visits and the subject diaries did not record lot number administered, it was not documented which of the lots was administered on a certain day. This was noted originally during the inspection of Dr. Rockman-Greenberg. The sponsor indicated during the inspection that they would respond in writing with a submission to the BLA, but, at the time of this review, there has not been a response. The significance of this issue is deferred to the review team.

*Reviewer comment: The sponsor has not responded at the time of this review. During the inspection, they indicated that these studies were not designed to accurately capture information concerning lot number, but that subsequent studies ENB-009 and 010 were capturing the lot number. If the specific lot number data for a specific dose for studies ENB 006 and 008 are important to the review, then the review division should request this information from the sponsor.*

3. Whyte site has been using subjects' weights obtained from local physicians (non-study doctors) to determine test article dose changes made between the 6 month study visits without written permission by the sponsor. Dr. Whyte wanted more frequent dose changes due to the subjects' rapid growth. Alexion did not approve this protocol deviation (use of weights obtained outside the study site). This was found at the sponsor inspection, not at the Whyte site

itself. It was noted that these occurrences have been reported to FDA in the data listings.

*Reviewer comment: Because the data is contained in the line listings, this is not considered a significant issue.*

- c. **Assessment of data integrity:** The studies appear to have been conducted adequately, and the data generated by the sponsor may be used in support of the respective indications. If the specific lot number data for a specific dose for studies ENB 006 and 008 are important to the review, then the review division should request this information from the sponsor.

### III. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Two clinical investigator sites and the sponsor were inspected for this application. Dr. Whyte site had the final classification of VAI and Dr. Rockman-Greenberg had the final classification of NAI. Although no significant violations were cited, there were issues discussed with the review division as noted above and the significance of these issues on the overall review is deferred to the review division.

The inspection of the sponsor has a preliminary classification of NAI and an addendum will be issued if conclusions change upon final review of the EIR. The studies appear to have been conducted adequately, and the data generated by these studies appear acceptable in support of the respective indications.

*{See appended electronic signature page}*

Susan Leibenhaut, M.D.  
Medical Reviewer  
Good Clinical Practice Assessment Branch  
Division of Clinical Compliance Evaluation  
Office of Scientific Investigations

CONCURRENCE:

*{See appended electronic signature page}*

Susan D. Thompson, M.D.  
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/s/  
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SUSAN LEIBENHAUT  
07/30/2015

SUSAN D THOMPSON  
07/30/2015

KASSA AYALEW  
07/30/2015



**DEPARTMENT OF HEALTH & HUMAN SERVICES** Public Health Service

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

**MEMORANDUM TO FILE**

**From:** Ethan D. Hausman, MD, Medical Officer  
Division of Pediatric and Maternal Health (DPMH)

**Through:** Hari Cheryl Sachs, MD, Medical Team Leader  
DPMH  
Lynne Yao, MD, Acting Division Director, DPMH

**BLA Number:** 125,513

**Sponsor:** Alexion

**Drug:** Strensiq (asfotase alfa), injection for intravenous (IV) administration

**Proposed dosing regimen:** 2 mg/kg IV three times per week (qW), or 1 mg/kg 6 times qW

**Indication:** Treatment of patients with infantile- and juvenile-onset hypophosphatasia (HPP)

**Division Consult Request:** The Division of Gastroenterology and Inborn Error Products (DGIEP) requests "DPMH's expertise in reviewing labeling for pediatrics and for nursing/lactating mothers sections of the labeling".

## Background

Strensiq (asfotase alfa or asfotase) is a tissue non-specific alkaline phosphatase enzyme replacement therapy (ERT) under development for the treatment of patients with infantile- and juvenile-onset hypophosphatasia (HPP). On September 12, 2008, asfotase received orphan designation for treatment of patients with HPP.

As described in prior review of this product under IND 100619 (Hausman, E.; May 13, 2013, and September 24, 2013), there are four types of HPP within the family of disease: infantile, perinatal, childhood, and adult onset, and odontohypophosphatasia (a form predominantly restricted to dental abnormalities). Earlier presentation may be associated with more severe phenotype expression. Phenotypic variation within the same family has been reported.<sup>1,2,3</sup> Perinatal HPP is characterized by severe skeletal hypomineralization and underdeveloped limbs leading to severe rachitic changes, respiratory compromise and death. Infantile HPP follows a similar course; however, symptoms do not manifest until approximately 6 months of age when patients present with feeding difficulty, failure to gain weight, rickets, intracranial pressure, papilledema, hypertelorism, and brachycephaly associated with premature cranial suture fusion. Childhood HPP has variable phenotype for age of onset, severity, and progression, but may present with early loss of deciduous teeth, typical rickets-like changes including short stature, and delayed walking. Adult HPP commonly presents during middle age with a prior history of premature loss of deciduous and adult teeth, osteomalacia, metatarsal stress fractures, or radiologic pseudofractures (Looser zones).<sup>4</sup> Adults may develop hyperparathyroidism and calcific peri-arthritis from periarticular calcium phosphate deposition.<sup>5</sup>

The sponsor submitted data from four clinical studies to support approval of asfotase treatment in affected patients, ages 1 day to 65 years at study entry, most of whom were treated for at least 1 year (range 0.1 to 260.9 weeks). The proposed efficacy endpoints for infantile-onset HPP were survival and ventilator-free survival compared to historical control. The proposed efficacy endpoints for juvenile-onset HPP were the rate of change per year in ambulation and gait using standardized visual assessment including step length, foot clearance and “step continuity”.

## DPMH Labeling Recommendations

The Pediatric Use subsection must describe what is known and unknown about use of the drug in the pediatric population, including limitations of use, and must highlight any differences in efficacy or safety in the pediatric population versus the adult population. For products with pediatric indications, the pediatric information must be placed in the labeling as required by 21 CFR 201.57(c)(9)(iv). This regulation describes the

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<sup>1</sup> Chitayat D, Hodgkinson KA, Azouz EM. Intrafamilial variability in cleidocranial dysplasia: a three generation family. *Am. J. Med. Genet.* 42: 298-303, 1992.

<sup>2</sup> Eastman J., Bixler D. Lethal and mild hypophosphatasia in half-sibs. *J. Craniofac. Genet. Dev. Biol.* 2: 35-44, 1982

<sup>3</sup> Eastman JR, Bixler D. Clinical, laboratory, and genetic investigations of hypophosphatasia: support for autosomal dominant inheritance with homozygous lethality. *J. Craniofac. Genet. Dev. Biol.* 3: 213-234, 1983

<sup>4</sup> Anonymous, Online Mendelian Inheritance in Man, Synopsis: entry # 241500. Hypophosphatasia, Infantile. (<http://omim.org/entry/241500>) Website accessed April 8, 2013

<sup>5</sup> Macfarlane J, Kroon H, van der Harten J. Phenotypically dissimilar hypophosphatasia in two sibships. *Am. J. Med. Genet.* 42: 117-121, 1992.

appropriate use statements to include in labeling based on findings of safety and effectiveness in the pediatric use population. (Also see draft Guidance for Industry and Review Staff Pediatric Information Incorporated Into Human Prescription Drug and Biological Products Labeling, February, 2013). Because asfotase may be approved in all pediatric patients, including neonates, pediatric information can be distributed in various sections of labeling, where appropriate.

The labeling is undergoing substantial revisions by DGEIP and consultant divisions. This review will focus on labeling sections 1 (Indications), 2 (Dosage and Administration), 5 (Warnings and Precautions) and 8.4 (Pediatric Use). Sections 8.1 (Pregnancy) and 8.3 (Nursing Mothers) will be addressed in the separate Maternal Health labeling review (pending). The description for sections 6 (Warnings and Precautions) and 14 (Clinical Studies) requires intensive data review and is deferred to DGIEP (pending). The labeling version in the SharePoint location as of June 11, 2015 is shown below.

For each section, the proposed language is presented first, followed by recommended changes, if any, in ***bold italics***.

### 1. Indications and Usage

#### Proposed

STRENSIQ™ is indicated for the (b) (4) treatment of patients with infantile- and juvenile-onset hypophosphatasia (HPP).

*Reviewer comment: DGIEP recommends deleting the modifier ‘ (b) (4) DPMH, therefore, agrees with deleting the modifier (b) (4) from the indication statement.*

### 2. Dosage and Administration

#### Proposed

“The recommended dosage regimen of STRENSIQ for the treatment of infantile- and juvenile-onset HPP is 2 mg/kg of body weight administered subcutaneously three times per week, or a dosage regimen of 1 mg/kg of body weight administered six times per week.”

*Reviewer comment: From review of the proposed labeling it is unclear if either the 2 mg/kg three times/week dose or the 1 mg/kg six times/week dose is preferred. If one regimen is superior, DPMH recommends describing the superior regimen as a single sentence. The secondary regimen should then be described in subsequently including reasons why it would be instituted in a particular patient.*

### 5. Warnings and Precautions

*Reviewer comment: The Warnings and Precautions section of labeling includes descriptions of hypersensitivity reactions including injection site reactions (5.1) and lipodystrophy at the injection sites (5.2). These two sections are undergoing substantial revisions. The description of hypersensitivity reactions is similar to labelling descriptions for other ERTs (e.g., Aldurazyme, BLA 125058); however, labeling states that (b) (4). The current text of the Warnings and Precautions is below.*

## 5.1 Hypersensitivity

(b) (4)

(b) (4)

## 5.2 Lipodystrophy

Localized lipoatrophy (b) (4) and lipohypertrophy (b) (4) have have been reported a injection sites after several months in patients treated with STRENSIQ in clinical studies. Advise patients to follow proper injection technique and to rotate injection sites [see Dosage and Administration (2.2)].

*Reviewer comment: DGIEP is requesting that the sponsor (b) (4) (b) (4) The language for hypersensitivity reactions (5.1) and injection site lipodystrophy at the (5.2) are otherwise generally appropriate and further revisions are deferred to DGIEP.*

## 6. Adverse Reactions

The description of patient exposure in the Adverse Reactions section of labeling is shown below.

(b) (4)

#### 8.4 Pediatric Use

Proposed

“Safety and efficacy of STRENSIQ have been established in pediatric patients

(b) (4)

*Reviewer comment: DPMH recommends the following revision to section 8.4 for clarity.*

*“The safety and effectiveness of STRENSIQ have been established in pediatric patients. Use of STRENSIQ is based on 4 prospective, open-label clinical trials conducted in 69 adult and pediatric patients. The majority of patients were pediatric patients 1 day to 16 years of age (58/69 [84%]). [see Clinical Studies (14)].”*

#### 14 Clinical Studies

Review of efficacy data and appropriate endpoints for labeling is deferred to DGIEP; however, the description of clinical studies is shown below.

(b) (4)

### **Conclusion and Recommendations**

The above comments were provided to DGIEP in advance of the internal labeling meeting on July 7, 2015. The reader is directed to final negotiated labeling (pending) for additional labeling revisions not described above.

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/s/  
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ETHAN D HAUSMAN  
06/29/2015

HARI C SACHS  
06/29/2015  
I agree with these recommendations.

LYNNE P YAO  
06/29/2015

## DNP Consult memo

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<b>BLA</b>	<b>122472</b>
<b>Sponsor:</b>	<b>Alexion</b>
<b>Drug:</b>	<b>Asfotase alfa</b>
<b>Proposed Indication:</b>	<b>Hypophosphatasia</b>
<b>Material Submitted:</b>	<b>BLA Submission</b>
<b>Correspondence Date:</b>	<b>12/23/14</b>
<b>Date Received / Agency:</b>	<b>12/23/15</b>
<b>Date Review Completed:</b>	<b>4/22/15</b>
<b>Reviewer:</b>	<b>Teresa Buracchio, M.D.</b>

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DGIEP requests DNP's assistance in evaluating the appropriateness of the modified Performance Oriented Mobility Assessment-Gait (mPOMA-G) endpoint and its relationship to the Six Minute Walk Test (6MWT) and strength assessments for study ENB-006-09/ENB-008-10 in juvenile-onset hypophosphatasia.

### **Background:**

Hypophosphatasia (HPP) is an autosomal recessive disease caused by a loss-of-function mutation in the gene encoding alkaline phosphatase, tissue-nonspecific isozyme (TNSALP).<sup>1</sup> HPP is characterized by defective mineralization of bone and/or teeth and impairment of calcium and phosphate regulation. Clinical symptoms may include deformity and destruction of bones, pain and profound muscle weakness, respiratory failure, seizures, impaired renal function, impaired mobility, and dental abnormalities. There are several different clinical phenotypes that are generally grouped by age of onset. A perinatal form of HPP may be lethal in infancy and is characterized by respiratory insufficiency and hypercalcemia. Infantile-onset HPP (onset at birth to 6 months) is characterized by rickets. Juvenile onset HPP (onset at 6 months to 17 years of age) is characterized by a variable presentation with a range of clinical signs from decreased bone mineralization with unexplained fractures to rickets. More severely affected children may have difficulty walking with a characteristic waddling myopathic gait. Adult-onset HPP (onset at  $\geq 18$  years) is characterized by early loss of adult dentition and stress fractures and pseudofractures of the lower extremities in middle age. There are no approved therapies for HPP and treatment is symptomatic.

Asfotase alfa is a human recombinant tissue-nonspecific alkaline phosphatase-Fc-deca-aspartate fusion protein. The sponsor is seeking an indication for long-term enzyme replacement therapy in patients with infantile- and juvenile-onset hypophosphatasia.

The sponsor conducted several open-label pivotal studies in HPP across different age groups. Study ENB-006-09/ENB-008-10(extension) was conducted in the infantile and juvenile-onset population and enrolled patients from 5 through 12 years of age. The study was designed to assess the safety, efficacy, PK and PD of asfotase alfa in HPP patients with the onset of first symptoms at  $< 18$  years of age. In the initial study protocol and report, the study's primary efficacy endpoint was the change in rickets severity on skeletal radiographs from Baseline to Week 24 (Study ENB-006-09) as measured by the RGI-C scale and compared to HPP historical controls. After discussions with the Agency it was determined that the study would need a clinical endpoint for juvenile-onset

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<sup>1</sup> Mornet E, Nunes ME. Hypophosphatasia. 2007 Nov 20 [Updated 2011 Nov 10]. In: Pagon RA, Adam MP, Ardinger HH, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2015.

patients in order to support full approval in this population. The 6MWT had also been collected as a secondary endpoint; however, there were no HPP historical controls for comparison. In a meeting with the Agency on July 8, 2014, the sponsor reported that marked changes in gait had been noted during treatment with asfotase alfa and they proposed a gait assessment scale, the modified Performance-Oriented Mobility Assessment- Gait (mPOMA-G), as a clinical endpoint for the juvenile-onset patients that could be assessed post-hoc based on videos taken during the 6MWT administration. An HPP historical control cohort could be identified from a natural history database maintained at Shriners Hospitals for Children (St. Louis, MO) that obtained videos of gait as part of the routine clinical evaluation. The Agency agreed that the proposal appeared reasonable and that the mPOMA-G was an appropriate endpoint; however, the final acceptability of the data would be a review issue.

### **Scales**

The Performance Oriented Mobility Assessment (POMA) was originally developed as a screening tool for the assessment fall risk in the elderly.<sup>2</sup> The scale consists of two subscales that assess qualitative measures of balance (POMA-B) and gait (POMA-G). The POMA-G assesses gait parameters that include: initiation of gait, step length and height, step symmetry, step continuity, path (deviation), trunk (instability), and walk stance. There are 16 items (9 items for balance and 7 items for gait) and each item is scored as 0-2 points with a maximum score of 28 (Appendix 1). A higher score indicates better performance. In the original publication, a cut-off score of <19 was found to predict a higher risk of falls in an elderly population.

The POMA-G uses qualitative assessments of common gait abnormalities in the elderly that may predispose individuals to falls. Although the POMA-G measures some commonly assessed gait parameters such as step or stride length and step symmetry, it should be noted that there is no established uniform set of gait parameters used in assessment of gait. The scale has been used clinically and in research studies in the elderly population as a risk assessment tool for falls. It has also been used to assess risk for falls in diseases common in the elderly such as dementia, stroke, and Parkinson's disease. It is not commonly used in the pediatric community but the sponsor has provided one literature reference of its use in children with hearing impairment.<sup>3</sup>

The POMA scale was developed for use as a screening tool to assess risk for falls with a cut-off score and it was not originally intended to be used as a continuous measure of gait change; however some observational longitudinal research studies have attempted to analyze it this way. The scale was also originally validated with combined administration of both gait and balance subscales and the subscales have not been independently validated. Although researchers have used the POMA subscales independently and as continuous measures, a clinically meaningful change on the total scale or on the gait subscale has not been established. One study has evaluated the performance characteristics of the POMA score in a geriatric population and found that at the individual level, a change in score of at least 5 points on the total scale (combined gait and balance) proved to be reliable, whereas a change in the mean score of 0.8 point

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<sup>2</sup> Tinetti M. Performance-Oriented Assessment of Mobility Problems in Elderly Patients. *JAGS* 1986; 34:119-126.

<sup>3</sup> de Souza Melo R, da Silva P, Tassitano R, Macky C, daSilva L. Balance and gait evaluation: comparative study between deaf and hearing students. *Rev Paul Pediatr.* 2012;30(3):385-91.

indicated a reliable change in the mean score for a group of 30 subjects.<sup>4</sup> It was not felt that a reliable change could be determined for the individual gait or balance subscales. As this study was performed in elderly patients with the original total POMA scale, these values cannot be extrapolated to the mPOMA-G in the HPP population.

The POMA scale has undergone many modifications for use and the sponsor has modified it for use in the HPP population as the mPOMA-G based on input from academic physical therapy experts experienced in evaluating HPP and also based on the ability to use the scale with the available video assessments (Appendix 2). The sponsor has removed the measure of gait initiation as this is more specific to neurologic disease such as Parkinson's disease. They have also removed the measure of "path" as this could not be reliably assessed on the available video recordings. They have expanded the scores for step length and height and step continuity to allow for greater precision.

***Comments: The removal of the gait initiation measure and expansion of the step length and height appear to be reasonable modifications. However, it is not clear the expansion of the step continuity measure adds additional meaningful information. Some modifications, such as removal of "path", were made specifically based on video recordings for this study which introduces potential for bias. It is not known if the measure of "path" captures an important feature of gait in this population or how removal of this feature impacts the scale. Overall, the modified scale appears to have reasonable face validity as a general assessment of gait; however, the performance characteristics have not been established in HPP or the pediatric population.***

### **Methods**

The mPOMA-G was assessed post-hoc in an integrated analysis comparing treated patients from study ENB-006-09/ENB-008-10 with untreated historical controls in studies ALX-HPP-502 and ALX-HPP-502s. Study ALX-HPP-502s was a single-center, non-interventional functional natural history substudy of ALX-HPP-502 in patients with juvenile-onset HPP designed to assess historical functional data and the evolution of gait in juvenile-onset HPP. The mPOMA-G was not prospectively collected in either study. The mPOMA-G was scored by three physical therapists experienced in evaluating HPP patients based on video recordings obtained during filming of the 6MWT in study ENB-006-09/ENB-008-10 and from videos of routine clinical assessments in ALX-HPP-502s. The identity of the patients and the timing of the assessments were obscured; however, the therapists were able to differentiate between the treatment and natural history studies based on the format of the videos. There were 8 patients in study ENB-006-09/ENB-008-10 and 6 patients in the natural history with evaluable videos for the mPOMA-G. The sponsor has included the videos in the submission.

***Comments: The sponsor has attempted to minimize bias in assessments by obscuring the faces of the patients and the timing of gait assessments; however, there are distinct differences in the format of the videos and the clinical assessments between the treatment study and the historical controls that do not allow the rater to be blinded to the treatment groups. There remain several other potential sources of bias or variability in the methods for assessment of gait in***

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<sup>4</sup> Faber MJ, Bosscher RJ, and van Wieringen P. Clinimetric Properties of the Performance-Oriented Mobility Assessment. *Phys Ther.* 2006;86:944–954.

**this study. As the gait assessment was performed post-hoc using previously filmed videos, there was not a pre-specified or standardized method for administration of the gait assessment. For instance, administration of the original POMA scale calls for gait assessments to be performed both at a “usual pace” and at a “more rapid than usual pace.” The POMA scale instructions also call for assessment of certain gait parameters from specific viewing angles, for example, step length and step height are best assessed from the side and truncal instability and walk stance from behind. For the videos in ENB-006-09/ENB-008-10, the raters were limited to a single view and patients would generally be walking as quickly as they can for the 6MWT. Consideration should also be given as to whether the quality of the videos is adequate to allow reliable scoring (e.g., are all gait parameters of the mPOMA-G clearly visible and evaluable). Although the raters were experienced physical therapists, it is unclear whether they were specifically trained on the mPOMA-G and whether there was adequate inter-rater reliability.**

**Results from ENB-006-09/ENB-008-10**

Strength: Strength of the hip extensor and hip abductor muscles were assessed in juvenile-onset HPP patients patients 5 to 12 years of age using hand-held dynamometry (HHD). At Baseline, patients demonstrated weakness in both hip extensor and abductor muscles and median percent predicted strength was <50% of predicted values based on a normative sample. Treatment with asfotase alfa resulted in increased strength in both muscle groups as measured by percent predicted values, with statistically significant changes from Baseline (p<0.05, Wilcoxon signed-rank test) beginning at Weeks 24 (hip abduction) and 48 (hip extension) and was sustained through Week 192. See Table 1.

**Table 1**

Muscle Group Test Test Statistic	Percent Predicted Actual Value (N=8)					
	Baseline	Week 24	Week 48	Week 96	Week 144	Week 192
<b>Hip Extension (Right Side *)</b>						
n	7	7	7	7	5	5
Mean (SD)	35.31 (13.044)	48.73 (23.147)	60.64 (38.509)	61.53 (36.620)	65.28 (34.877)	64.02 (26.497)
Median (min, max)	31.90 (18.8, 52.7)	41.20 (23.5, 91.8)	38.20 (21.7, 116.8)	44.10 (18.1, 120.6)	63.60 (34.7, 122.3)	60.20 (38.2, 100.8)
p-value <sup>b</sup>	–	0.2188	0.0156	0.0313	0.0625	0.0625
<b>Hip Abduction (Right Side *)</b>						
n	7	7	7	7	5	5
Mean (SD)	49.21 (17.413)	65.31 (27.375)	77.11 (34.773)	77.24 (29.360)	75.72 (27.038)	99.14 (42.679)
Median (min, max)	48.70 (23.2, 72.0)	61.50 (20.6, 103.6)	65.80 (30.5, 125.8)	73.10 (38.0, 122.3)	83.00 (45.7, 111.2)	85.20 (54.9, 163.7)
p-value <sup>b</sup>	–	0.0313	0.0156	0.0156	0.0625	0.0625

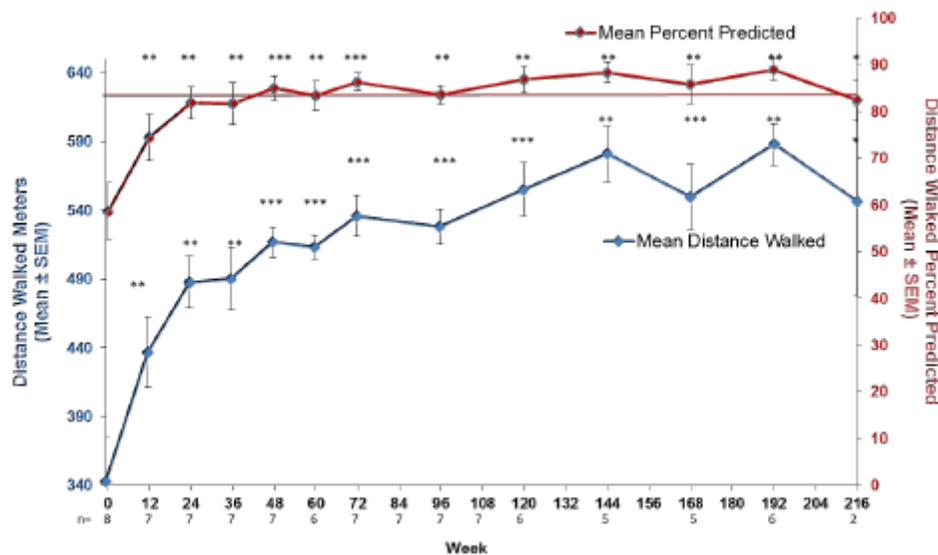
\* The right side was the dominant side for all patients (ENB-006-09/ENB-008-10 CSR, Listing 16.2.6.9.0)

<sup>b</sup> p-value based on Wilcoxon signed rank test (comparison of change from Baseline)

Source: Table 3.2.9.1.1 (for both right and left side data).

Mobility: Improvements in 6MWT from Baseline were demonstrated with asfotase alfa treatment in percent predicted values to control for factors known to affect performance on the 6MWT (age, sex, and height). These improvements were observed as early as Week 12 and were sustained through Week 192. See Figure 1.

**Figure 1**



Gait: All 6 patients with juvenile-onset HPP in the natural history study ALX-HPP-502s (n=6) had a history of gait disturbance. Bone deformity (bowing of the long bones), arthralgia/joint pain, bone pain, fracture and muscular weakness were observed (3 of 6 patients), and were the most frequent symptoms reported across the patient groups.

In the primary analysis, asfotase alfa treatment (n=8) was associated with significant improvement in patient gait compared with Baseline, whereas historical control patients (n=6) showed no change in gait. The median (range) rate of change per year was 2.51/year (0.0, 4.6) in asfotase alfa-treated patients compared with 0.33/year (0.0, 0.9) for untreated historical controls (p=0.0303, Wilcoxon rank-sum test). As patients had different durations of treatment, the absolute change in mPOMA-G scores from Baseline to Last Assessment was evaluated as a secondary analysis and showed a median increase of 3.0 (0, 7) for asfotase alfa-treated patients, compared with a median increase of 1.5 (0, 2) for historical controls (p=0.2561, Wilcoxon rank-sum test).

In the listing of changes in individual components of the mPOMA-G (Table 3.2.1.6.1.5), it appears that the greatest improvement was seen in step length. There were 6/8 patients from Study ENB-006-09/ENB-008-10 who showed at least a 1 point improvement in step length in either foot while only 1/6 patients showed any improvement with either foot in the historical controls.

Historical controls: Based on a review of available literature and natural history studies, the Sponsor has concluded that there is no spontaneous improvement expected over the clinical course in HPP patients, including survival, radiologic and overall functional ability assessments.

**Comments: In this open-label study, it would be possible for a patient to demonstrate some level of improvement in gait due to expectation bias; however, it is less likely that large improvements in gait could be attributed to this effect.**

**It appears that most of the improvements on the mPOMA-G were seen in step length. Increases in step length may be related to improvements seen in strength;**

***however, improvements in pain or skeletal abnormalities could also be contributing factors. Step length may increase with increasing age (due to increase in height); therefore, consideration should be given to the ages (or change in height) of patients in the treated group and the historical controls in the clinical review.***

### **Questions from DGIEP**

#### **1. DGIEP requests your expertise in evaluating the relationship of gait/mobility to muscle strength in juvenile-onset HPP patients.**

The sponsor uses the terms gait and mobility interchangeably, and while they are clearly related they represent somewhat different concepts. An assessment of gait measures physical signs of walking, such as stride length and step symmetry, whereas mobility is an overall functional measure of movement or ambulation. Gait is an important component of mobility but mobility is a broader functional measure. The 6MWT appears to capture the functional concept of mobility while the POMA-G measures physical signs of gait. Similarly, a change in strength measured by dynamometry also measures a physical sign that is also an important component of both gait and mobility. Changes in gait or strength are of uncertain independent clinical significance; their clinical significance generally lies in their relationship to the risk of falls or to improve the ability to perform a functional task. However, an improvement in mobility (such as the ability to walk further on the 6MWT) provides a measure of “everyday function” that may demonstrate a direct clinical benefit that is perceptible to the patient.

Mobility, as measured by the 6MWT in these studies, is influenced by many different factors, including gait, strength, respiratory function, pain, etc. In this study, improvements in gait and strength measures could contribute to improvements seen on the 6MWT; however, mobility can also be influenced by other important symptoms in this disease such as pain and stabilization of skeletal abnormalities.

#### **2. Please comment on the correlation between MPOMA-G scores and 6MWT scores for juvenile-onset HPP patients.**

The sponsor has reported a high correlation between the mPOMA-G and 6MWT. The 6MWT (expressed as distance walked in meters) and mPOMA-G, for Baseline and the last mPOMA-G assessment, showed a strong correlation (Pearson's Correlation Coefficient of 0.8574) that was statistically significant ( $p < 0.001$ ). I could find no previously reported correlations between the two measures for comparison. It is expected that there will be some correlation between the 6MWT and the mPOMA-G as certain measures such as step length captured on the mPOMA-G will clearly influence the distance that is walked. However, the correlation reported by the sponsor may be inflated since the mPOMA-G was assessed by a video taken as a part of the 6MWT. For a more accurate correlation, the two measures should be obtained independently.

#### **3. Please comment on DNP's experience with the 6 Minute Walk Test and the MPOMA-G score in registration clinical trials, including the merits and limitations of each assessment. Have these assessments been used as primary endpoints for efficacy in registration trials?**

The 6MWT has been used in pivotal trials for Duchenne muscular dystrophy but to date it has not been used as the basis for approval of a drug in DNP. The primary limitation of the test is that it is effort-dependent so results can be biased in open-label studies or by partial unblinding in placebo-controlled trials. Test results may be influenced by the patient's mood or other health conditions or may be influenced by external factors such as encouragement or time of day. It requires cooperation from the patient so it is limited in use to patients who are old enough and have the cognitive capacity to follow instructions. Administration of the test also needs to be standardized.

The POMA-G has not been used in any pivotal trials in DNP. The POMA scale was developed to assess common gait abnormalities in the elderly that may predispose individuals to falls. Although the sponsor has modified the scale to be more suitable to the HPP population and the mPOMA-G and the scale appears to have face validity as a general assessment of gait, the performance characteristics have not been established in HPP or a pediatric population. It is not clear what represents a clinically meaningful change on the mPOMA-G. Some modifications, such as removal of "path", were made specifically based on video recordings for this study which introduces to potential for bias. Additionally, the mPOMA-G was assessed post-hoc on previously filmed videos from the 6MWT and there are many potential sources of bias in the method of assessment.

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Teresa Buracchio, M.D.  
Medical Reviewer

**Appendix 1. Original POMA-G Scale**

Assessment	Observation	Score
1	Initiation of gait	Any hesitancy or multiple attempts = 0
		No hesitancy = 1
2	Step length and height	
	a) Right swing foot	Does not pass the left stance foot with step = 0
		Passes the left stance foot = 1
	b) Right foot clear	Does not clear floor completely with step = 0
		Right foot completely clears floor = 1
	c) Left swing foot	Does not pass the right stance foot with step = 0
Passes the right stance foot = 1		
d) Left foot clear	Does not clear floor completely with step = 0	
	Left foot completely clears floor = 1	
3	Step symmetry	Right and left step length not equal = 0
		Left foot completely clears floor = 1
4	Step continuity	Stopping or discontinuity between steps = 0
		Steps appear continuous = 1
5	Path	Marked deviation = 0
		Mild/moderate deviation or uses walking aid = 1
		Straight without walking aid = 2
6	Trunk	Marked sway or uses walking aid = 0
		No sway but flexion of knees or back or spreads arms out while walking = 1
		No sway, no flexion, no use of arms, and no walking aid = 2
7	Walk stance	Heels apart = 0
		Heels almost touching while walking = 1
Gait score		/12

Abbreviations: POMA-G = Performance-Oriented Mobility Assessment, Gait subtest.

**Appendix 2. Modified POMA-G Scale**

Assessment	Observation	Score	
1	Step length and height		
	a) Right swing foot	Does not pass the left stance foot with step	= 0
		Right heel passes the left stance foot	= 1
		Right foot passes the left stance foot by at least the length of individual's foot between the stance toe and swing heel	= 2
	b) Right foot clear	Right foot does not clear floor completely with step or raises foot by more than 1 - 2 inches	= 0
		Right foot completely clears floor	= 1
	c) Left swing foot	Does not pass the right stance foot with step	= 0
		Left heel passes the right stance foot	= 1
		Left foot passes the right stance foot by at least the length of individual's foot between the stance toe and swing heel	= 2
	d) Left foot clear	Left foot does not clear floor completely with step or raises foot by more than 1 - 2 inches	= 0
Left foot completely clears floor		= 1	
2	Step symmetry		
3	Step continuity	Right and left step length not equal (estimate)	= 0
		Right and left step appear equal	= 1
		Stopping or discontinuity between steps	= 0
		Steps appear continuous unilaterally (observe raising heel of 1 foot as heel of other foot touches the floor, unilaterally) or flat foot contact on stance limb when heel of other foot touches the floor bilaterally, no breaks or stops in stride	= 1
		Steps appear continuous bilaterally (observe raising heel of 1 foot as heel of other foot touches the floor, bilaterally), no breaks or stops in stride, step lengths equal	= 2
4	Trunk	Marked sway or uses walking aid. Marked sway = moderate lateral flexion as the result of instability bilateral or unilateral	= 0
		No marked sway but compensatory patterns such as trunk flexion, knee flexion, arm abduction or retraction to increase postural stability while walking	= 1
		No sway, no flexion, no use of arms, and no walking aid	= 2
5	Walk stance	Heels always apart, wide base of support utilized to increase postural stability	= 0
		Heels intermittently apart	= 1
Gait score		/12	

Abbreviations: MPOMA-G = Modified Performance-Oriented Mobility Assessment, Gait subtest.

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/s/  
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TERESA J BURACCHIO  
06/22/2015

RONALD H FARKAS  
06/22/2015

WILLIAM H Dunn  
06/24/2015

## 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 # BLA# 125513	NDA Supplement #: S- BLA Supplement #: S-	Efficacy Supplement Category: <input type="checkbox"/> New Indication (SE1) <input type="checkbox"/> New Dosing Regimen (SE2) <input type="checkbox"/> New Route Of Administration (SE3) <input type="checkbox"/> Comparative Efficacy Claim (SE4) <input type="checkbox"/> New Patient Population (SE5) <input type="checkbox"/> Rx To OTC Switch (SE6) <input type="checkbox"/> Accelerated Approval Confirmatory Study (SE7) <input type="checkbox"/> Animal Rule Confirmatory Study (SE7) <input type="checkbox"/> Labeling Change With Clinical Data (SE8) <input type="checkbox"/> Manufacturing Change With Clinical Data (SE9) <input type="checkbox"/> Pediatric
Proprietary Name: STRENSIQ Established/Proper Name: asfotase alfa Dosage Form: solution for subcutaneous injection Strengths: 40 mg/ml and 100 mg/ml		
Applicant: Alexion Pharmaceuticals Inc Agent for Applicant (if applicable):		
Date of Application: 12/23/2014 Date of Receipt: 12/23/2014 Date clock started after UN:		
PDUFA/BsUFA Goal Date: 08/23/2015		Action Goal Date (if different):
Filing Date: 02/21/2015		Date of Filing Meeting: 01/21/2015
Chemical Classification (original NDAs only) : <input type="checkbox"/> Type 1- New Molecular Entity (NME); NME and New Combination <input type="checkbox"/> Type 2- New Active Ingredient; New Active Ingredient and New Dosage Form; New Active Ingredient and New Combination <input type="checkbox"/> Type 3- New Dosage Form; New Dosage Form and New Combination <input type="checkbox"/> Type 4- New Combination <input type="checkbox"/> Type 5- New Formulation or New Manufacturer <input type="checkbox"/> Type 7- Drug Already Marketed without Approved NDA <input type="checkbox"/> Type 8- Partial Rx to OTC Switch		
Proposed indication(s)/Proposed change(s): treatment of infantile and juvenile-onset hypophosphatasia		
Type of Original NDA: AND (if applicable) Type of NDA Supplement:		<input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)
<b><i>If 505(b)(2): Draft the "505(b)(2) Assessment" review found at:</i></b> <a href="http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499">http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499</a>		

Type of BLA	<input checked="" type="checkbox"/> 351(a) <input type="checkbox"/> 351(k)
<b><i>If 351(k), notify the OND Therapeutic Biologics and Biosimilars Team</i></b>	
Review Classification:	<input type="checkbox"/> Standard <input checked="" type="checkbox"/> Priority
<b><i>The application will be a priority review if:</i></b>	<input type="checkbox"/> Pediatric WR
<ul style="list-style-type: none"><li><i>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)</i></li></ul>	<input type="checkbox"/> QIDP
<ul style="list-style-type: none"><li><i>The product is a Qualified Infectious Disease Product (QIDP)</i></li></ul>	<input type="checkbox"/> Tropical Disease Priority Review Voucher
<ul style="list-style-type: none"><li><i>A Tropical Disease Priority Review Voucher was submitted</i></li></ul>	<input type="checkbox"/> Pediatric Rare Disease Priority Review Voucher
<ul style="list-style-type: none"><li><i>A Pediatric Rare Disease Priority Review Voucher was submitted</i></li></ul>	
Resubmission after withdrawal? <input type="checkbox"/>	Resubmission after refuse to file? <input type="checkbox"/>
Part 3 Combination Product? <input type="checkbox"/>	<input type="checkbox"/> Convenience kit/Co-package
<b><i>If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults</i></b>	<input type="checkbox"/> Pre-filled drug delivery device/system (syringe, patch, etc.)
	<input type="checkbox"/> Pre-filled biologic delivery device/system (syringe, patch, etc.)
	<input type="checkbox"/> Device coated/impregnated/combined with drug
	<input type="checkbox"/> Device coated/impregnated/combined with biologic
	<input type="checkbox"/> Separate products requiring cross-labeling
	<input type="checkbox"/> Drug/Biologic
	<input type="checkbox"/> Possible combination based on cross-labeling of separate products
	<input type="checkbox"/> Other (drug/device/biological product)

<input checked="" type="checkbox"/> Fast Track Designation	<input type="checkbox"/> PMC response
<input checked="" type="checkbox"/> Breakthrough Therapy Designation <i>(set the submission property in DARRTS and notify the CDER Breakthrough Therapy Program Manager)</i>	<input type="checkbox"/> PMR response:
<input checked="" type="checkbox"/> Rolling Review	<input type="checkbox"/> FDAAA [505(o)]
<input checked="" type="checkbox"/> Orphan Designation	<input type="checkbox"/> PREA deferred pediatric studies (FDCA Section 505B)
<input type="checkbox"/> Rx-to-OTC switch, Full	<input type="checkbox"/> Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41)
<input type="checkbox"/> Rx-to-OTC switch, Partial	<input type="checkbox"/> Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)
<input type="checkbox"/> Direct-to-OTC	
Other:	

Collaborative Review Division (if OTC product):

List referenced IND Number(s): 100619

Goal Dates/Product Names/Classification Properties	YES	NO	NA	Comment
PDUFA/BsUFA and Action Goal dates correct in tracking system?  <b><i>If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.</i></b>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Are the established/proper and applicant names correct in tracking system?  <b><i>If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name</i></b>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		

<i>to the supporting IND(s) if not already entered into tracking system.</i>				
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)? <i>Check the New Application and New Supplement Notification Checklists for a list of all classifications/properties at:</i> <a href="http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm">http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm</a> <i>If no, ask the document room staff to make the appropriate entries.</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<b>Application Integrity Policy</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is the application affected by the Application Integrity Policy (AIP)? <i>Check the AIP list at:</i> <a href="http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm">http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</a> <i>If yes, explain in comment column.</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>		
<b>If affected by AIP, has OC/OMPQ been notified of the submission? If yes, date notified:</b>	<input type="checkbox"/>	<input type="checkbox"/>		
<b>User Fees</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is Form 3397 (User Fee Cover Sheet)/Form 3792 (Biosimilar User Fee Cover Sheet) included with authorized signature?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<u>User Fee Status</u> <i>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.</i>	Payment for this application ( <i>check daily email from <a href="mailto:UserFeeAR@fda.hhs.gov">UserFeeAR@fda.hhs.gov</a></i> ): <input type="checkbox"/> Paid <input checked="" type="checkbox"/> Exempt (orphan, government) <input type="checkbox"/> Waived (e.g., small business, public health) <input type="checkbox"/> Not required			
<i>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.</i>	Payment of other user fees: <input checked="" type="checkbox"/> Not in arrears <input type="checkbox"/> In arrears			
<u>User Fee Bundling Policy</u> <i>Refer to the guidance for industry, Submitting Separate Marketing Applications and Clinical Data for Purposes of Assessing User Fees at:</i> <a href="http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079320.pdf">http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079320.pdf</a>	Has the user fee bundling policy been appropriately applied? <i>If no, or you are not sure, consult the User Fee Staff.</i> <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No			
<b>505(b)(2) (NDAs/NDA Efficacy Supplements only)</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is the application a 505(b)(2) NDA? ( <i>Check the 356h form,</i>	<input type="checkbox"/>	<input type="checkbox"/>		

cover letter, and annotated labeling). <b>If yes</b> , 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?		<input type="checkbox"/>	<input type="checkbox"/>		
• 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)].		<input type="checkbox"/>	<input type="checkbox"/>		
• 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)]?		<input type="checkbox"/>	<input type="checkbox"/>		
<i>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.</i>					
• Is there unexpired exclusivity on another listed drug product containing the same active moiety (e.g., 5-year, 3-year, orphan, or pediatric exclusivity)?		<input type="checkbox"/>	<input type="checkbox"/>		
<i>Check the Electronic Orange Book at: <a href="http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm">http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm</a></i>					
<b>If yes</b> , please list below:					
Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration		
<i>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.</i>					
<b>Exclusivity</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>	
Does another product (same active moiety) have orphan exclusivity for the same indication? <i>Check the Orphan Drug Designations and Approvals list at: <a href="http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm">http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm</a></i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>			
<b>If another product has orphan exclusivity</b> , is the product considered to be the same product according to the orphan drug definition of sameness [see 21 CFR 316.3(b)(13)]?	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>		
<i>If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy</i>					
<b>NDAs/NDA efficacy supplements only:</b> Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity?	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>		
<b>If yes</b> , # years requested:					
<i>Note: An applicant can receive exclusivity without requesting it;</i>					

<i>therefore, requesting exclusivity is not required.</i>				
<b>NDAs only:</b> Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use?	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
<b>If yes,</b> 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)?  <i>If yes, contact the Orange Book Staff (CDER-Orange Book Staff).</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
<b>BLAs only:</b> Has the applicant requested 12-year exclusivity under section 351(k)(7) of the PHS Act?  <i>If yes, notify Marlene Schultz-DePalo, OBP Biosimilars RPM</i>  <i>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.</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	

<b>Format and Content</b>				
<i>Do not check mixed submission if the only electronic component is the content of labeling (COL).</i>	<input type="checkbox"/> All paper (except for COL) <input checked="" type="checkbox"/> All electronic <input type="checkbox"/> Mixed (paper/electronic)			
	<input checked="" type="checkbox"/> CTD <input type="checkbox"/> Non-CTD <input type="checkbox"/> Mixed (CTD/non-CTD)			
<b>If mixed (paper/electronic) submission,</b> which parts of the application are submitted in electronic format?				
<b>Overall Format/Content</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
<b>If electronic submission,</b> does it follow the eCTD guidance? <sup>1</sup> <b>If not,</b> explain (e.g., waiver granted).	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<b>Index:</b> Does the submission contain an accurate comprehensive index?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
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:	<input checked="" type="checkbox"/>	<input type="checkbox"/>		

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<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf>

<input checked="" type="checkbox"/> legible <input checked="" type="checkbox"/> English (or translated into English) <input checked="" type="checkbox"/> pagination <input checked="" type="checkbox"/> navigable hyperlinks (electronic submissions only)				
<b>If no, explain.</b>				
<b>BLAs only:</b> Companion application received if a shared or divided manufacturing arrangement?	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
<b>If yes, BLA #</b>				
<b>Forms and Certifications</b>				
<i>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.</i>				
<b>Application Form</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<i>If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].</i>				
Are all establishments and their registration numbers listed on the form/attached to the form?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<b>Patent Information (NDAs/NDA efficacy supplements only)</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
<b>Financial Disclosure</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<i>Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].</i>				
<i>Note: Financial disclosure is required for bioequivalence studies that are the basis for approval.</i>				
<b>Clinical Trials Database</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is form FDA 3674 included with authorized signature?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<i>If yes, ensure that the application is also coded with the supporting document category, "Form 3674."</i>				

<i>If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant</i>				
<b>Debarment Certification</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is a correctly worded Debarment Certification included with authorized signature?  <i>Certification is not required for supplements if submitted in the original application; If foreign applicant, <b>both</b> the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].</i>  <i>Note: Debarment Certification should use wording in FD&amp;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...”</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<b>Field Copy Certification (NDAs/NDA efficacy supplements only)</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
<b>For paper submissions only:</b> Is a Field Copy Certification (that it is a true copy of the CMC technical section) included?  <i>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)</i>  <i>If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
<b>Controlled Substance/Product with Abuse Potential</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
<u>For NMEs:</u> Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)?  <i>If yes, date consult sent to the Controlled Substance Staff:</i>  <u>For non-NMEs:</u> <i>Date of consult sent to Controlled Substance Staff:</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
<b>Pediatrics</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
<b><u>PREA</u></b>  Does the application trigger PREA?  <i>If yes, notify <a href="mailto:PeRC@fda.hhs.gov">PeRC@fda.hhs.gov</a> to schedule required PeRC meeting<sup>2</sup></i>  <i>Note: NDAs/BLAs/efficacy supplements for new active ingredients (including new fixed combinations), new indications, new dosage</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>		Orphan designation

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<http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/PediatricandMaternalHealthStaff/ucm027829.htm>

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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.				
<b>If the application triggers PREA, is there an agreed Initial Pediatric Study Plan (iPSP)?</b>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
<i>If no, may be an RTF issue - contact DPMH for advice.</i>				
<b>If required by the agreed iPSP, are the pediatric studies outlined in the agreed iPSP completed and included in the application?</b>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
<i>If no, may be an RTF issue - contact DPMH for advice.</i>				
<b><u>BPCA:</u></b>				
Is this submission a complete response to a pediatric Written Request?	<input type="checkbox"/>	<input checked="" type="checkbox"/>		
<i>If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)<sup>3</sup></i>				
<b>Proprietary Name</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is a proposed proprietary name submitted?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<i>If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."</i>				
<b>REMS</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is a REMS submitted?	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
<i>If yes, send consult to OSE/DRISK and notify OC/OSI/DSC/PMSB via the CDER OSI RMP mailbox</i>				
<b>Prescription Labeling</b>	<input type="checkbox"/> <b>Not applicable</b>			
Check all types of labeling submitted.	<input checked="" type="checkbox"/> Package Insert (PI) <input type="checkbox"/> Patient Package Insert (PPI) <input type="checkbox"/> Instructions for Use (IFU) <input checked="" type="checkbox"/> Medication Guide (MedGuide) <input type="checkbox"/> Carton labels <input type="checkbox"/> Immediate container labels <input type="checkbox"/> Diluent <input type="checkbox"/> Other (specify)			
	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is Electronic Content of Labeling (COL) submitted in SPL format?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<i>If no, request applicant to submit SPL before the filing date.</i>				

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<http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/PediatricandMaternalHealthStaff/ucm027837.htm>

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Is the PI submitted in PLR format? <sup>4</sup>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<b>If PI not submitted in PLR format</b> , was a waiver or deferral requested before the application was received or in the submission? <b>If requested before application was submitted</b> , what is the status of the request?  <i>If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to OPDP?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (send WORD version if available)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office (OBP or ONDQA)?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<b>OTC Labeling</b>	<input checked="" type="checkbox"/> <b>Not Applicable</b>			
Check all types of labeling submitted.	<input type="checkbox"/> Outer carton label <input type="checkbox"/> Immediate container label <input type="checkbox"/> Blister card <input type="checkbox"/> Blister backing label <input type="checkbox"/> Consumer Information Leaflet (CIL) <input type="checkbox"/> Physician sample <input type="checkbox"/> Consumer sample <input type="checkbox"/> Other (specify)			
	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is electronic content of labeling (COL) submitted?  <i>If no, request in 74-day letter.</i>	<input type="checkbox"/>	<input type="checkbox"/>		
Are annotated specifications submitted for all stock keeping units (SKUs)?  <i>If no, request in 74-day letter.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
If representative labeling is submitted, are all represented SKUs defined?  <i>If no, request in 74-day letter.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
All labeling/packaging sent to OSE/DMEPA?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<b>Other Consults</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team)  <i>If yes, specify consult(s) and date(s) sent:</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	DBRUP and DNP regarding endpoints of efficacy. Sent on 02/13/2015
<b>Meeting Minutes/SPAs</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>

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<http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/StudyEndpointsandLabelingDevelopmentTeam/ucm025576.htm>

End-of Phase 2 meeting(s)? <b>Date(s):</b> 31 May 2011  <i>If yes, distribute minutes before filing meeting</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? <b>Date(s):</b> 08 Jul 2014  <i>If yes, distribute minutes before filing meeting</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Any Special Protocol Assessments (SPAs)? <b>Date(s):</b>  <i>If yes, distribute letter and/or relevant minutes before filing meeting</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>		

ATTACHMENT

**MEMO OF FILING MEETING**

**DATE:** 01/21/2015

**BACKGROUND:** See attached presentation.

**REVIEW TEAM:**

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Kevin Bugin	Y
	CPMS/TL:	Richard Ishihara	N
Cross-Discipline Team Leader (CDTL)	Anil Rajpal		Y
Division Director/Deputy	Donna Griebel		Y
Office Director/Deputy	Julie Beitz		Y
Clinical	Reviewer:	Carla Epps	Y
	TL:	Anil Rajpal	Y
Clinical Pharmacology	Reviewer:	Christine Hon	Y
	TL:	Yow-Ming Wang	Y
Biostatistics	Reviewer:	Benjamin Vali	Y
	TL:	Yeh-Fong Chen	Y

Nonclinical (Pharmacology/Toxicology)	Reviewer:	Dinesh Gautam	Y
	TL:	Sushanta Chakder	Y
Immunogenicity (assay/assay validation) <i>(for protein/peptide products only)</i>	Reviewer:	Frederick Mills	Y
	TL:		
Product Quality (CMC)	Reviewer:	Joslyn Brunelle, Gunther Boekhoudt	Y
	TL:	Cristina Ausin	Y
Quality Microbiology	Reviewer:	Candace Gomez-Broughton	Y
	TL:	Patricia Hughes	Y
CMC Labeling Review	Reviewer:	Jibril Abdus-Samil	Y
	TL:		
Facility Review/Inspection	Reviewer:	Christina Capacci-Daniel	Y
	TL:		
OSE/DMEPA (proprietary name, carton/container labels))	Reviewer:	Matthew Barlow	Y
	TL:	Kendra Worthy	Y

Bioresearch Monitoring (OSI)	Reviewer:	Susan Liebenhaut	Y
	TL:	Susan Thompson	N
Other reviewers/disciplines	Reviewer:	Pharmacometrics: Justin Earp	Y
	TL:	Nitin Mehrotra	Y
Other attendees			

**FILING MEETING DISCUSSION:**

<p><b>GENERAL</b></p> <ul style="list-style-type: none"> <li>• 505(b)(2) filing issues: <ul style="list-style-type: none"> <li>○ Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?</li> <li>○ Did the applicant provide a scientific “bridge” demonstrating the relationship between the proposed product and the referenced product(s)/published literature?</li> </ul> </li> </ul> <p>Describe the scientific bridge (e.g., BA/BE studies):</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> <li>• Per reviewers, are all parts in English or English translation?</li> </ul> <p><b>If no, explain:</b></p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> <li>• Electronic Submission comments</li> </ul> <p><b>List comments:</b></p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> No comments
<p><b>CLINICAL</b></p> <p><b>Comments:</b></p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> <li>• Clinical study site(s) inspections(s) needed?</li> </ul> <p><b>If no, explain:</b></p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> <li>• Advisory Committee Meeting needed?</li> </ul>	<input type="checkbox"/> YES Date if known:

<p><b>Comments:</b></p> <p><i>If no, for an NME NDA or original BLA, include the reason. For example:</i></p> <ul style="list-style-type: none"> <li>○ <i>this drug/biologic is not the first in its class</i></li> <li>○ <i>the clinical study design was acceptable</i></li> <li>○ <i>the application did not raise significant safety or efficacy issues</i></li> <li>○ <i>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</i></li> </ul>	<input checked="" type="checkbox"/> NO <input type="checkbox"/> To be determined  Reason: <i>the application did not raise significant safety or efficacy issues</i>
<ul style="list-style-type: none"> <li>• 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?</li> </ul> <p><b>Comments:</b></p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<p><b>CONTROLLED SUBSTANCE STAFF</b></p> <ul style="list-style-type: none"> <li>• Abuse Liability/Potential</li> </ul> <p><b>Comments:</b></p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE  <input type="checkbox"/> Review issues for 74-day letter
<p><b>CLINICAL MICROBIOLOGY</b></p> <p><b>Comments:</b></p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE  <input type="checkbox"/> Review issues for 74-day letter
<p><b>CLINICAL PHARMACOLOGY</b></p> <p><b>Comments:</b></p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE  <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> <li>• Clinical pharmacology study site(s) inspections(s) needed?</li> </ul>	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
<p><b>BIOSTATISTICS</b></p> <p><b>Comments:</b></p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE  <input type="checkbox"/> Review issues for 74-day letter
<p><b>NONCLINICAL (PHARMACOLOGY/TOXICOLOGY)</b></p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE

<p><b>Comments:</b></p>	<input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p><b>IMMUNOGENICITY</b> (protein/peptide products only)</p> <p><b>Comments:</b></p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p><b>PRODUCT QUALITY (CMC)</b></p> <p><b>Comments:</b></p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input checked="" type="checkbox"/> Review issues for 74-day letter
<p><b>New Molecular Entity (NDAs only)</b></p> <ul style="list-style-type: none"> <li>Is the product an NME?</li> </ul>	<input type="checkbox"/> YES <input type="checkbox"/> NO
<p><b><u>Environmental Assessment</u></b></p> <ul style="list-style-type: none"> <li>Categorical exclusion for environmental assessment (EA) requested?</li> </ul> <p><b>If no</b>, was a complete EA submitted?</p> <p><b>If EA submitted</b>, consulted to EA officer (OPS)?</p> <p><b>Comments:</b></p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO
<p><b><u>Quality Microbiology</u></b></p> <ul style="list-style-type: none"> <li>Was the Microbiology Team consulted for validation of sterilization?</li> </ul> <p><b>Comments:</b></p>	<input type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input checked="" type="checkbox"/> NO

<p><b><u>Facility Inspection</u></b></p> <ul style="list-style-type: none"> <li>• Establishment(s) ready for inspection?</li> <li>▪ Establishment Evaluation Request (EER/TBP-EER) submitted to OMPQ?</li> </ul> <p><b>Comments:</b></p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<p><b><u>Facility/Microbiology Review (BLAs only)</u></b></p> <p><b>Comments:</b></p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input checked="" type="checkbox"/> Review issues for 74-day letter
<p><b><u>CMC Labeling Review</u></b></p> <p><b>Comments:</b></p>	<input type="checkbox"/> Review issues for 74-day letter
<p><b>APPLICATIONS IN THE PROGRAM (PDUFA V) (NME NDAs/Original BLAs)</b></p> <ul style="list-style-type: none"> <li>• 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?</li> <li>• If so, were the late submission components all submitted within 30 days?</li> </ul>	<input type="checkbox"/> N/A <input type="checkbox"/> YES <input checked="" type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> <li>• What late submission components, if any, arrived after 30 days?</li> </ul>	
<ul style="list-style-type: none"> <li>• Was the application otherwise complete upon submission, including those applications where there were no agreements regarding late submission components?</li> </ul>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO

<ul style="list-style-type: none"> <li>• Is a comprehensive and readily located list of all clinical sites included or referenced in the application?</li> </ul>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> <li>• Is a comprehensive and readily located list of all manufacturing facilities included or referenced in the application?</li> </ul>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<b>REGULATORY PROJECT MANAGEMENT</b>	
<p><b>Signatory Authority:</b> Amy Egan</p> <p><b>Date of Mid-Cycle Meeting</b> (for NME NDAs/BLAs in “the Program” PDUFA V): 27 March 2015</p> <p><b>21<sup>st</sup> Century Review Milestones (see attached)</b> (listing review milestones in this document is optional):</p> <p><b>Comments:</b></p>	
<b>REGULATORY CONCLUSIONS/DEFICIENCIES</b>	
<input type="checkbox"/>	The application is unsuitable for filing. Explain why:
<input checked="" type="checkbox"/>	The application, on its face, appears to be suitable for filing.  <u>Review Issues:</u>  <input type="checkbox"/> No review issues have been identified for the 74-day letter. <input checked="" type="checkbox"/> Review issues have been identified for the 74-day letter.  <u>Review Classification:</u>  <input type="checkbox"/> Standard Review <input checked="" type="checkbox"/> Priority Review
<b>ACTIONS ITEMS</b>	
<input checked="" type="checkbox"/>	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into tracking system (e.g., chemical classification, combination product classification, orphan drug).
<input type="checkbox"/>	If RTF, notify everyone who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER).
<input type="checkbox"/>	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.
<input type="checkbox"/>	351(k) BLA/supplement: If filed, send filing notification letter on day 60

<input checked="" type="checkbox"/>	If priority review: <ul style="list-style-type: none"> <li>• notify sponsor in writing by day 60 (see CST for choices)</li> <li>• notify OMPQ (so facility inspections can be scheduled earlier)</li> </ul>
<input checked="" type="checkbox"/>	Send review issues/no review issues by day 74
<input checked="" type="checkbox"/>	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
<input checked="" type="checkbox"/>	Update the PDUFA V DARRTS page (for applications in the Program)
<input type="checkbox"/>	Other

Annual review of template by OND ADRAAs completed: September 2014



A green and yellow curved line graphic above the text.  
**Strensiq**<sup>™</sup>  
(asfotase alfa)  
for injection



BLA 125513

Filing Meeting

21 January 2015

Reference ID: 3707945

A blue and red curved line graphic above the text.  
**ALEXION**  
pharmaceuticals

# Agenda

- Team Introductions
- Application and Product Introduction
- Regulatory History
- Filing Reviews
  - Clinical
  - Nonclinical
  - Clinical Pharmacology/Pharmacometrics
  - Statistics
  - CMC
  - CMC Micro
- Confirm Review Timeline
- Discuss/Confirm AC
- Labeling

# Team Introductions

Clinical TL	Anil Rajpal
Clinical Reviewer	Carla Epps
Clinical Pharmacology TL	Yow-Ming Wang
Clinical Pharmacology	Christine Hon
Clinical Pharmacometrics	Justin Earp
Product Quality TL	Cris Ausin
Product Quality Reviewer (Drug Substance)	Joslyn Brunelle
Product Quality Reviewer (Drug Product)	Gunther Boekhoudt
Product Quality Labeling Reviewer	Jibril Abdus-Samad
Micro TL	Patricia Hughes
Micro Reviewer	Cadace Gomez-Broughton

OSE RPM	Aleksander Winiarski
OPDP (DDMAC)	TBD
DMEPA TL	Kendra Worthy
DMEPA Reviewer	Matthew Barlow
DPV Evaluator	Joel Weissfeld
TB-EER	Christina Capacci-Daniel
OSI TL	Susan Leibenhaut
Biometrics TL	Yeh-Fong Chen
Biometrics Reviewer	Benjamin Vali
Nonclinical TL	Sushanta Chakder
Nonclinical Reviewer	Dinesh Gautam

# Application Introduction

Applicant: Alexion Pharmaceuticals, Inc

Product: Long-Term Enzyme Replacement Therapy  
Asfotase alfa (human recombinant tissue nonspecific alkaline phosphatase fusion protein; ENB-0040; *STRENSIQ*)

Application

Properties: Breakthrough Therapy Designation  
(21 May 2013)

Orphan Drug Designation (ODD #08-2666)

Fast Track Designation (14 May 2009)

Referenced

IND: IND 100619

# Application Introduction

Indication: Treatment of hypophosphatasia (HPP)

Review

Priority/ Applicant has requested a Priority Review

Timeline: PDUFA V Program, Priority, 8 month clock  
Pediatric Rare Disease Voucher Requested

# Application Introduction

Submitted on a Rolling Review basis

1<sup>st</sup> Submission on 31 Mar 2014 – Quality

2<sup>nd</sup> Submission on 30 Jun 2014 – Nonclinical

3<sup>rd</sup> Submission on 23 Dec 2014 – Clinical and remaining  
components

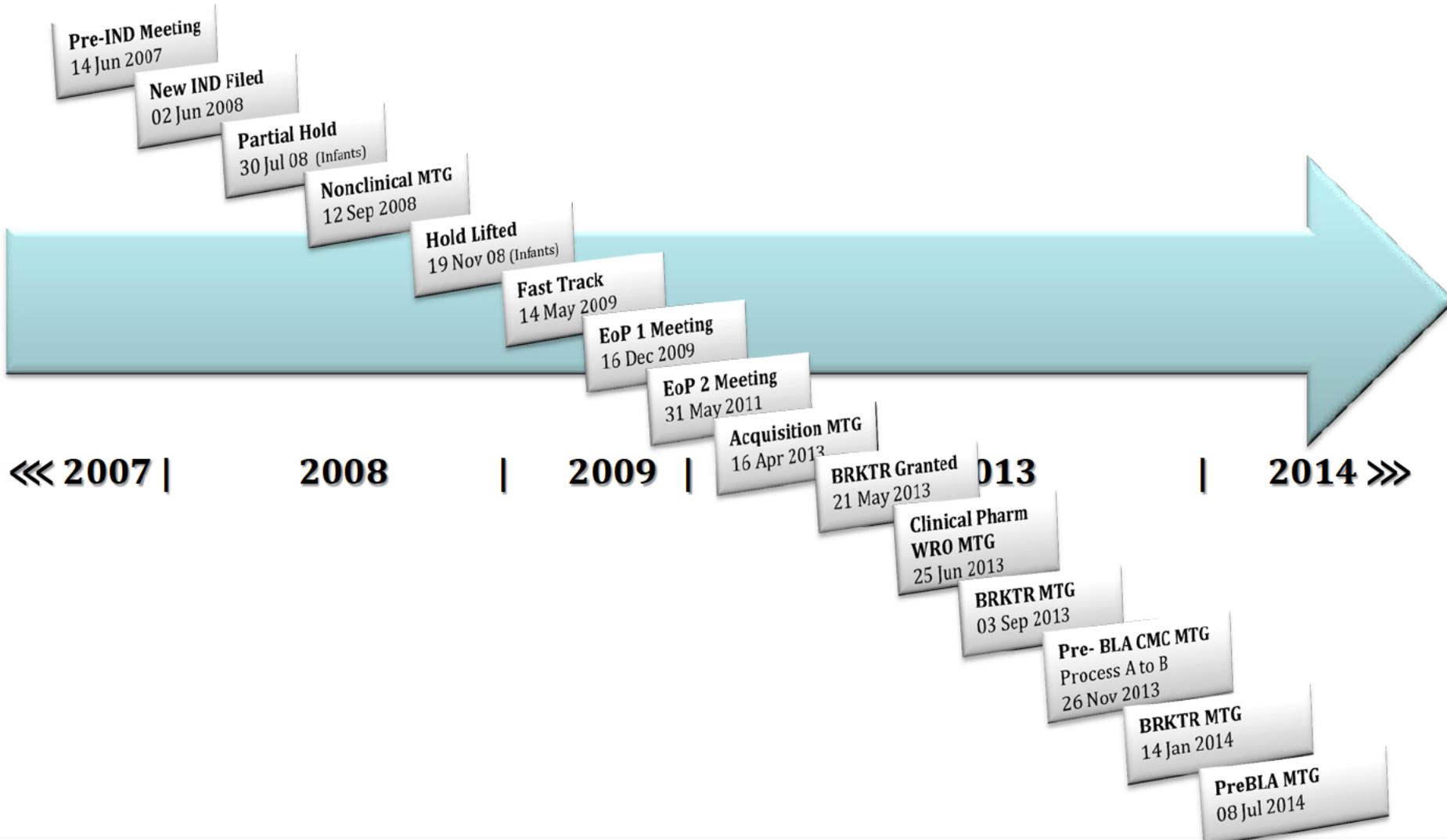
# Product Information

Fusion protein incorporating the catalytic domain of human tissue non-specific alkaline phosphatase (TNSALP; ALPL), a bone-targeting peptide (polyaspartate), and human IgG1Fc

(b) (4)

(b) (4)

# Regulatory History



## Clinical Filing Discussion

- A summary of the application relevant to the discipline
- Any deficiencies that may warrant a refusal to file decision
- Other substantive deficiencies that may have an impact on their ability to complete the review or recommend approval of the application (issues to be transmitted in the Filing Communication – 74-day letter)

# Nonclinical Filing Discussion

- A summary of the application relevant to the discipline
- Any deficiencies that may warrant a refusal to file decision
- Other substantive deficiencies that may have an impact on their ability to complete the review or recommend approval of the application (issues to be transmitted in the Filing Communication – 74-day letter)

# Clinical Pharmacology Filing Discussion

- A summary of the application relevant to the discipline
  - Slides to follow
- Any deficiencies that may warrant a refusal to file decision
  - No
- Other substantive deficiencies that may have an impact on their ability to complete the review or recommend approval of the application (issues to be transmitted in the Filing Communication – 74-day letter)
  - A few IRs and an OSI inspection
  - Slides to follow

# Summary of Clinical Pharmacology Studies

- PK, PD, and immunogenicity assessments were conducted using data from 73 subjects (15 adults and 58 pediatric subjects) in all clinical trials
- Visual assessments of the PK, PD, immunogenicity, and safety data at the individual patient level to explore the potential impact of immunogenicity on PK, PD, and safety
- NCA to determine absolute bioavailability of asfostase alfa in the adult dose-finding study ENB-001-08

# Summary of Clinical Pharmacology Studies

- Model-based assessments using pooled PK, PD, safety, and efficacy data across the 7 clinical studies
- 6 PK-PD models, 2 PK-Efficacy models

Endpoints		Phenotype
PD (Biochemical)	PPi	Infantile-, juveniles, adult-onset
	PLP	Infantile-, juveniles, adult-onset
PD (Radiologic)	RGI-C	Infantile-, juvenile-onset ( $\geq 4$ and $>13$ y.o.)
	RSS (knee, wrist)	Infantile-, juvenile-onset ( $\geq 4$ and $>13$ y.o.)
PD (Functional)	BOT-2	Juvenile-onset
	6MWT	Juvenile-onset
Efficacy	MPOMA-G	Juvenile-onset
	Survival	Severe infantile-onset

# Summary of Clinical Pharmacology Studies

- Simulations from the population PK and PK-PD models were used to justify the proposed regimens in infantile- and juvenile-onset HPP and product specifications
- Proposed dosing regimens for infantile- and juvenile-onset HPP
  - 1 mg/kg SC 6x/week
  - 2 mg/kg SC 3x/week
- Proposed product specifications

(b) (4)



# Initial Clin Pharm Findings

- **No RTF issues**
- Clinical pharmacy related review issues
  - PK comparability between drug products of different batchsize and different formulation strength
  - Validity of the PK and PD bioanalytical assays and appropriateness of the PK and PD data
  - Appropriateness of the population PK-PD/Efficacy modeling
  - Immunogenicity/safety assessment
  - Appropriateness of the model-based simulations to support dosing regimens and product specifications

## Review Issues – PK comparability

- Batchsize: [REDACTED] (b) (4)
- Formulation strength: 40 mg/mL and 100 mg/mL
- Both [REDACTED] (b) (4) and [REDACTED] (b) (4) and 40 mg/mL and 100 mg/mL drug products were used in clinical trials
- No dedicated clin pharm study to assess PK comparability
- Population PK analysis to support that the [REDACTED] (b) (4) and [REDACTED] (b) (4) are comparable; additional NCA PK analysis in Study ENB-010-10 may help assess PK comparability between the 2 products
- A biocomparability assessment of a prototype asfotase alfa formulation that is not subject of this BLA registration is currently ongoing in healthy volunteers; data from this study will become available post-filing of this BLA

## Review Issues – PK and PD Assays and Data

- Asfotase PK concentrations (in terms of enzyme activity)
  - Analyzed by 2 bioanalytical assays
  - A retrospective cross-validation exercise was performed between the 2 assays
  - Pooled for population analyses
- Inorganic pyrophosphate (PPi)
  - Collected by 3 different procedures and analyzed by 2 assays
  - A comparability study of the 2 assays were conducted
- Pyridoxal-5'-phosphate (PLP)
  - Collected by 2 different procedures and analyzed by 2 assays
  - A retrospective correlation analysis between data from 2 assays for conversion of some data

## Review Issues – PK-PD/Efficacy Modeling

- Evaluated age, weight, sex, batchsize, (b) (4) (b) (4) antidrug antibody (ADA) status, neutralizing antibody (NAb) status, PK bioanalytical assay method, renal function, liver function, and race as covariates
- Whether population PK Results are supportive of PK comparability between the (b) (4) and (b) (4) drug products is a review issue
- No assessment of the impact of formulation strength on PK-PD
- Appropriateness of the population PK-PD analyses and the results is a review issue

# Review Issues – Immunogenicity/Safety Assessment

- Formulation strength, especially administered as SC injection, may have an impact on PK and immunogenicity
- The appropriateness of the population PK approach and the analyses for immunogenicity assessment will be a review issue
- No assessment of the impact of formulation strength on immunogenicity-related safety such as the incidence and severity of the injection/infusion associated reactions

# Review Issues – Modeling-Based Simulations

- To support proposed dosing regimens
  - PK-PD models for RGI-C and RSS were developed using data from patients  $\geq 4$  y.o.; models for BOT-2, 6MWT, and MPOMA-G used juvenile-onset HPP data
  - Dose justification using simulations from these PK-PD models may not be most appropriate for severe infantile-onset HPP
  - Justification in the context of survival data and data analysis should be provided for severe infantile-onset HPP
- To support the product specifications
  - The proposed product specifications encompass wide ranges of (b) (4) and specific activity that were used in the clinical trials
  - Whether the simulations support the proposed product specifications is a review issue

## Clin Pharm IRs

- Obtain information on an ongoing biocomparability study to evaluate if the data could help assess PK comparability of the 40 mg/mL and 100 mg/mL formulations
- Perform NCA on PK data in Study ENB-010-10 to help assess the PK comparability of the (b) (4) and (b) (4) drug product
- Include formulation strength in the population PK dataset
- Assess the impact of formulation strength on PK/PD as a covariate in the population PK/PD analyses or using other appropriate analysis

## Clin Pharm IRs

- Assess the impact of formulation strength on immunogenicity related safety such as the incidence and severity of the injection/infusion associated reactions
- Provide justification for the proposed dosing regimens in the context of survival for the severe infantile-onset patient population
- OSI inspection on a PK assay method validation procedures and results

## Statistics Filing Discussion

- A summary of the application relevant to the discipline
- Any deficiencies that may warrant a refusal to file decision
- Other substantive deficiencies that may have an impact on their ability to complete the review or recommend approval of the application (issues to be transmitted in the Filing Communication – 74-day letter)

## Quality Filing Discussion

- A summary of the application relevant to the discipline
- Any deficiencies that may warrant a refusal to file decision
- Other substantive deficiencies that may have an impact on their ability to complete the review or recommend approval of the application (issues to be transmitted in the Filing Communication – 74-day letter)

# Microbial Quality and Pre-License Inspections

- Overall microbial control appears to be appropriate and FILEABLE; missing information will be requested.
- Drug substance facility inspection was conducted in September by DMA (Micro Quality) and OBP

(b) (4)

– NAI

- Drug product facility inspection will be waived

(b) (4)

– Surveillance inspection scheduled for next week

# Discuss Priority Review Plans

- 8 month clock
- MCM @ month 3
- Reviews and Labeling @ month 5
- LCM @ month 5.5
- *ACM @ month 6 (not applicable)*

## Confirm Advisory Committee is Not Needed

- *~ Month 6 (not applicable)*
- *GIDAC or EMDAC (not applicable)*

# Labeling

See [SharePoint](#)

**Receipt Date:** 23 Dec 2014

**Action Goal Date:** 23 Jul 2015

**PDUFA Goal Date:** 21 Aug 2015

**Signatory Authority:** Amy Egan

**Division Authority:** Donna Griebel

**CDTL:** Anil Rajpal

<b>Goals:</b>	
Filing Determination Date	02/21/2015
Primary Reviews Due	05/08/2015
Labeling to Sponsor	05/08/2015
CDTL Review Due	06/25/2015
DD/OD Review Due	07/23/2015

**Reviewers:**

Clinical TL	Anil Rajpal
Clinical Reviewer	Carla Epps
Clinical Pharmacology TL	Yow-Ming Wang
Clinical Pharmacology	Christine Hon
Clinical Pharmacometrics	Justin Earp
Product Quality TL	Cris Ausin
Product Quality Reviewer (Drug Substance)	Joslyn Brunelle
Product Quality Reviewer (Drug Product)	Gunther Boekhoudt
Product Quality Labeling Reviewer	Jibril Abdus-Samad
Micro TL	Patricia Hughes
Micro Reviewer	Cadace Gomez- Broughton

**Consultants:**

OSE RPM	Aleksander Winiarski
OPDP (DDMAC)	Adewale Adeleye
DMEPA TL	Kendra Worthy
DMEPA Reviewer	Matthew Barlow
DPV Evaluator	Joel Weissfeld
TB-EER	Christina Capacci- Daniel
OSI TL	Susan Leibenhaut
Biometrics TL	Yeh-Fong Chen
Biometrics Reviewer	Benjamin Vali
Nonclinical TL	Sushanta Chakder
Nonclinical Reviewer	Dinesh Gautam

**Links:**

<b>EDR:</b>	<a href="\\CDSESUB1\evsprod\BLA125513\125513.enx">\\CDSESUB1\evsprod\BLA125513\125513.enx</a>
<b>SharePoint:</b>	<a href="#">SharePoint Link</a>
<b>21<sup>st</sup> Century Desk Reference Guide</b>	<a href="#">Link</a>

**Meeting Conference Info:**

**Phone –** (b) (4)

**Web –** <https://collaboration.fda.gov/bla125513>

**Meeting Timeline:**

<b>Meeting</b>	<b>Date</b>
Filing Meeting	01/21/2015
Planning Meeting	02/02/2015
Team Meeting	Feb 27
Mid Cycle Meeting	March 27
Labeling Planning Meeting	April 07/or Skip
Labeling Meeting 1 (Quality & Nonclinical)	April 09
Labeling Meeting 2 (Clinical & Clin Pharm)	April 13
Mid Cycle Communication	April 14
Labeling Meeting 3 (Clinical & Consultants)	April 20
PMR/PMC Meeting	April 21
SCPI to Consultants	April 22
Labeling Meeting 4 (Finalize Labeling)	May 05
Primary Reviews Due	May 08
Labeling to Applicant	May 08
Pre-Late Cycle Meeting	May 19
Late Cycle Meeting Package to Applicant	May 22
Late Cycle Meeting	June 03
Wrap Up Meeting	June 23
CDTL Review Due	June 25
1 month early action	July 23
PDUFA Goal Date	August 21

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

KEVIN B BUGIN  
02/25/2015

RICHARD W ISHIHARA  
02/27/2015

# REGULATORY PROJECT MANAGER PHYSICIAN'S LABELING RULE (PLR) FORMAT REVIEW OF THE PRESCRIBING INFORMATION

**Complete for all new NDAs, BLAs, Efficacy Supplements, and PLR Conversion Labeling Supplements**

**Application:** 125513

**Application Type:** New BLA

**Name of Drug/Dosage Form:** STRENSIQ (asfotase alfa) for injection

**Applicant:** Alexion Pharmaceuticals

**Receipt Date:** 12/23/2015

**Goal Date:** 08/23/2015

## 1. Regulatory History and Applicant's Main Proposals

Asfotase alfa is a bone-targeted (b) (4) designed to address the underlying cause of hypophosphatasia (HPP), a rare, serious and potentially fatal, genetic disorder caused by loss-of-function mutations in the gene encoding tissue non-specific alkaline phosphatase.

## 2. Review of the Prescribing Information

This review is based on the applicant's submitted Word format of the prescribing information (PI). The applicant's proposed PI was reviewed in accordance with the labeling format requirements listed in the "Selected Requirements for Prescribing Information (SRPI)" checklist (see the Appendix).

## 3. Conclusions/Recommendations

SRPI format deficiencies were identified in the review of this PI. For a list of these deficiencies see the Appendix.

In addition, the following labeling issues were identified:

It appears two versions of proposed labeling, in MS Word format, were submitted with the application. In one version submitted, Highlights is in a two-column format and is one-half page length or less, which is in compliance with the formatting requirements. However, in the other, the formatting does not meet the SRPI requirements.

All SRPI format deficiencies of the PI and other labeling issues identified above will be conveyed to the applicant in the 74-day letter. The applicant will be asked to correct these deficiencies and resubmit the PI in Word format by March 13. The resubmitted PI will be used for further labeling review.

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## Appendix

## Selected Requirements of Prescribing Information

The Selected Requirement of Prescribing Information (SRPI) is a 42-item, drop-down checklist of important format elements of the prescribing information (PI) based on labeling regulations (21 CFR 201.56 and 201.57) and guidances.

---

### Highlights

See Appendix A for a sample tool illustrating the format for the Highlights.

#### HIGHLIGHTS GENERAL FORMAT

- YES** 1. Highlights (HL) must be in a minimum of 8-point font and should be in two-column format, with ½ inch margins on all sides and between columns.

**Comment:**

- YES** 2. The length of HL must be one-half page or less unless a waiver has been granted in a previous submission. The HL Boxed Warning does not count against the one-half page requirement. Instructions to complete this item: If the length of the HL is one-half page or less, select “YES” in the drop-down menu because this item meets the requirement. However, if HL is longer than one-half page, select “NO” unless a waiver has been granted.

**Comment:**

- YES** 3. A horizontal line must separate HL from the Table of Contents (TOC). A horizontal line must separate the TOC from the FPI.

**Comment:**

- YES** 4. All headings in HL must be **bolded** and presented in the center of a horizontal line (each horizontal line should extend over the entire width of the column as shown in Appendix A). The headings should be in UPPER CASE letters.

**Comment:**

- YES** 5. White space should be present before each major heading in HL. There must be no white space between the HL Heading and HL Limitation Statement. There must be no white space between the product title and Initial U.S. Approval. See Appendix A for a sample tool illustrating white space in HL.

**Comment:**

- YES** 6. Each summarized statement or topic in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contain more detailed information. The preferred format is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each summarized statement or topic.

**Comment:**

- YES** 7. Section headings must be presented in the following order in HL:

Section	Required/Optional
• Highlights Heading	Required
• Highlights Limitation Statement	Required
• Product Title	Required
• Initial U.S. Approval	Required
• Boxed Warning	Required if a BOXED WARNING is in the FPI
• Recent Major Changes	Required for only certain changes to PI*

## Selected Requirements of Prescribing Information

• <b>Indications and Usage</b>	Required
• <b>Dosage and Administration</b>	Required
• <b>Dosage Forms and Strengths</b>	Required
• <b>Contraindications</b>	Required (if no contraindications must state "None.")
• <b>Warnings and Precautions</b>	Not required by regulation, but should be present
• <b>Adverse Reactions</b>	Required
• <b>Drug Interactions</b>	Optional
• <b>Use in Specific Populations</b>	Optional
• <b>Patient Counseling Information Statement</b>	Required
• <b>Revision Date</b>	Required

\* RMC only applies to the BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS sections.

**Comment:**

### HIGHLIGHTS DETAILS

#### Highlights Heading

- YES** 8. At the beginning of HL, the following heading must be **bolded** and should appear in all UPPER CASE letters: "**HIGHLIGHTS OF PRESCRIBING INFORMATION**".

**Comment:**

#### Highlights Limitation Statement

- YES** 9. The **bolded** HL Limitation Statement must include the following verbatim statement: "**These highlights do not include all the information needed to use (insert name of drug product) safely and effectively. See full prescribing information for (insert name of drug product).**" The name of drug product should appear in UPPER CASE letters.

**Comment:**

#### Product Title in Highlights

- YES** 10. Product title must be **bolded**.

**Comment:**

#### Initial U.S. Approval in Highlights

- NO** 11. Initial U.S. Approval in HL must be **bolded**, and include the verbatim statement "**Initial U.S. Approval:**" followed by the **4-digit year**.

**Comment:** *Initial U.S. Approval in HL must include the verbatim statement "Initial U.S. Approval:" followed by the 4-digit year. Please remove "Pending" and replace with the 4-digit year.*

#### Boxed Warning (BW) in Highlights

- N/A** 12. All text in the BW must be **bolded**.

**Comment:**

- N/A** 13. The BW must have a heading in UPPER CASE, containing the word "**WARNING**" (even if more than one warning, the term, "**WARNING**" and not "**WARNINGS**" should be used) and other words to identify the subject of the warning (e.g., "**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**"). The BW heading should be centered.

## Selected Requirements of Prescribing Information

### Comment:

- N/A** 14. The BW must always have the verbatim statement “*See full prescribing information for complete boxed warning.*” This statement should be centered immediately beneath the heading and appear in *italics*.

### Comment:

- N/A** 15. The BW must be limited in length to 20 lines (this includes white space but does not include the BW heading and the statement “*See full prescribing information for complete boxed warning.*”).

### Comment:

### Recent Major Changes (RMC) in Highlights

- NO** 16. RMC pertains to only the following five sections of the FPI: BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS. RMC must be listed in the same order in HL as the modified text appears in FPI.

Comment: *As this is a New BLA, please remove this section.*

- N/A** 17. The RMC must include the section heading(s) and, if appropriate, subsection heading(s) affected by the recent major change, together with each section’s identifying number and date (month/year format) on which the change was incorporated in the PI (supplement approval date). For example, “Warnings and Precautions, Acute Liver Failure (5.1) --- 9/2013”.

### Comment:

- N/A** 18. The RMC must list changes for at least one year after the supplement is approved and must be removed at the first printing subsequent to one year (e.g., no listing should be one year older than revision date).

### Comment:

### Indications and Usage in Highlights

- N/A** 19. If a product belongs to an established pharmacologic class, the following statement is required under the Indications and Usage heading in HL: “(Product) is a (name of established pharmacologic class) indicated for (indication)”.

### Comment:

### Dosage Forms and Strengths in Highlights

- YES** 20. For a product that has several dosage forms (e.g., capsules, tablets, and injection), bulleted subheadings or tabular presentations of information should be used under the Dosage Forms and Strengths heading.

### Comment:

### Contraindications in Highlights

**YES**

## Selected Requirements of Prescribing Information

21. All contraindications listed in the FPI must also be listed in HL or must include the statement “None” if no contraindications are known. Each contraindication should be bulleted when there is more than one contraindication.

Comment:

### Adverse Reactions in Highlights

- YES** 22. For drug products other than vaccines, the verbatim **bolded** statement must be present: “**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer’s U.S. phone number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch**”.

Comment:

### Patient Counseling Information Statement in Highlights

- NO** 23. The Patient Counseling Information statement must include one of the following three **bolded** verbatim statements that is most applicable:

If a product **does not** have FDA-approved patient labeling:

- “**See 17 for PATIENT COUNSELING INFORMATION**”

If a product **has** FDA-approved patient labeling:

- “**See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling**”
- “**See 17 for PATIENT COUNSELING INFORMATION and Medication Guide**”

Comment: *A Medication Guide is proposed and therefore the title should be revised to "See 17 for PATIENT COUNSELING INFORMATION and Medication Guide"*

### Revision Date in Highlights

- YES** 24. The revision date must be at the end of HL, and should be **bolded** and right justified (e.g., “**Revised: 9/2013**”).

Comment:

## Selected Requirements of Prescribing Information

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### Contents: Table of Contents (TOC)

See Appendix A for a sample tool illustrating the format for the Table of Contents.

- YES** 25. The TOC should be in a two-column format.  
*Comment:*
- YES** 26. The following heading must appear at the beginning of the TOC: “**FULL PRESCRIBING INFORMATION: CONTENTS**”. This heading should be in all UPPER CASE letters and **bolded**.  
*Comment:*
- N/A** 27. The same heading for the BW that appears in HL and the FPI must also appear at the beginning of the TOC in UPPER CASE letters and **bolded**.  
*Comment:*
- NO** 28. In the TOC, all section headings must be **bolded** and should be in UPPER CASE.  
*Comment:* *Headings are not bolded.*
- NO** 29. In the TOC, all subsection headings must be indented and not bolded. The headings should be in title case [first letter of all words are capitalized except first letter of prepositions (through), articles (a, an, and the), or conjunctions (for, and)].  
*Comment:* *Subsection headings are not indented.*
- YES** 30. The section and subsection headings in the TOC must match the section and subsection headings in the FPI.  
*Comment:*
- YES** 31. In the TOC, when a section or subsection is omitted, the numbering must not change. If a section or subsection from 201.56(d)(1) is omitted from the FPI and TOC, the heading “FULL PRESCRIBING INFORMATION: CONTENTS” must be followed by an asterisk and the following statement must appear at the end of TOC: “\*Sections or subsections omitted from the full prescribing information are not listed.”  
*Comment:*

## Selected Requirements of Prescribing Information

### Full Prescribing Information (FPI)

#### FULL PRESCRIBING INFORMATION: GENERAL FORMAT

- YES** 32. The **bolded** section and subsection headings in the FPI must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below (section and subsection headings should be in UPPER CASE and title case, respectively). If a section/subsection required by regulation is omitted, the numbering must not change. Additional subsection headings (i.e., those not named by regulation) must also be **bolded** and numbered.

<b>BOXED WARNING</b>
<b>1 INDICATIONS AND USAGE</b>
<b>2 DOSAGE AND ADMINISTRATION</b>
<b>3 DOSAGE FORMS AND STRENGTHS</b>
<b>4 CONTRAINDICATIONS</b>
<b>5 WARNINGS AND PRECAUTIONS</b>
<b>6 ADVERSE REACTIONS</b>
<b>7 DRUG INTERACTIONS</b>
<b>8 USE IN SPECIFIC POPULATIONS</b>
<b>8.1 Pregnancy</b>
<b>8.2 Labor and Delivery</b>
<b>8.3 Nursing Mothers</b>
<b>8.4 Pediatric Use</b>
<b>8.5 Geriatric Use</b>
<b>9 DRUG ABUSE AND DEPENDENCE</b>
<b>9.1 Controlled Substance</b>
<b>9.2 Abuse</b>
<b>9.3 Dependence</b>
<b>10 OVERDOSAGE</b>
<b>11 DESCRIPTION</b>
<b>12 CLINICAL PHARMACOLOGY</b>
<b>12.1 Mechanism of Action</b>
<b>12.2 Pharmacodynamics</b>
<b>12.3 Pharmacokinetics</b>
<b>12.4 Microbiology (by guidance)</b>
<b>12.5 Pharmacogenomics (by guidance)</b>
<b>13 NONCLINICAL TOXICOLOGY</b>
<b>13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility</b>
<b>13.2 Animal Toxicology and/or Pharmacology</b>
<b>14 CLINICAL STUDIES</b>
<b>15 REFERENCES</b>
<b>16 HOW SUPPLIED/STORAGE AND HANDLING</b>
<b>17 PATIENT COUNSELING INFORMATION</b>

**Comment:**

- NO** 33. The preferred presentation for cross-references in the FPI is the section (not subsection) heading followed by the numerical identifier. The entire cross-reference should be in *italics* and enclosed within brackets. For example, “[*see Warnings and Precautions (5.2)*]” or “[*see Warnings and Precautions (5.2)*]”.

**Comment:** For example, in subsection 5.2, a reference to section 12.3 is incorrectly formatted.

## Selected Requirements of Prescribing Information

- N/A** 34. If RMCs are listed in HL, the corresponding new or modified text in the FPI sections or subsections must be marked with a vertical line on the left edge.

*Comment:*

### FULL PRESCRIBING INFORMATION DETAILS

#### FPI Heading

- YES** 35. The following heading must be **bolded** and appear at the beginning of the FPI: “**FULL PRESCRIBING INFORMATION**”. This heading should be in UPPER CASE.

*Comment:*

#### BOXED WARNING Section in the FPI

- N/A** 36. In the BW, all text should be **bolded**.

*Comment:*

- N/A** 37. The BW must have a heading in UPPER CASE, containing the word “**WARNING**” (even if more than one Warning, the term, “**WARNING**” and not “**WARNINGS**” should be used) and other words to identify the subject of the Warning (e.g., “**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**”).

*Comment:*

#### CONTRAINDICATIONS Section in the FPI

- YES** 38. If no Contraindications are known, this section must state “None.”

*Comment:*

#### ADVERSE REACTIONS Section in the FPI

- NO** 39. When clinical trials adverse reactions data are included (typically in the “Clinical Trials Experience” subsection of ADVERSE REACTIONS), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

“Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.”

*Comment:* *Please add the required text.*

- N/A** 40. When postmarketing adverse reaction data are included (typically in the “Postmarketing Experience” subsection of ADVERSE REACTIONS), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

“The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.”

*Comment:*

#### PATIENT COUNSELING INFORMATION Section in the FPI

- NO** 41. Must reference any FDA-approved patient labeling in Section 17 (PATIENT COUNSELING INFORMATION section). The reference should appear at the beginning of Section 17 and

## Selected Requirements of Prescribing Information

include the type(s) of FDA-approved patient labeling (e.g., Patient Information, Medication Guide, Instructions for Use).

**Comment:** Please add the reference.

- YES** 42. FDA-approved patient labeling (e.g., Medication Guide, Patient Information, or Instructions for Use) must not be included as a subsection under section 17 (PATIENT COUNSELING INFORMATION). All FDA-approved patient labeling must appear at the end of the PI upon approval.

**Comment:**

# Selected Requirements of Prescribing Information

## Appendix A: Format of the Highlights and Table of Contents

### HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use [DRUG NAME] safely and effectively. See full prescribing information for [DRUG NAME].

[DRUG NAME (nonproprietary name) dosage form, route of administration, controlled substance symbol]  
Initial U.S. Approval: [year]

**WARNING: [SUBJECT OF WARNING]**

*See full prescribing information for complete boxed warning.*

- [text]
- [text]

### RECENT MAJOR CHANGES

[section (X.X)] [m/year]  
[section (X.X)] [m/year]

### INDICATIONS AND USAGE

[DRUG NAME] is a [name of pharmacologic class] indicated for [text]

### DOSAGE AND ADMINISTRATION

- [text]
- [text]

### DOSAGE FORMS AND STRENGTHS

[text]

### CONTRAINDICATIONS

- [text]
- [text]

### WARNINGS AND PRECAUTIONS

- [text]
- [text]

### ADVERSE REACTIONS

Most common adverse reactions (incidence > x%) are [text].

To report SUSPECTED ADVERSE REACTIONS, contact [name of manufacturer] at [phone #] or FDA at 1-800-FDA-1088 or [www.fda.gov/medwatch](http://www.fda.gov/medwatch).

### DRUG INTERACTIONS

- [text]
- [text]

### USE IN SPECIFIC POPULATIONS

- [text]
- [text]

See 17 for PATIENT COUNSELING INFORMATION [and FDA-approved patient labeling OR and Medication Guide].

Revised: [m/year]

### FULL PRESCRIBING INFORMATION: CONTENTS\*

WARNING: [SUBJECT OF WARNING]

#### 1 INDICATIONS AND USAGE

#### 2 DOSAGE AND ADMINISTRATION

2.1 [text]

2.2 [text]

#### 3 DOSAGE FORMS AND STRENGTHS

#### 4 CONTRAINDICATIONS

#### 5 WARNINGS AND PRECAUTIONS

5.1 [text]

5.2 [text]

#### 6 ADVERSE REACTIONS

6.1 [text]

6.2 [text]

#### 7 DRUG INTERACTIONS

7.1 [text]

7.2 [text]

#### 8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

8.2 Labor and Delivery

8.3 Nursing Mothers

8.4 Pediatric Use

8.5 Geriatric Use

#### 9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

9.2 Abuse

9.3 Dependence

#### 10 OVERDOSAGE

#### 11 DESCRIPTION

#### 12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

12.2 Pharmacodynamics

12.3 Pharmacokinetics

12.4 Microbiology

12.5 Pharmacogenomics

#### 13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

13.2 Animal Toxicology and/or Pharmacology

#### 14 CLINICAL STUDIES

14.1 [text]

14.2 [text]

#### 15 REFERENCES

#### 16 HOW SUPPLIED/STORAGE AND HANDLING

#### 17 PATIENT COUNSELING INFORMATION

\*Sections or subsections omitted from the full prescribing information are not listed.

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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KEVIN B BUGIN  
02/25/2015

RICHARD W ISHIHARA  
02/27/2015