

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

125460Orig1s000

OTHER REVIEW(S)

PMR/PMC Development Template

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

NDA/BLA # BLA 125460
Product Name: Vimizim (elosulfase alfa)

PMR/PMC Description: Evaluate the long-term safety of Vimizim in adult and pediatric patients enrolled in the Morquio A Registry for a period of ten years, including but not limited to the occurrence of serious hypersensitivity reactions, anaphylaxis, and changes in antibody status (i.e., detection and titers of binding and neutralizing antibodies, and detection of IgE antibodies). Pregnancy exposure data, including maternal, neonatal and infant outcomes, will also be collected and analyzed. Include incidence rate calculations as part of long-term safety evaluation assessments to monitor and characterize risk of exposure to Vimizim. In addition, assessment of clinical outcomes (e.g., anthropometric measures, progression of skeletal deformities, frequency and time to orthopedic surgeries) will be performed. All safety, immunogenicity, and clinical outcome assessments will be conducted every 6 months. Patients previously enrolled in clinical trials MOR-005 and MOR-007 may be rolled over to this study but will be monitored using the MOR-005 and MOR-007 protocols, respectively.

PMR/PMC Schedule Milestones:	Final Protocol Submission:	<u>09/30/2014</u>
	Study Completion:	<u>09/30/2024</u>
	Final Report Submission:	<u>03/31/2025</u>
Other:	Final Protocol Submission (Updated Final Protocol for MOR-005)	<u>12/31/2014</u>
	Final Protocol Submission (Updated Final Protocol for MOR-007)	<u>03/31/2015</u>
	Interim Study Report Submission	<u>09/30/2017</u>
	Interim Study Report Submission	<u>03/31/2018</u>
		(Final report for MOR-007)
	Interim Study Report Submission	<u>09/30/2019</u>
	Interim Study Report Submission	<u>03/31/2020</u>
		(Final report for MOR-005)

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

Upon approval, Vimizim will be the only medical therapy available for patients with Mucopolysaccharidosis IVA, or Morquio A Syndrome, which is a rare, serious, life-threatening, lysosomal storage disorder. In the phase 3 placebo-controlled trial, all of the patients receiving to-be-marketed dose developed anti-drug antibodies by Week 4, and 96% developed neutralizing antibodies by Week 16. Their extension trial data up to 72 weeks showed sustained antibody response. Hypersensitivity reactions and anaphylaxis occurred in 19% and 8% of patients treated with Vimizim in premarketing clinical trials, respectively. Long-term data are needed to better understand the role of antibody development and immune tolerance on safety and clinical outcomes.

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.”

In the phase 3 trial, all of the patients receiving to-be-marketed dose developed anti-drug antibodies by Week 4, and 96% developed neutralizing antibodies by Week 16. Their extension trial data up to 72 weeks showed sustained antibody response. Hypersensitivity reactions and anaphylaxis occurred in 19% and 8% of patients treated with Vimizim in premarketing clinical trials, respectively. It is important to note that another group of MPS patients (i.e., MPS I) who developed immune reactions on enzyme replacement therapy showed declining antibody reactivity by 26 weeks and low antibody titers by 104 weeks. It is not clear whether MPS IVA patients treated with elosulfase alfa will experience similar immune tolerance with continued therapy, as they seem to have sustained or increased antibody titers after 72 weeks of treatment. Therefore, longer-term data are needed to better understand the role of antibody development and immune tolerance on safety (i.e., increased incidence of life-threatening anaphylaxis and hypersensitivity reactions) and clinical outcomes, and to identify unexpected serious risks associated with long-term Vimizim treatment. The registry should also collect and analyze pregnancy exposure data, including maternal, neonatal and infant outcomes. In nonclinical studies conducted in rats, treatment with elosulfase alfa resulted in three maternal deaths during pregnancy, dose-related stillbirths, and mortality of offspring during nursing.

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.

Evaluate the long-term safety of Vimizim in adult and pediatric patients enrolled in the Morquio A Registry for a period of ten years, including but not limited to the occurrence of serious hypersensitivity reactions, anaphylaxis, and changes in antibody status (i.e., detection and titers of binding and neutralizing antibodies, and detection of IgE antibodies). Pregnancy exposure data, including maternal, neonatal and infant outcomes, will also be collected and analyzed. Include incidence rate calculations as part of long-term safety evaluation assessments to monitor and characterize risk of exposure to Vimizim. In addition, assessment of clinical outcomes (e.g., anthropometric measures, progression of skeletal deformities, frequency and time to orthopedic surgeries) will be performed. All safety, immunogenicity, and clinical outcome assessments will be conducted every 6 months. Patients previously enrolled in clinical trials MOR-005 and MOR-007 may be rolled over to this study but will be monitored using the MOR-005 and MOR-007 protocols, respectively.

Required

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

Continuation of Question 4

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

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

Agreed upon:

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

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

- Does the study/clinical trial meet criteria for PMRs or PMCs?
 - Are the objectives clear from the description of the PMR/PMC?
 - Has the applicant adequately justified the choice of schedule milestone dates?
 - Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?
- Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

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

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

PMR/PMC Development Coordinator:

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

(signature line for BLAs)

PMR/PMC Development Template

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

NDA/BLA # BLA 125460
Product Name: Vimizin (elosulfase alfa)

PMR/PMC Description: Develop and validate an assay to determine the titer of anti-elosulfase alfa neutralizing antibodies that inhibits binding to the mannose-6-phosphate receptor. The final report will contain a summary of the validation exercise including supporting data, a summary of the development data showing assay suitability for parameters not assessed in the validation exercise, and the assay Standard Operating Procedure (SOP). This assay will be used to assess anti-elosulfase alfa neutralizing antibody titers in patient samples obtained in PMRs 1, 3, and 6.

PMR/PMC Schedule Milestones:

Final Report Submission:

03/31/2015

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

Vimizim (elosulfase alfa) will be used to treat a rare disease, Mucopolysaccharidosis Type IVA. Patients with severe phenotype generally only survive into their 20s. There is currently no treatment for MPS Type IVA. During clinical trials, almost all Vimizim-treated patients developed neutralizing antibodies against elosulfase alfa. A detailed analysis of the impact of neutralizing antibodies could not be performed because neutralizing antibody titers were not determined. In other diseases, high titer neutralizing antibodies, but not the mere presence of antibodies, was found to have clinical impact. Nevertheless, an effect of the presence of neutralizing antibodies on safety and clinical outcomes in Vimizim-treated patients was not observed. Therefore, this analysis can be done as a PMR. This PMR is to develop the assay that will be used to evaluate serum samples obtained in other PMRs.

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.”

Hypersensitivity reactions, including anaphylaxis, were observed during the clinical trial. These did not correlate with total antibody titers. These assays will be used to assess whether hypersensitivity reactions are associated with neutralizing (Nab) titers. They will also be used to evaluate whether other clinical outcomes are impacted by NAb titers.

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 assay will be used to evaluate samples obtained in the pivotal phase 3 trial MOR-004 (PMR 3). The assay will also be used to evaluate samples obtained under the clinical studies/trials described in PMRs 1 and 6.

Required

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

Continuation of Question 4

- Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
-
- Meta-analysis or pooled analysis of previous studies/clinical trials
 - Immunogenicity as a marker of safety
 - Other (provide explanation)
-

Agreed upon:

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

- Other
-

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

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

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

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

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

PMR/PMC Development Coordinator:

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

(signature line for BLAs)

PMR/PMC Development Template

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

NDA/BLA # BLA 125460
Product Name: Vimizin (elosulfase alfa)

PMR/PMC Description: Analyze anti-elosulfase alfa neutralizing antibody titers in patient samples
PMR 3 obtained in the completed MOR-004 trial.

PMR/PMC Schedule Milestones:	Final Protocol Submission:	NA
	Study Completion:	NA
	Final Report Submission:	3/31/2016
	Other: _____	NA

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

Vimizim (elosulfase alfa) will be used to treat a rare disease, Mucopolysaccharidosis Type IVA. Patients with severe phenotype generally only survive into their 20s. There is currently no treatment for MPS Type IVA. During clinical trials, almost all Vimizim-treated patients developed neutralizing antibodies against elosulfase alfa. A detailed analysis of the impact of neutralizing antibodies could not be performed because neutralizing antibody titers were not determined. In other diseases, high titer neutralizing antibodies, but not the mere presence of antibodies, was found to have clinical impact. Nevertheless, an effect of the presence of neutralizing antibodies on safety and clinical outcomes in Vimizim-treated patients was not observed. Therefore, this analysis can be done as a PMR. This PMR is to test samples from the completed MOR-004 trial using the assay developed in PMR 2.

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.”

Hypersensitivity reactions, including anaphylaxis, were observed during the clinical trial. These did not correlate with total antibody titers. These assays will be used to assess whether hypersensitivity reactions are associated with neutralizing (Nab) titers. They will also be used to evaluate whether other clinical outcomes are impacted by NAb titers

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.

Samples from the pivotal phase 3 trial (MOR-004) will be assessed for neutralizing antibody titers. The impact of antibody titers on safety and clinical outcomes will be evaluated.

Required

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

Continuation of Question 4

- Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
-
- Meta-analysis or pooled analysis of previous studies/clinical trials
 - Immunogenicity as a marker of safety
 - Other (provide explanation)
-

Agreed upon:

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

- Other
-

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

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

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

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

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

PMR/PMC Development Coordinator:

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

(signature line for BLAs)

PMR/PMC Development Template

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

NDA/BLA # BLA 125460
Product Name: Vimizin (elosulfase alfa)

PMR/PMC Description: Develop and validate an IgE assay suitable for detection of anti-elosulfase IgE antibodies in the presence of high titers of IgG. This assay will be used to assess for the presence of elosulfase alfa-specific IgE antibodies in patient samples obtained in PMRs 1, 5, and 6.
PMR 4

PMR/PMC Schedule Milestones:	Final Protocol Submission:	NA
	Study Completion:	NA
	Final Report Submission:	3/31/2015
	Other:	NA

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

Vimizim will be used to treat a rare disease, Mucopolysaccharidosis Type IVA. Patients with severe phenotype generally only survive into their 20s. There is currently no treatment for MPS Type IVA. During clinical trials, patients developed hypersensitivity reactions including anaphylaxis. The IgE assay developed by the applicant may result in false negative results because patients had high titers of IgG that were not accounted for in the assay design. Since anaphylaxis and hypersensitivity reactions can be diagnosed in the absence of an IgE assay, the inadequacy of the applicant's assay can be addressed in a PMR.

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 purpose of this study is to determine the extent of IgE-mediated anaphylactic and hypersensitivity reactions in Vimizim-treated patients. This information may be used to determine whether anti-IgE treatment would benefit some patients.

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 assay will be used to evaluate for the presence of antigen specific IgE in samples obtained in the pivotal phase 3 trial MOR-004 (PMR 5). The assay will also be used to evaluate samples obtained under the clinical studies/trials described in PMRs 1 and 6.

Required

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

Continuation of Question 4

- Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
-
- Meta-analysis or pooled analysis of previous studies/clinical trials
 - Immunogenicity as a marker of safety
 - Other (provide explanation)
-

Agreed upon:

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

- Other
-

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

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

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

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

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

PMR/PMC Development Coordinator:

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

(signature line for BLAs)

PMR/PMC Development Template

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

NDA/BLA # BLA 125460
Product Name: Vimizm (elosulfase alfa)

PMR/PMC Description: Analyze elosulfase alfa-specific IgE antibody titers in patient samples
PMR 5 obtained in the completed MOR-004 trial.

PMR/PMC Schedule Milestones:	Final Protocol Submission:	NA
	Study Completion:	NA
	Final Report Submission:	3/31/2016
	Other:	NA

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

Vimizim will be used to treat a rare disease, Mucopolysaccharidosis Type IVA. Patients with severe phenotype generally only survive into their 20s. There is currently no treatment for MPS Type IVA. During clinical trials, patients developed hypersensitivity reactions including anaphylaxis. The IgE assay developed by the applicant may result in false negative results because patients had high titers of IgG that were not accounted for in the assay design. Since anaphylaxis and hypersensitivity reactions can be diagnosed in the absence of an IgE assay, this can be addressed in a PMR.

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 this study is to evaluate serum samples collected in the MOR-004 study for the presence of elosulfase alfa-specific IgE. This information will be used to evaluate whether anaphylactic and hypersensitivity reactions observed in the study can be attributed to the presence of IgE. This information may be useful to determine whether there are patients who could benefit from anti-IgE treatment.

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 study will be to assess samples from the MOR-004 trial for the presence of IgE and to determine whether anaphylactic and hypersensitivity reactions might be IgE mediated.

Required

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

Continuation of Question 4

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

Meta-analysis or pooled analysis of previous studies/clinical trials

Immunogenicity as a marker of safety

Other (provide explanation)

Agreed upon:

Quality study without a safety endpoint (e.g., manufacturing, stability)

Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)

Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E

Dose-response study or clinical trial performed for effectiveness

Nonclinical study, not safety-related (specify)

Other

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

Does the study/clinical trial meet criteria for PMRs or PMCs?

Are the objectives clear from the description of the PMR/PMC?

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

Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

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

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

There is a significant question about the public health risks of an approved drug

There is not enough existing information to assess these risks

Information cannot be gained through a different kind of investigation

The trial will be appropriately designed to answer question about a drug's efficacy and safety, and

The trial will emphasize risk minimization for participants as the protocol is developed

PMR/PMC Development Coordinator:

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

(signature line for BLAs)

PMR/PMC Development Template

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

NDA/BLA # BLA 125460
Product Name: Vimizim (elosulfase alfa)

PMR/PMC Description: Evaluate the occurrence of serious infections associated with administration of a prophylactic immune tolerance regimen in a cohort of Morquio A syndrome patients treated with Vimizim (elosulfase alfa) who are at high risk of developing persistent neutralizing antibodies. This immune tolerance regimen will be implemented before or concomitant with the onset of Vimizim (elosulfase alfa) therapy.

PMR/PMC Schedule Milestones:	Final Protocol Submission:	<u>09/30/2016</u>
	Trial Completion:	<u>03/31/2020</u>
	Final Report Submission:	<u>09/30/2020</u>
	Other:	_____

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

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

Upon approval, Vimizim will be the only medical therapy available for patients with Mucopolysaccharidosis IVA, or Morquio A Syndrome, which is a rare, serious, life-threatening, lysosomal storage disorder. In the phase 3 placebo-controlled trial, all of the patients receiving to-be-marketed dose developed anti-drug antibodies by Week 4, and 96% developed neutralizing antibodies by Week 16. Their extension trial data up to 72 weeks showed sustained antibody response. Hypersensitivity reactions and anaphylaxis occurred in 19% and 8% of patients treated with Vimizim in premarketing clinical trials, respectively. An immune tolerance induction regimen could help mitigate the risk of hypersensitivity reaction and anaphylaxis, but carries with it a risk of serious infections. This trial will help establish whether patients receiving treatment with Vimizim (elosulfase alfa) and an immune tolerance regimen are at increased risk of serious infection.

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.”

Emerging data support that patients who develop highly sustained antibody titers may be at risk of developing anaphylaxis and hypersensitivity reactions and other effects on clinical outcomes from enzyme replacement therapy, but are able to achieve immune tolerance through immune tolerance induction therapy. Therefore, the applicant will be asked to design and implement a prophylactic immune tolerance regimen in patients who are at high risk of developing persistent anti-drug antibodies that could result in increased risk of adverse reactions and altered clinical outcomes to determine whether such a regimen increases the risk of serious infections in Vimizim (elosulfase alfa)-treated patients.

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.

Evaluate the safety of a prophylactic immune tolerance regimen in a cohort of Morquio A syndrome patients treated with Vimizim who are at high risk of developing persistent neutralizing antibody. This immune tolerance regimen will be implemented before or concomitant with onset of Vimizim therapy.

Required

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

Continuation of Question 4

- Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
-
- Meta-analysis or pooled analysis of previous studies/clinical trials
 - Immunogenicity as a marker of safety
 - Other (provide explanation)
-

Agreed upon:

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

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

- Does the study/clinical trial meet criteria for PMRs or PMCs?
 - Are the objectives clear from the description of the PMR/PMC?
 - Has the applicant adequately justified the choice of schedule milestone dates?
 - Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?
- Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

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

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

PMR/PMC Development Coordinator:

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

(signature line for BLAs)

PMR/PMC Development Template: 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

BLA #	125460
Product Name:	elosulfase alfa
PMC #7 Description:	Develop and implement, as a release and stability test method, a potency assay that measures the K_m and k_{cat} of elosulfase alfa formulated bulk drug substance (FBDS) and drug product (DP) using a physiologically relevant substrate.
PMC Schedule Milestones:	Study Completion: <u>06/30/2015</u> Final Report Submission: <u>09/30/2015</u>
PMC #8 Description:	Revise the RP-HPLC test method used for elosulfase alfa FBDS and DP release and stability testing in order to improve baseline resolution between (b) (4) peak. The revised specification together with the validation report will be submitted to your BLA in accordance with 21 CFR 601.12.
PMC Schedule Milestones:	Study Completion: <u>06/30/2015</u> Final Report Submission: <u>09/30/2015</u>
PMC #9 Description:	Demonstrate that SEC-HPLC is able to measure the true aggregate content, using an orthogonal test method and testing in a side by side analysis samples of Vimizim that have been subjected to forced degradation conditions.
PMC Schedule Milestones:	Study Completion: <u>09/30/2014</u> Final Report Submission: <u>01/31/2015</u>
PMC #10 Description:	Include parallel line analysis as an additional system suitability criterion for the cellular uptake assay.
PMC Schedule Milestones:	Study Completion: <u>06/30/2014</u> Final Report Submission: <u>09/30/2014</u>
PMC #11 Description:	Include quantitative system suitability criteria for retention time, number of peaks and relative peak heights in the peptide map assay.
PMC Schedule Milestones:	Study Completion: <u>06/30/2014</u> Final Report Submission: <u>09/30/2014</u>

- **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 FDA 2013 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 analytical methods and their corresponding acceptance criteria are already in place allowing for approval of the BLA. However, optimization is necessary for the following test methods: determination of kinetic parameters, RP-HPLC, SEC-HPLC, cellular uptake, and peptide mapping.

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

The sponsor should: (i) improve the assay capability of the RP-HPLC test method to resolve the signals corresponding to main product and its impurities; (ii) develop a more appropriate substrate to determine kinetic parameters; (iii) confirm the accuracy of the results reported by SEC-HPLC; (iv) improve the determination of system suitability from the cellular uptake assay, and (v) improve the determination of system suitability of the peptide mapping test method. These developments will allow BioMarin to confirm that they have appropriate control on their manufacturing process.

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:

BioMarin will continue to develop a physiologically relevant substrate, to be used to measure elosulfase alfa kinetic enzymatic parameters K_m and k_{cat} , and use this assay for drug substance and drug product release and stability testing.

The resolution of the main peak and impurities is poor, and this leads to difficulties in measuring the individual peaks. BioMarin will implement improvements in the assay capabilities of the RP-HPLC test method that will allow better baseline resolution in the RP-HPLC chromatograms or will identify and develop an alternate test method, which can identify the substances found in the ^{(b) (4)} peaks seen in the existing RP-HPLC method.

BioMarin will demonstrate that the SEC-HPLC test method is able to appropriately measure the amount of aggregates present in Vimizim samples subjected to forced degradation conditions.

BioMarin will add the parallel line analysis as an additional system suitability criterion for the Vimizim cellular uptake assay.

BioMarin will perform a retrospective evaluation of historical peptide map results and establish appropriate quantitative system suitability criteria for the peptide mapping assay.

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?

PMR/PMC Development Coordinator:

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

(signature line for BLAs 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

BLA # 125460
Product Name: elosulfase alfa

PMC #12 Description: Add cellular uptake as a release assay for drug product and establish an appropriate acceptance criterion when a statistically significant number of drug product lots is tested.

PMC Schedule Milestones: Final Report Submission: 04/30/2014

- **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 FDA AA 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 sponsor currently measures the cellular uptake of drug substance and controls drug product potency measuring enzymatic activity, glycosylation profile, and formylglycine content. In order to improve control of Vimizim drug product, the sponsor needs to determine its cellular uptake as part of the drug product release protocol.

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

BioMarin should measure cellular uptake of the final product to ensure consistency in this quality attribute. This change in the DP release protocol will allow BioMarin to confirm that they have appropriate control on their manufacturing process.

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:

BioMarin will add the cellular uptake assay as a drug product release assay for future drug product lots. The original acceptance criterion will be the same as that of the formulated bulk drug substance. Upon manufacture and testing of a statistically significant number of commercial drug product lots, the sponsor will re-evaluate the acceptance criterion.

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?

PMR/PMC Development Coordinator:

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

(signature line for BLAs 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

BLA # 125460
Product Name: elosulfase alfa

PMC #13 Description: Conduct studies to understand the mechanism of low endotoxin recovery in the formulated bulk drug substance and drug product. These studies should investigate the endotoxin degradation or association pathway and determine whether or not depyrogenation is reversible (and if so, the conditions under which depyrogenation is reversible). Based on the results of these studies, modify the endotoxin release test and/or determine the suitability of alternative endotoxin test methods.

PMC Schedule Milestones: Study Completion: 3/31/2015
Final Report Submission: 9/30/2015

PMC #14 Description: Provide summary data and the associated reports for the endotoxin recovery studies performed under protocols QC-1209-M and QC-1224-M.

PMC Schedule Milestones: Study Completion: Completed
Final Report Submission: 4/30/2014

PMC #15 Description: Conduct an additional study comparing rabbit pyrogen and LAL test results. The study should include formulated bulk drug substance spiked with 20 EU/ml and 100 EU/ml endotoxin. The time points and controls should be the same as for the previous studies.

PMC Schedule Milestones: Study Completion: 11/30/2014
Final Report Submission: 1/31/2015

- **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 FDA 21 CFR 314.101 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 endotoxin release test method underreports the amount of endotoxin spike solution added to undiluted formulated drug substance or the final drug product (low endotoxin recovery). Data provided thus far suggest that the endotoxin spike solution is rendered non-pyrogenic over time in the undiluted product. Although additional studies should be conducted, these studies are not required pre-approval because: (1) the test method accurately measures endotoxin in in-process intermediates up to the final formulation step in the drug substance manufacturing process; (2) the amount of endotoxin present immediately before the final formulation step is a specification reported on the drug substance Certificate of Analysis; (3) the drug product manufacturing process has controls in place that are expected to minimize introduction of endotoxin; and (4) the data provided thus far suggest that endotoxin is rendered non-pyrogenic in the product over time.

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

The sponsor should: (1) repeat the study comparing the endotoxin release test method to the rabbit pyrogen test; (2) conduct studies to better understand the mechanism of low endotoxin recovery in the product; (3) determine whether alternative endotoxin test methods can accurately detect endotoxin in the product; and (4) modify or change the endotoxin test method if a more accurate method is identified. The PMC studies will (1) clarify the relationship between low endotoxin recovery and pyrogenicity in this product, and (2) may lead to the identification or development of a more accurate endotoxin release test method.

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:

BioMarin will repeat the comparison study for the endotoxin release test method and the rabbit pyrogen test method to clarify the relationship between low endotoxin recovery and pyrogenicity of the product.

BioMarin will submit PMC final study reports for the endotoxin recovery studies that were completed near the end of the review cycle and will continue to investigate low endotoxin recovery in formulated elosulfase alfa. BioMarin will modify or change the endotoxin release test method based on data from the new studies, if applicable.

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?

PMR/PMC Development Coordinator:

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

(signature line for BLAs only)

PMR/PMC Development Template

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

NDA/BLA # BLA 125460
Product Name: Vimizim (elosulfase alfa)

PMR/PMC Description: Provide results from protocol PVP-101037 (b) (4)
PMC 16 (b) (4) to be executed during the 2014 manufacturing campaign.

PMR/PMC Schedule Milestones:	Final Protocol Submission:	NA
	Study/Trial Completion:	03/31/2015
	Final Report Submission:	06/30/2015
	Other:	NA

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

The (b) (4) protocol states that the validation will be conducted two parts: (1) summary of the existing validation data supporting microbial control of the rhGALNS manufacturing process and (2) the microbial analysis of in-process intermediate samples collected following the maximum (b) (4). Part 1 of the validation plan has already been completed as the existing microbial control data has been submitted with the original BLA. Part 2 of the protocol will have to be completed during the next manufacturing campaign scheduled for 2014 which is beyond the review timeline.

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 this study is to analyze in-process samples collected at the beginning and after maximum (b) (4) for bioburden and endotoxin. Testing will be completed by the quality control personnel and evaluated based on in-process alert and action limits. The results will be used to demonstrate microbial control during hold times. This is not a FDAAA PMR.

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 sponsor has agreed to complete the (b) (4) (PVP-101037) and provide results from samples collected during the 2014 manufacturing campaign.

Required

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

Continuation of Question 4

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

Meta-analysis or pooled analysis of previous studies/clinical trials

Immunogenicity as a marker of safety

Other (provide explanation)

Agreed upon:

Quality study without a safety endpoint (e.g., manufacturing, stability)

Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)

Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E

Dose-response study or clinical trial performed for effectiveness

Nonclinical study, not safety-related (specify)

Other

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

Does the study/clinical trial meet criteria for PMRs or PMCs?

Are the objectives clear from the description of the PMR/PMC?

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

Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

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

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

There is a significant question about the public health risks of an approved drug

There is not enough existing information to assess these risks

Information cannot be gained through a different kind of investigation

The trial will be appropriately designed to answer question about a drug's efficacy and safety, and

The trial will emphasize risk minimization for participants as the protocol is developed

PMR/PMC Development Coordinator:

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

(signature line for BLAs)

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

/s/

JESSICA J LEE
02/14/2014

Therapeutic Biological Establishment Evaluation Request (TB-EER) Form

Instructions:

The review team should email this form to the email account "CDER-TB-EER" to submit:

- 1) an initial TB-EER within 10 business days of the application filing date
- 2) a final TB-EER 15-30 days prior to the action date

Note: All manufacturing³ locations named in the pending submission, whether contract facilities or facilities owned by the applicant, should be listed on this form. For bundled supplements, one TB-EER to include all STNs should be submitted.

APPLICATION INFORMATION

PDUFA Action Date: February 28, 2014; **Action may be taken as early as January 31, 2014**

Applicant Name: Biomarin Pharmaceutical Inc.

U.S. License #: 1649

STN(s):125460/0

Product: Vimizim® (elosulfase alfa)

Short summary of application: New BLA

FACILITY INFORMATION

Manufacturing Location: Novato, CA
Firm Name: BioMarin Pharmaceutical Inc.
Address: Novato Campus
46 Galli Drive
Novato, CA 94949

FEI: 3004079983

Short summary of manufacturing activities performed: (b) (4)

This site was inspected by SAN-DO from June 24 – 28, 2013 and classified NAI. This was a PLI and a routine CGMP surveillance inspection covering elosulfase alfa drug substance manufacturing and testing operations. The BTP and CTX profiles were updated and are acceptable.

Manufacturing Location: St. Paul, MN

Firm Name: [REDACTED] (b) (4)
Address: [REDACTED]
FEI: [REDACTED]
Short summary of manufacturing activities performed: [REDACTED] (b) (4)

This site was inspected by MIN-DO from May 16 – 17, 2012 and classified NAI. This was a routine CGMP surveillance inspection covering drug product testing operations. The CTL profile was updated and is acceptable.

Manufacturing Location: [REDACTED] (b) (4)
Firm Name: [REDACTED]
Address: [REDACTED]
FEI: [REDACTED]
Short summary of manufacturing activities performed: [REDACTED] (b) (4)

This site was inspected by PHI-DO from August 20 – 24, 2012 and classified NAI. This was a routine CGMP surveillance inspection covering biotech drug testing operations. The CTX profile was updated and is acceptable.

Manufacturing Location: [REDACTED] (b) (4)
Firm Name: [REDACTED]
Address: [REDACTED]
FEI: [REDACTED]
Short summary of manufacturing activities performed: [REDACTED] (b) (4)

This site was inspected by BLT-DO from June 20 – July 3, 2012 and classified VAI. This was a routine CGMP surveillance inspection covering biotech drug testing operations. The CTL profile was updated and is acceptable.

Manufacturing Location: [REDACTED] (b) (4)
Firm Name: [REDACTED]
Address: [REDACTED]
FEI: [REDACTED]
Short summary of manufacturing activities performed: [REDACTED] (b) (4)

This site was inspected by IOG from October 21 – 28, 2013. This inspection offered CGMP coverage of biotech drug product manufacturing operations. No issues were cited on a 483. The field recommendation for this inspection has been reviewed by DIDQ. On

the basis of that review, DIDQ does not oppose approval of this supplement from a CGMP perspective. However, the approval of this supplement does not preclude the FDA from other actions related to the ongoing evaluation of this site.

Manufacturing Location:
Firm Name:
Address:

(b) (4)

FEI:

Short summary of manufacturing activities performed:

(b) (4)

This site was inspected by IOG from December 2 – 5, 2013 and classified VAI. This was a routine CGMP surveillance inspection covering (b) (4)
The BTP profile was updated and is acceptable.

Manufacturing Location:
Firm Name:
Address:

(b) (4)

FEI:

Short summary of manufacturing activities performed:

(b) (4)

This site was inspected by IOG from July 9 – 17, 2012 and classified NAI. This was a routine CGMP surveillance inspection covering biotech drug product testing operations. The (b) (4) profile was updated and is acceptable.

Manufacturing Location:
Firm Name:
Address:

(b) (4)

FEI:

Short summary of manufacturing activities performed:

(b) (4)

This site was inspected by IOG from December 2 – 5, 2013 and classified VAI. This was a routine CGMP surveillance inspection covering (b) (4)
The BTP profile was updated and is acceptable.

Manufacturing Location:
Firm Name:
Address:

(b) (4)

(b) (4)
FEI:
Short summary of manufacturing activities performed: sterility (b) (4)

This site was inspected by IOG from March 11 – 14, 2013 and classified NAI. This was a routine CGMP surveillance inspection covering drug testing operations. The CTL profile was updated and is acceptable.

Manufacturing Location: Ireland
Firm Name: BioMarin Manufacturing Ireland Ltd.
Address: Shanbally, Ringaskiddy,
Co. Cork, Ireland
FEI: 3010085632
Short summary of manufacturing activities performed: (b) (4)

This site was inspected by IOG from July 22 – 23, 2013 and classified NAI. This was a PLI covering Vimizim drug product testing and quality unit operations. The BTP profile was updated and is acceptable.

(b) (4)
Manufacturing Location:
Firm Name:
Address:
FEI:
Short summary of manufacturing activities performed: (b) (4)

This site was inspected by IOG from February 23 – 24, 2011 and classified VAI. This was a routine CGMP surveillance inspection covering biotech (b) (4)
(b) (4) The (b) (4)) was updated and is acceptable.

(b) (4)
Manufacturing Location:
Firm Name:
Address:
FEI:
Short summary of manufacturing activities performed: (b) (4)

This site was inspected by CHI-DO from August 26 – 30, 2013 and classified NAI. This was a routine CGMP surveillance inspection covering (b) (4) (b) (4) The (b) (4) profile (b) (4) was updated and is acceptable.

OVERALL RECOMMENDATION

There are no pending or ongoing compliance actions that prevent approval of this supplement.

³ The regulations at 21 C.F.R. § 207.3(a)(8) defines “manufacturing or processing” as “the manufacture, preparation, propagation, compounding, or processing of a drug or drugs as used in section 510 of the act [21 U.S.C. § 360] and is the making by chemical, physical, biological, or other procedures of any articles that meet the definition of drugs in section 201(g) of the act. The term includes manipulation, sampling, testing, or control procedures applied to the final product or to any part of the process. The term also includes repackaging or otherwise changing the container, wrapper, or labeling of any drug package to further the distribution of the drug from the original place of manufacture to the person who makes final delivery or sale to the ultimate consumer.”

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/s/

RANJANI PRABHAKARA
02/14/2014

MEMORANDUM

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

DATE: February 07, 2014

TO: Donna Griebel, M.D.
Director
Division of Gastroenterology and Inborn Errors
Products (DGIEP)
Office of Drug Evaluation III
Office of New Drugs

FROM: Sripal R. Mada, Ph.D.
TL (Acting), GLP Branch
Division of Bioequivalence and GLP Compliance (DBGC)
Office of Scientific Investigations (OSI)

THROUGH: Charles Bonapace, Pharm.D.
Chief (Acting), GLP Branch
Division of Bioequivalence and GLP Compliance
Office of Scientific Investigations

William H. Taylor, Ph.D.
Director
Division of Bioequivalence and GLP Compliance
Office of Scientific Investigations

SUBJECT: **Cancellation of inspection**, BLA 125-460, Elosulfase
Alfa from BioMarin Pharmaceutical Inc., USA

The Division of Gastroenterology and Inborn Errors Products (DGIEP) requested an inspection of the analytical site on May 24, 2013. The Division of Bioequivalence and GLP Compliance discussed the inspection with the Office of Clinical Pharmacology (OCP) on January 29, 2014 and reached an agreement to cancel the analytical site inspection at Bioanalytical Testing, **BioMarin Pharmaceutical Inc., 95 Digital Drive, Novato, CA 94949** for the following assay validation study:

BMN110-12-017: "Detection of BMN110 in Human K3EDTA Plasma using a Ligand Binding Assay"

Page 2 - BLA 125-460, Elosulfase Alfa from BioMarin
Pharmaceutical Inc., USA

Sripal R. Mada, Ph.D.
GLP Branch, DBGLPC, OSI

cc:

CDER OSI PM TRACK

OSI/Moreno

OSI/DBGLPC/Taylor/Dejernett

OSI/DBGC/GLPB/Mada/Bonapace

OSI/DBGC/BB/Haidar

OMPT/CDER/OND/ODEIII/DGIEP/Ford/Griebel

OMPT/CDER/OTS/OCP/Hon/Wang

Draft: SRM 02/05/2014

Edit: CB 02/06/2014

File: BE6668; O:\BE\EIRCOVER\125460.bio.elo.doc

FACTS: Not assigned

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/s/

SRIPAL R MADA
02/07/2014

CHARLES R BONAPACE
02/07/2014

SEALD Director Sign-Off Review of the End-of-Cycle Prescribing Information: Outstanding Format Deficiencies

Product Title¹	Vimizim™ (elosulfase alfa), concentrate for infusion
Applicant	BioMarin Pharmaceutical Inc.
Application/Supplement Number	BLA 125460
Type of Application	Original Submission
Indication(s)	For patients with Mucopolysaccharidosis type IVA (MPS IVA; Morquio A syndrome)
Office/Division	ODE III/DGIEP
Division Project Manager	Elizabeth Ford
Date FDA Received Application	May 28, 2013
Goal Date	February 28, 2014
Date PI Received by SEALD	January 8, 2014
SEALD Review Date	January 9, 2014
SEALD Labeling Reviewer	Jeanne M. Delasko
Acting SEALD Division Director	Sandra Kweder

¹ Product Title that appears in draft agreed-upon prescribing information (PI)

This Study Endpoints and Labeling Development (SEALD) Director sign-off review of the end-of-cycle, prescribing information (PI) for important format items reveals **outstanding format deficiencies** that should be corrected before taking an approval action. After these outstanding format deficiencies are corrected, the SEALD Director will have no objection to the approval of this PI.

The Selected Requirements of Prescribing Information (SRPI) is a checklist of 42 important format PI items based on labeling regulations [21 CFR 201.56(d) and 201.57] and guidances. The word “must” denotes that the item is a regulatory requirement, while the word “should” denotes that the item is based on guidance. Each SRPI item is assigned with one of the following three responses:

- **NO:** The PI does not meet the requirement for this item (**deficiency**).
- **YES:** The PI meets the requirement for this item (**not a deficiency**).
- **N/A:** This item does not apply to the specific PI under review (**not applicable**).

Selected Requirements of Prescribing Information

Highlights

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

HIGHLIGHTS GENERAL FORMAT and HORIZONTAL LINES IN THE PI

- 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 (the HL Boxed Warning does not count against the one-half page requirement) unless a waiver has been granted in a previous submission (e.g., the application being reviewed is an efficacy supplement).

Instructions to complete this item: If the length of the HL is one-half page or less, then select “YES” in the drop-down menu because this item meets the requirement. However, if HL is longer than one-half page:

➤ **For the Filing Period:**

- *For efficacy supplements:* If a waiver was previously granted, select “YES” in the drop-down menu because this item meets the requirement.
- *For NDAs/BLAs and PLR conversions:* Select “NO” because this item does not meet the requirement (deficiency). The RPM notifies the Cross-Discipline Team Leader (CDTL) of the excessive HL length and the CDTL determines if this deficiency is included in the 74-day or advice letter to the applicant.

➤ **For the End-of-Cycle Period:**

- Select “YES” in the drop down menu if a waiver has been previously (or will be) granted by the review division in the approval letter and document that waiver was (or will be) 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.

Selected Requirements of Prescribing Information

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

- NO** 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: For the HL Limitation Statement, the name of the drug product should appear as "VIMIZIM" (i.e., upper case letters), not "Vimizim."

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: Insert 4-digit year (i.e., 2014), not "xxx."

Selected Requirements of Prescribing Information

Boxed Warning (BW) in Highlights

- YES** 12. All text in the BW must be **bolded**.
Comment:
- YES** 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.
Comment:
- YES** 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:
- YES** 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

- N/A** 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:
- 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

- YES** 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

- N/A** 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.

Selected Requirements of Prescribing Information

Comment:

Contraindications in Highlights

- YES** 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

- YES** 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:

Revision Date in Highlights

- NO** 24. The revision date must be at the end of HL, and should be **bolded** and right justified (e.g., “**Revised: 9/2013**”).

Comment: *Insert revision date, not "xx/xxx." If approved in February, revision date will be 2/2014.*

Selected Requirements of Prescribing Information

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:
- YES** 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:
- YES** 28. In the TOC, all section headings must be **bolded** and should be in UPPER CASE.
Comment:
- YES** 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:
- YES** 30. The section and subsection headings in the TOC must match the section and subsection headings in the FPI.
Comment:
- NO** 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: This statement must appear at the END of the TOC (i.e., right justified, below section 17). It appears left justified below subsection 6.2. "Right justify" statement so that it is correctly placed. Also, the words "Full Prescribing Information" should be "full prescribing information" (i.e., use lower case letters "f" "p" and "i").

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.

BOXED WARNING
1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
6 ADVERSE REACTIONS
7 DRUG INTERACTIONS
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 (by guidance)
12.5 Pharmacogenomics (by guidance)
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology
14 CLINICAL STUDIES
15 REFERENCES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

Comment:

- YES** 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:

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

- YES** 36. In the BW, all text should be **bolded**.

Comment:

- YES** 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

- YES** 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:

- 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

- N/A** 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:

- N/A** 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]
- [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.

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

- 1.1 [text]
- 1.2 [text]

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.

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

/s/

JEANNE M DELASKO
01/09/2014

ERIC R BRODSKY
01/09/2014

I agree. Eric Brodsky, SEALD labeling team leader, signing for Sandra Kweder, acting SEALD Division Director.

**Determining When Pre-License / Pre-Approval Inspections are Necessary
Inspection Waiver Memorandum**

Date: 14 November 2013

From: Colleen Thomas, Ph.D., OC/OMPQ/DGMPA/BMAB
Richard Ledwidge, Ph.D., OPS/OBP/DTP

To: BLA File, STN 125460/0

Endorsed: Patricia F. Hughes, Ph.D., Team Leader, CDER/OC/OMPQ/DGMPA/BMAB

Subject: Recommendation to waive a pre-license inspection

Applicant: BioMarin Pharmaceutical, Inc.

Facility: (b) (4)

Product: Vimizim™ (elosulfase alfa)

Dosage: Sterile, preservative-free 1 mg/ml solution for infusion supplied in single-use vials. The drug product is diluted with 0.9% Sodium Chloride Injection (USP) and then administered by intravenous infusion.

Indication: Treatment of Mucopolysaccharidosis Type IVA (Morquio A syndrome)

Waiver Recommendation

We recommend that the pre-approval inspection of the (b) (4) which manufactures Vimizim drug product be waived. The site was inspected by IOG from 9-17 July 2012 and classified NAI. This was a routine GMP surveillance inspection covering biotech drug product manufacturing and testing. The (b) (4) profile was updated and is acceptable.

Summary

BLA 125460 was submitted on 29 March 2013 to license elosulfase alfa (recombinant human N-acetylgalactosamine-6-sulfatase) for treatment of Mucopolysaccharidosis Type IVA (Morquio A syndrome). Elosulfase alfa was granted Orphan Drug Designation. The drug substance is produced in CHO cells at the BioMarin site located in Novato, CA. The drug product is a sterile, preservative-free 1 mg/ml solution for infusion supplied in single-use vials. The solution is diluted in 0.9% (w/v) sodium chloride prior to administration. The drug product is manufactured by (b) (4)

Facility Information

Vimizim drug product is manufactured under contract at the (b) (4). Vimizim drug product is manufactured by (b) (4). The facility is designed and licensed for multi-product cGMP manufacturing. (b) (4) uses facility and equipment design features, operating procedures, in process controls, training, and changeover to prevent contamination and cross-contamination. Other products manufactured in the same clean room as Vimizim include (b) (4). The (b) (4) does not handle beta-lactams, cytotoxic products, or products containing live or attenuated viruses or microorganisms.

The following information is provided in support of waiving the pre-approval inspection:

1. *The manufacturer does not hold an active U.S. license, or in the case of a contract manufacturer, is not approved for use in manufacturing a licensed product.*
 - a. The (b) (4) site located in (b) (4) will manufacture Vimizim drug product which is the subject of BLA 125460 that is currently under review at the Agency.
 - b. The (b) (4) is approved for manufacturing (b) (4) which is a licensed product.
2. *FDA has not inspected the establishment in the last 2 years.*

The (b) (4) was inspected by IOG from 9-17 July 2012 and classified NAI. This was a routine GMP surveillance inspection covering biotech drug product manufacturing and testing. The (b) (4) profile was updated and is acceptable.
3. *The previous inspection revealed significant GMP deficiencies in areas related to the processes in the submission (similar processes) or systematic problems, such as QC/QA oversight.*

The July 2012 inspection of the site was classified NAI and acceptable for the (b) (4) profile. The previous drug inspection was conducted in 2010 and was classified VAI.
4. *The establishment is performing significant manufacturing step(s) in new (unlicensed) areas using different equipment (representing a process change). This would include areas that are currently dedicated areas that have not been approved as multi-product facilities/buildings/areas.*

The (b) (4) is approved to manufacture multiple products. Vimizim is manufactured using standard (b) (4).
5. *The manufacturing process is sufficiently different (new production methods, specialized equipment or facilities) from that of other approved products produced by the establishment. Point to consider:*

Vimizim is manufactured using (b) (4)

Signatures:

Colleen Thomas, Ph.D.
OC/OMPQ/DGMPA/BMAB

Richard Ledwidge, Ph.D.
OPS/OBP/DTP

Clearance Routing

Emanuela Lacana, Ph.D.
Lead Biologist, Division of Therapeutic Proteins, Office of Biotechnology Products, Office of
Pharmaceutical Science, CDER

David Doleski,
Director, Division of Good Manufacturing Practice Assessment,
Office of Manufacturing and Product Quality, Office of Compliance, CDER

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/s/

COLLEEN THOMAS
11/18/2013

RICHARD LEDWIDGE
11/18/2013

EMANUELA LACANA
11/18/2013

JOSEPH D DOLESKI
11/26/2013

**Determining When Pre-License / Pre-Approval Inspections are Necessary
Inspection Waiver Memorandum**

Date: 14 November 2013

From: Colleen Thomas, Ph.D., OC/OMPQ/DGMPA/BMAB
Richard Ledwidge, Ph.D., OPS/OBP/DMA

To: BLA File, STN 125460/0

Endorsed: Patricia F. Hughes, Ph.D., Team Leader, CDER/OC/OMPQ/DGMPA/BMAB

Subject: Recommendation to waive a pre-license inspection

Applicant: BioMarin Pharmaceutical, Inc.

Facility: (b) (4)

Product: Vimizim™ (elosulfase alfa)

Dosage: Sterile, preservative-free 1 mg/ml solution for infusion supplied in single-use vials. The drug product is diluted with 0.9% Sodium Chloride Injection (USP) and then administered by intravenous infusion.

Indication: Treatment of Mucopolysaccharidosis Type IVA (Morquio A syndrome)

Waiver Recommendation

We recommend that the pre-approval inspection of the (b) (4) which manufactures Vimizim drug product be waived. The site was inspected by IOG from 17-20 July 2012 and classified NAI. This was a routine GMP surveillance inspection covering biotech drug product manufacturing and testing. The (b) (4) profile was updated and is acceptable.

Summary

BLA 125460 was submitted on 29 March 2013 to license elosulfase alfa (recombinant human N-acetylgalactosamine-6-sulfatase) for treatment of Mucopolysaccharidosis Type IVA (Morquio A syndrome). Elosulfase alfa was granted Orphan Drug Designation. The drug substance is produced in CHO cells at the BioMarin site located in Novato, CA. The drug product is a sterile, preservative-free 1 mg/ml solution for infusion supplied in single-use vials. The solution is diluted in 0.9% (w/v) sodium chloride prior to administration. The drug product is manufactured by (b) (4)

Facility Information

Vimizim drug product is manufactured under contract at one of the (b) (4)
(b) (4) Vimizim drug product is manufactured by (b) (4)

The facility is designed and licensed for multi-product cGMP manufacturing. (b) (4) uses facility and equipment design features, operating procedures, in process controls, training, and changeover to prevent contamination and cross-contamination. Other products manufactured in the same clean room as Vimizim include (b) (4)

The (b) (4) facility does not handle beta-lactams, cytotoxic products, or products containing live or attenuated viruses or microorganisms.

The following information is provided in support of waiving the pre-approval inspection:

1. *The manufacturer does not hold an active U.S. license, or in the case of a contract manufacturer, is not approved for use in manufacturing a licensed product.*
 - a. The (b) (4) site located in (b) (4) will manufacture Vimizim drug product which is the subject of BLA 125460 that is currently under review at the Agency.
 - b. The (b) (4) is approved for manufacturing of products such as (b) (4) which is an NDA biotech product.
2. *FDA has not inspected the establishment in the last 2 years.*

The (b) (4) was inspected by IOG from 17-20 July 2012 and classified NAI. This was a routine GMP surveillance inspection covering biotech drug product manufacturing and testing. The (b) (4) profile was updated and is acceptable.
3. *The previous inspection revealed significant GMP deficiencies in areas related to the processes in the submission (similar processes) or systematic problems, such as QC/QA oversight.*

The July 2012 inspection of the site was classified NAI and acceptable for the (b) (4) profile. The previous drug inspection was conducted in 2010 and was classified VAI.
4. *The establishment is performing significant manufacturing step(s) i* (b) (4)
(b) (4)
The (b) (4) is approved to manufacture multiple products. Vimizim is manufactured using (b) (4)
5. *The manufacturing process is sufficiently different* (b) (4)
(b) (4)
Point to consider:
Vimizim is manufactured using (b) (4)
(b) (4)

Signatures:

Colleen Thomas, Ph.D.
OC/OMPQ/DGMPA/BMAB

Richard Ledwidge, Ph.D.
OPS/OBP/DTP

Clearance Routing

Emanuela Lacana, Ph.D.
Lead Biologist, Division of Therapeutic Proteins, Office of Biotechnology Products, Office of
Pharmaceutical Science, CDER

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Director, Division of Good Manufacturing Practice Assessment,
Office of Manufacturing and Product Quality, Office of Compliance, CDER

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/s/

COLLEEN THOMAS
11/18/2013

RICHARD LEDWIDGE
11/18/2013

EMANUELA LACANA
11/18/2013

JOSEPH D DOLESKI
11/26/2013

MEMORANDUM

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

CLINICAL INSPECTION SUMMARY

DATE: October 24, 2013

TO: Elizabeth Ford, Regulatory Project Manager
Tamara Johnson, M.D., Medical Officer
Division of Gastroenterology and Inborn Errors Products

FROM: Susan Leibenhaut, M.D.
Acting Team Leader
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

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

SUBJECT: Evaluation of Clinical Inspections

BLA: 125460

APPLICANT: BioMarin Pharmaceutical Inc.

DRUG: Elosulfase Alfa
NME: Yes
THERAPEUTIC CLASSIFICATION: Priority

INDICATIONS: Treatment of Patients with Mucopolysaccharidosis IVA (Morquio A Syndrome)

CONSULTATION REQUEST DATE: May 29, 2013
INSPECTION SUMMARY GOAL DATE: October 28, 2013
DIVISION ACTION GOAL DATE: February 28, 2014
PDUFA DATE: February 28, 2014

I. BACKGROUND:

BioMarin Pharmaceutical Inc. submitted a BLA for elosulfase alfa (BMN 110) for the treatment of Mucopolysaccharidosis IVA (Morquio A syndrome). Mucopolysaccharidosis IVA is an inherited autosomal recessive disorder characterized by deficient activity of N-acetylgalactosamine-6-sulfatase (GALNS), resulting in macroscopic accumulation of the glycosaminoglycan (GAG) keratan sulfate in tissue macrophages, hyaline cartilage and other connective tissues, as well as heart valves, and corneas. This accumulation causes multiple clinical manifestations including impaired functional capacity, endurance, and quality of life. Currently, there is no treatment for MPS IVA other than supportive care. Enzyme replacement therapy with BMN 110 may be a potential new treatment.

The sponsor submitted Protocol MOR-004 entitled “A Phase 3, Randomized, Double-Blind, Placebo-Controlled, Multinational Clinical Study to Evaluate the Efficacy and Safety of 2.0 mg/kg/week and 2.0 mg/kg every other week BMN 110 in Patients with Mucopolysaccharidosis IVA (Morquio A Syndrome)” in support of the application. The study compared the efficacy and safety of 24 weeks of infusion of BMN 110 at doses of 2.0 mg/kg/week and 2.0 mg/kg/every other week in patients with Mucopolysaccharidosis IVA. The every other week regimen was selected based on the intra-lysosomal half-life of BMN 110 of 5-7 days in human Morquio fibroblasts. Eligible subjects are randomized 1:1:1 to 2.0 mg/kg/week BMN 110, 2.0 mg/kg/every other week of BMN 110 and placebo (i.e. BMN 110 one week and placebo one week), or placebo every week, for 24 consecutive weeks by infusion. As patients may experience hypersensitivity reactions, antihistamine is administered prior to infusion for all patients. The primary efficacy variable was the 6-minute walk (6MW), increase in number of meters walked from baseline to Week 24.

The study was conducted from February 2011 to August 2012 at 33 sites in 17 countries and enrolled a total of 177 subjects. Clinical sites were chosen for inspection on the basis of high enrollment, efficacy results, and significant financial support from the sponsor. The sponsor was inspected because the product is a new molecular entity.

II. RESULTS (by Site):

Type and Name of Inspected Entity	Protocol # Site # and # of Subjects	Inspection Date	Final Classification
CI: Roberto Giugliani, M.D. Hospital de Clinicas de Porto Alegre Rua Ramirio, Barcelos 2350 Predio21-6 andar-Sala 21615 Porto Alegre, NA RS 90035-903 Brazil	MOR-004 Site 0024 18 Subjects	July 29 to August 02, 2013	NAI
CI: Rossella Parini, M.D. Azienda Ospedaliera San Gerardo di Monza Unita Operativa Semplice Malattie Metaboliche Rare Centro Fondazione Mariani per le malattie metaboliche dell-infanzia Via Pergolesi 33 Monza (MB), NA 20090-Italy	MOR-004 Site 1073 10 Subjects	August 5 to 9, 2013	VAI
CI: Paul Harmatz, M.D. Children's Hospital and Research Center Oakland 747 52nd Street, Oakland CA 94609	MOR-004 Site 0018 15 Subjects	September 25 to October 2, 2013	VAI
Sponsor: BioMarin Pharmaceuticals Inc. A105 Digital Drive Novato, CA	MOR-004	September 16 to 24, 2013	Pending (preliminary VAI)

Key to Classifications

NAI = No deviation from regulations.

VAI = Deviation(s) from regulations.

OAI = Significant deviations from regulations.

Pending = Preliminary classification based on information in 483 or preliminary communication with the field; EIR has not been received from the field, and complete review of EIR is pending.

**1. Roberto Giugliani, M.D.
Porto Alegre, Brazil**

- a. **What was inspected:** At this site, 20 subjects were screened, 18 subjects were randomized, and all subjects completed the study. One subject withdrew his/her consent prior to randomization and the other did not meet inclusion criteria. The field investigator reviewed all study related documents. All subjects' records reviewed consisted of source documents, eCRFs and medical records. The review also included informed consent documents, inclusion/exclusion criteria, clinical laboratory criteria, efficacy parameters, study drug accountability and adverse events.

- b. **General Observations/Commentary:** Minor items were noted. Two AEs were not reported in the AE data listings: Subject 4172 reported pain in the left eye with a slight protrusion and Subject 4174 reported pain in the right eye. There were two AEs that were reported in the line listings in the NDA for which there were no source documents. This was a productive cough in Subject 4167 and a fall to the ground for Subject 4168. These are considered minor discrepancies. No violations of federal regulations were cited and a Form FDA 483 was not issued. The data obtained from this site are reliable and can be used in support of the BLA application.
- c. **Assessment of data integrity:** The data obtained from this site are reliable and can be used in support of the BLA application.

2. Rossella Parini, M.D.
Monza (MB), NA 20090-Italy

- a. **What was inspected:** At this site, 13 subjects were screened, 10 subjects were randomized, and all subjects completed the study. The field investigator reviewed study related documents for five enrolled subjects. All subjects' records reviewed consisted of source documents, eCRFs and medical records. The review also included informed consent documents, inclusion/exclusion criteria, clinical laboratory criteria, efficacy parameters, study drug accountability and adverse events.
- b. **General observations/commentary:** The primary and secondary efficacy data were verified. As per the assignment request, the field investigator reviewed the procedures for the Six Minute Walk Test and the Three Minute Stair Climb and found them adequate. There were two instances of adverse events, redness of the tympanic membrane, that were not reported to the sponsor that were cited on the Form FDA 483. These are not considered significant and there was no other evidence of under-reporting of adverse events. A Form FDA 483 was issued for the following additional items:
1. An investigation was not conducted according to the investigational plan.
 - a. Specifically, there is no documentation that vital signs were obtained within 30 minutes of termination of the infusion.

Reviewer comment: In her undated response Dr. Parini notes that vital signs (VS) were always taken immediately after the infusion was stopped. Because stopping infusion and taking VS occurred so close together, the VS were recorded on the source document as having been taken at the same time as the infusion was stopped and were recorded on the CRF as "during infusion" rather than "after infusion". Thus, one can reconstruct from the CRF that the last time point of "during infusion" is actually the time point for "after infusion." This is considered a finding of inadequate record keeping rather than a protocol violation and does not significantly impact the data integrity or subject safety.

b. A study drug was not under the investigator's personal supervision. Specifically, for four subjects, there was no documentation who administered the study drug and the study drug was administered by personnel who were not delegated to do so.

Reviewer comment: There was a note to file documenting the associated responsibilities so this is not considered a violation.

2. Failure to maintain adequate histories.

Reviewer comment: This violation concerned the failure to report the AEs noted above and also the completion of a questionnaire for the tertiary endpoint. These are not considered significant.

c. **Assessment of data integrity:** The study appears to have been conducted adequately, and the data generated by this site may be used in support of the respective indication.

3. Paul Harmatz, M.D. Oakland, CA

a. **What was inspected:** At this site, 19 subjects were screened, 15 subjects were randomized and completed the study. The field investigator reviewed study related documents for all 19 subjects. All subjects' records reviewed consisted of source documents, eCRFs and medical records. The review also included informed consent documents, inclusion/exclusion criteria, clinical laboratory criteria, efficacy parameters, study drug accountability and adverse events.

b. **General Observations/Commentary:** The primary and secondary efficacy endpoint data were verified. There was no evidence of under-reporting of adverse events. There were no issues identified concerning clinical trial conduct. A Form FDA 483 was issued because of lack of calibration of the thermometer where the test article was stored. There was no evidence that the product was not kept at the required temperature, however, there was also no evidence that it was kept at the required temperature. Documentation of the temperature was conducted only when the pharmacy was open so there are many days when a "min/max" temperature determination was missing. There is no record of any maintenance, monitoring or testing since installation. The maintenance records are spotty and there is no clear plan for maintenance. The significance of these findings on the stability of the product and the impact on the results from this site are deferred to the review division. It is suggested that site specific findings related to possible product instability, such as lack of efficacy or evidence of immunogenicity or infusion reactions, be evaluated.

c. **Assessment of data integrity:** The significance of the findings concerning lack of documentation of temperature control is deferred to the review division. Otherwise, the data obtained from this site are reliable and can be used in support of the BLA application.

4. BioMarin Pharmaceuticals Inc. Novato, CA

- a. **What was inspected:** The inspection reviewed regulatory files for Protocol MOR-004. Monitoring files for the following six sites were reviewed (first three sites had been inspected by FDA): Dr. Harmatz, M.D. Site 0018; Dr. Parini, M.D. Site 1073; Dr. Giugliani, M.D. Site 0024; Dr. Santra Site 0121; Dr. Wijburg Site 1075; and Dr. Lin Site 0090. Dr. Santra's and Dr. Wijburg's sites were selected because each had a high number of protocol deviations and were audited by the sponsor. Dr. Lin's site had a relatively large number of SAEs, so the FDA investigator chose to review this site as well.
- b. **General observations/commentary:** There was no evidence of noncompliant clinical sites and no clinical sites were closed. There was no evidence of under-reporting of AEs. A Form FDA 483 was issued for failure to ensure proper monitoring of the study. For Site 0121, there was an issue in which Subject 0121-439 was overdosed because of a discrepancy in the weight reported for the subject. This was not discovered by the monitor. In fact the CRO stated that the source documentation and CRF review were verified and validated. The discrepancy was reported by the pharmacist and was discovered after the subject had been dosed four times (Weeks 5 through 8) with the incorrect dose. There was an isolated instance of inadequate monitoring cited on the Form FDA 483. The conclusion is that, overall, except for the isolated instance cited on the Form FDA 483, the sponsor maintained adequate oversight of the clinical trial and provided adequate monitoring.
- c. **Assessment of data integrity:** The study appears to have been conducted adequately, and the data generated by the sponsor may be used in support of the respective indication.

Note: Observations noted above for the inspection of BioMarin are based on the Form FDA 483 and communications with the field investigator. An inspection summary addendum will be generated if conclusions change upon receipt and review of the establishment inspection report (EIR).

III. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Three clinical investigator sites and the sponsor site were inspected for this BLA. The inspection of Dr. Giugliani's site found no regulatory violations. The inspections of the sites for Drs Parini, Harmatz and the sponsor found regulatory violations and were classified at "voluntary action indicated." The significance of the findings concerning lack of documentation of temperature control at Dr. Harmatz's site is deferred to the review division. The data generated by the sites and the sponsor are considered reliable in support of the application. The observations noted above for the sponsor are based on the Form FDA 483 and communications with the field investigator. An inspection summary

addendum will be generated if conclusions change upon receipt and review of the EIR.

{See appended electronic signature page}

Susan Leibenhaut, M.D.
Acting Team Leader
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

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

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/s/

SUSAN LEIBENHAUT
10/25/2013

KASSA AYALEW
10/25/2013

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management**

Label and Labeling Memorandum

Date: October 22, 2013

Reviewer: Denise V. Baugh, PharmD, BCPS
Division of Medication Error Prevention and Analysis

Team Leader: Lubna Merchant, PharmD, M.S.
Division of Medication Error Prevention and Analysis

Drug Name and Strength: Vimizim (Elosulfase alfa)
Injection, 1 mg/mL

Application Type/Number: BLA 125460

Sponsor: Biomarin

OSE RCM #: 2013-1046-1

*** This document contains proprietary and confidential information that should not be released to the public.***

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1 INTRODUCTION

This memorandum evaluates the revised label and labeling for Vimizim (Elosulfase alfa) Injection submitted on October 10, 2013 to BLA 125460. The Division of Medication Error Prevention and Analysis (DMEPA) previously reviewed the label and labeling under OSE Review # 2013-1046 dated September 13, 2013.

2 MATERIALS REVIEWED

DMEPA evaluated the following labels and labeling.

- Revised container labels and carton labeling submitted on October 10, 2013 (see images Appendices A and B);

Additionally, our recommendations in OSE Review 2013-1046 dated September 13, 2013 were reviewed to assess whether the revised labels and labeling adequately address our concerns from a medication error perspective.

3 CONCLUSION AND RECOMMENDATIONS

Review of the revised documents show that the Applicant has implemented all of DMEPA's recommendations and we find them acceptable. Therefore, we have no further recommendations.

If you have further questions or need clarifications, please contact, Phong Do, OSE Project Manager, at 301-796-4795.

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/s/

DENISE V BAUGH
10/22/2013

LUBNA A MERCHANT
10/22/2013



DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Office of New Drugs - Immediate Office
Pediatric and Maternal Health Staff
Silver Spring, MD 20993
Telephone 301-796-2200
FAX 301-796-9744

M E M O R A N D U M

Date: October 18, 2013

From: Erica Radden, MD
Pediatric and Maternal Health Staff, Office of New Drugs

Through: Hari Cheryl Sachs, MD, Team Leader, Pediatrics Team
Pediatric and Maternal Health Staff, Office of New Drugs

Jeanine Best, MSN, RN, PNP, Team Leader, Maternal Health Team
Pediatric and Maternal Health Staff, Office of New Drugs

Lynne Yao, MD, OND Associate Director
Pediatric and Maternal Health Staff, Office of New Drugs

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

Drug: Vimizim (elosulfase alfa)

Re: Labeling review

Sponsor: BioMarin Pharmaceuticals, Inc.

Application Number: BLA 125460

Proposed Indication: Treatment of Mucopolysaccharidosis IVA (Morquio A syndrome) in patients 5 years of age and older

Proposed Dosage form and Route of administration: 1 mg/mL concentrate to be diluted for infusion

Proposed Dosing regimen: 2 mg/kg administered once every week as an intravenous infusion over approximately 4 hours

Consult Request:

“This consult is requesting assistance from the Pediatric and Maternal Health Staff in review of the proposed labeling subsections of 8.1 Pregnancy, 8.3 Nursing Mothers and 8.4 Pediatrics for this new drug product.”

Materials Reviewed:

- Proposed Vimizim (elosulfase alfa) Labeling (March 29, 2013)
- Cover letter for original Biologics License Application for Vimizim, BLA 125-460 (March 29, 2013)

Background:

Vimizim (elosulfase alfa) is recombinant human N-acetylgalactosamine-6-sulfatase, an enzyme replacement therapy proposed for the treatment of Mucopolysaccharidosis type IVA (MPS IVA; Morquio A syndrome) in patients 5 years of age and older. MPS IVA or Morquio A syndrome is a rare, autosomal recessive, lysosomal storage disease resulting from deficiency of the lysosomal enzyme N-acetylgalactosamine-6-sulfate-sulfatase which leads to accumulation of keratan sulfate and chondroitin-6 sulfate in multiple organs and tissues, mainly bone and cornea. Multisystemic complications result from this disorder involving the musculoskeletal, respiratory, cardiovascular, and digestive systems.¹ Both the age of onset and rate of progression are variable with MPS IVA. Generally, MPS IVA patients with a severe form do not survive beyond the third decade of life whereas those patients with milder forms may survive over 70 years. There is no approved, effective therapy for MPS IVA, and current management options are palliative.² The sponsor requested priority review claiming that elosulfase alfa has the potential to provide safe and effective therapy for the treatment of MPS IVA where no satisfactory alternative therapy exists.

Note that a trial is currently ongoing that is also evaluating pediatric patients less than 5 years of age. Orphan designation was granted on May 15, 2009; therefore, PREA does not apply.

The Division has requested PMHS’ input on proposed labeling for the subsections 8.1 Pregnancy, 8.3 Nursing Mothers and 8.4 Pediatrics for this new drug product.

¹ Algham MF, Almassi GH. Current and emerging management options for patients with Morquio A syndrome. *Ther Clin Risk Manag.* 2013;9:45-53.

² Tomatsu S, Montañó AM, Oikawa H, Smith M, Barrera L, Chinen Y, Thacker MM, Mackenzie WG, Suzuki Y, Orii T. Mucopolysaccharidosis type IVA (Morquio A disease): clinical review and current treatment. *Curr Pharm Biotechnol.* 2011 Jun;12(6):931-45.

Sponsor's proposed labeling for Vimizim dated March 29, 2013:

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy Category

(b) (4)

[Redacted text block for 8.1 Pregnancy Category]

(b) (4)

8.3 Nursing Mothers

[Redacted text block for 8.3 Nursing Mothers]

(b) (4)

8.4 Pediatric Use

[Redacted text block for 8.4 Pediatric Use]

(b) (4)

Discussion on Labeling Recommendations:

Pregnancy and Nursing Mothers Labeling:

The Maternal Health Team (MHT) has been working to develop a more consistent and clinically useful approach to the Pregnancy and Nursing Mothers subsections of labeling. This approach complies with current regulations but incorporates “the spirit” of the Proposed Pregnancy and Lactation Labeling Rule (PLLR) (published on May 29, 2008). As part of the labeling review, the MHT reviewer conducts a literature search to determine if relevant published pregnancy and lactation data are available that would add clinically useful information to the Pregnancy and Nursing Mothers labeling subsections. In addition, the MHT works with the pharmacology/toxicology reviewers to present animal data, in the Pregnancy and Nursing Mothers subsections, to make it as clinically relevant as possible for prescribers. This includes expressing animal data in terms of species exposed, timing and route of drug administration, animal dose including human dose equivalents (with the basis for calculation), and outcomes for dams and offspring. The first paragraph in the pregnancy subsection of labeling summarizes available data from published literature, outcomes of studies conducted in pregnant women (when available), and outcomes of studies conducted in animals, as well as the required regulatory language for the designated pregnancy category. The paragraphs that follow

provide more detailed descriptions of the available human and animal data, and when appropriate, clinical information that may affect patient management. For the Nursing Mothers subsection, when animal data are available, only the presence or absence of drug in milk is presented in the label. The goal of this restructuring is to make the pregnancy and lactation section of labeling a more effective communication tool for clinicians.

No teratogenicity was observed in animal reproduction studies with elosulfase alfa, even under conditions of maternal toxicity. However, a dose-dependent increase in still births was observed in pre- and post-natal animal reproduction studies, and an increase in pup deaths occurred at doses producing maternal toxicity. The sponsor proposed a pregnancy category (b) (4) classification for elosulfase alfa, based on a lack of teratogenic findings in animals; however, both DGIEP and PMHS-MHT decided that a pregnancy category C⁴ classification accurately reflects the animal findings observed in the pre- and post-natal animal studies. No human pregnancy or lactation data was submitted with this application and no elosulfase alfa pregnancy or lactation use information was found in a review of published literature. PMHS-MHT notes that pregnancy categories will be eliminated with the publication of the PLLR and replaced with clinically relevant information to assist prescribers with benefit/risk decision making for using a drug during pregnancy.

Pediatric Use Labeling:

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 appropriate use statements to include in labeling based on findings of safety and effectiveness in the pediatric use population.

If the division determines that the submitted data demonstrates safety and effectiveness for elosulfase alfa in pediatric patients 5 to 17 years of age, information regarding the data used to support this pediatric indication should be included in the relevant sections per 21 CFR 201.57(c)(9)(iv) throughout labeling. Labeling should clarify that elosulfase alfa is indicated for the treatment of Mucopolysaccharidosis IVA (Morquio A syndrome) in patients 5 years of age and older, but that safety and effectiveness have not been established for elosulfase alfa in patients less than 5 years of age.



(b) (4)

⁴ Pregnancy Category C - Animal reproduction studies have shown an adverse effect on the fetus, there are no AWC studies in humans, AND the benefits from the use of the drug in pregnant women may be acceptable despite its potential risks. OR animal studies have not been conducted and there are no AWC studies in humans.

The basis used to support the pediatric indication should be outlined in the Pediatric Use subsection (e.g., adequate and well-controlled studies with additional data supporting pediatric use). Additionally, the pediatric clinical trial supporting the pediatric indication should be summarized in the Pediatric Use section of elosulfase alfa labeling with cross-references to a more detailed description in the appropriate sections of labeling. Any differences between pediatric and adult responses (e.g., pharmacodynamic/pharmacokinetic data) should also be cited in the Pediatric Use subsection.

Conclusions:

PMHS-MHT structured the pregnancy and nursing mothers subsections of elosulfase alfa labeling in the spirit of the proposed PLLR, while complying with current labeling regulations. Recommended labeling for the pediatric population is provided below per 21 CFR 201.57(c)(9)(iv).

PMHS participated in the team and labeling meetings with DGIEP held between May, 2013 and October, 2013. Final labeling will be negotiated with the applicant and may not fully reflect changes recommended here.

PMHS Recommended labeling for Vimizim (elosulfase alfa):

Provided below are PMHS' recommended revisions to the sponsor's proposed labeling based on labeling from March 29, 2013. This version of the labeling includes recommendations made by the Pharmacology/Toxicology Reviewers, Dr. David Joseph and Dr. Fang Cai.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy Category C

Risk Summary

There are no adequate and well-controlled studies with VIMIZIM in pregnant women. However, animal reproduction studies have been conducted for elosulfase alfa. In these studies, no maternal toxicity or effects on embryo-fetal development were observed in rats given daily doses of elosulfase alfa up to 33 times the recommended human (b) (4) through the period of organogenesis. No effects on embryo-fetal development were observed in rabbits given daily administration of elosulfase alfa at doses (b) (4). A dose-dependent increase in stillbirths was observed when elosulfase alfa was administered daily in rats during organogenesis through lactation at doses 5 times the (b) (4). An increase in pup mortality was observed at doses producing maternal toxicity. VIMIZIM should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus

Clinical Considerations

Disease-associated maternal and embryo/fetal risk

Pregnancy can adversely affect the health of females affected with MPS IVA (b) (4) and lead to adverse pregnancy outcomes for both mother and fetus.

Animal Data

All reproductive studies with rats included pre-treatment with diphenhydramine to prevent or minimize hypersensitivity reactions. The effects of elosulfase alfa were evaluated based on comparison to a control group treated with diphenhydramine alone. Daily intravenous administration of up to 20 mg/kg elosulfase alfa in rats (33 times the human steady-state (b) (4) at the recommended weekly dose of 2 mg/kg) during a 15-day pre-mating period, mating, and the period of organogenesis, produced no maternal toxicity or effects on embryo-fetal development. Daily intravenous administration of up to 10 mg/kg in rabbits (b) (4) during the period of organogenesis had no effects on embryo-fetal development. However, maternal toxicity (gross changes in liver) was observed in rabbits given doses of 1 mg/kg/day and higher (b) (4). Elosulfase alfa produced an increase in the percentage of stillbirths when administered daily to rats at doses of 6 mg/kg IV and higher (5 times the human steady-state exposure at the recommended weekly dose) during the period of organogenesis through lactation. Daily administration of 20 mg/kg IV (33 times the human steady-state (b) (4) at the recommended weekly dose) produced maternal toxicity and an increase in mortality of offspring during the lactation period. This study lacked a complete evaluation of (b) (4); however, no effects of elosulfase alfa were noted in tests for learning and memory.

8.3 Nursing Mothers

It is not known if VIMIZIM is present in human milk. Elosulfase alfa is present in milk from treated rats [*see Use in Specific Populations (8.1)*]. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for VIMIZIM and any potential adverse effects on the breastfed child from the drug or from the MPS IVA. Exercise caution when administering VIMIZIM to a nursing mother.

8.4 Pediatric Use

Safety and effectiveness of VIMIZIM have been established in pediatric patients 5 years of age and older. Use of VIMIZIM in patients 5 years of age and older is supported by an adequate and well-controlled study in pediatric and adult patients. Clinical trials with VIMIZIM were conducted in 176 patients (median age 12 years, range 5 to 57 years old) with the majority of the patients in the pediatric age group (53% aged 5 to 11 years, 27% aged 12 to 17 years) [*see Clinical Studies (14)*]. Safety and effectiveness in pediatric patients below 5 years of age have not been established.

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/s/

ERICA D RADDEN
10/18/2013

HARI C SACHS
10/18/2013

JEANINE A BEST
10/20/2013

LYNNE P YAO
10/21/2013

MEMORANDUM OF MEETING MINUTES

MEETING DATE: September 27, 2013
TIME: 1:00 PM
LOCATION: teleconference
APPLICATION: 125460/0
DRUG NAME: BMN110 (elosulfase alfa)
TYPE OF MEETING: teleconference

SPONSOR ATTENDEES: Robert Baffi
Victoria Sluzky
Loc Vo
Erno Pungor
Art Blum
Lisa Bell
Marjorie Tano
Brad Glasscock
Laurel Konkol

FDA ATTENDEES: Emanuela Lacana, Ph.D., DTP
Cristina Ausin, Ph.D., DTP
Richard Ledwidge, Ph.D., DTP
Lyndsay Hennessey, Regulatory Project Manager, OBP

The Agency sent an Information Request letter to BioMarin on September 24, 2013 and offered to hold a teleconference to discuss the issue of comparability among sites.

The sponsor presented slides (attached).

The Agency stated that Statistics would need to be involved to go over data provided in slides. The sponsor was informed that in general when a linear regression is done, the mean data points are not looked at but rather the individual slopes. The Agency stated that even though there may not be a statistically significant difference among the sites, they look different. The sponsor agreed to the difference but stated that at this time, the amount of data is small. The Agency responded that saying there was not enough evidence to prove the sites were not significantly different is not the same as saying there is no difference. The Agency further stated that another way of showing the sites are comparable will be needed.

The sponsor stated that from a bulk stability perspective, there doesn't appear to be a difference. The Agency was not sure of this analysis. When looking at forced degradation studies, conducted at 50°C, a difference in degradation slope was shown, suggesting a difference between lots of DS manufactured at the clinical and at the commercial sites. The sponsor responded that data was submitted in the original BLA in response to characterization. In original forced degradation the sponsor did see a difference and that is why an additional expanded study with 17 batches was done. With any random 3 batches, a difference would be seen based on batch to batch variability. In the new expanded study, there wasn't a statistically significant difference.

The Agency asked the sponsor if they had an explanation why DS lot P4014-10003 has a significantly different degradation rate when it becomes DP lot BSJL05. The sponsor responded that the

(b) (4)

The Agency stated that when reporting specific activity,

(b) (4)

The Agency recommended the best path forward for the sponsor would be to submit as much additional data on DP and DS as possible, including description of statistical analysis and detailed information on specific analyses. Also, it was recommended they reanalyze the data already provided using a different method such as equivalency testing to give a larger confidence to show that there really are no differences between the two filling sites and therefore the two products.

The sponsor stated they would provide a quality update by October 16th.

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/s/

LYNDSAY J HENNESSEY
10/08/2013

EMANUELA LACANA
10/08/2013

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

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

Memorandum

Date: September 23, 2013

To: Elizabeth Ford, 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)

CC: Kathleen Klemm, Pharm.D., Acting Team Leader, OPDP

Subject: BLA# 125460
OPDP Labeling Comments for VIMIZIM™ (elosulfase alfa)
concentrate for infusion (Vimizim)

Reference is made to DGIEP's consult request dated June 27, 2013, requesting review of the proposed Package Insert (PI) and Carton/Container Labeling for Vimizim.

OPDP's comments on the PI are based on the proposed draft mark-up labeling titled "BioMarin draft-labeling-text" (version 53) that was available in the e-room on September 23, 2013. OPDP's comments on the PI are provided directly on the attached marked-up copy of the labeling (see below).

OPDP has reviewed the proposed Carton and Container labeling titled "vimizim-carton-us" and vimizim-container-us" respectively, submitted by the sponsor on March 29, 2013. OPDP does not have comments on the proposed Carton and Container labeling at this time.

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

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/s/

ADEWALE A ADELEYE
09/23/2013

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management**

Label, Labeling and Packaging Review

Date: September 13, 2013

Reviewer: Denise V. Baugh, PharmD, BCPS
Division of Medication Error Prevention and Analysis

Team Leader: Lubna Merchant, PharmD, M.S.
Division of Medication Error Prevention and Analysis

Drug Name and Strength: Vimizim (Elosulfase alfa)
Injection, 1 mg/mL

Application Type/Number: BLA 125460

Applicant: Biomarin

OSE RCM #: 2013-1046

*** This document contains proprietary and confidential information that should not be released to the public.***

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1 INTRODUCTION

This review evaluates the proposed container label, carton, and insert labeling for Vimizim (BLA 125460) for areas of vulnerability that could lead to medication errors.

1.1 PRODUCT INFORMATION

The following product information is provided in the June 11, 2013 submission:

- Active Ingredient: elosulfase alfa
- Indication of Use: enzyme replacement therapy for all MPS IVA (Morquio) patients
- Route of Administration: intravenous infusion
- Dosage Form: Injection
- Strength: 1 mg/mL
- Dose and Frequency: 2 mg/kg given over 4 hours intravenously once weekly
- How Supplied: single dose pack (vials)
- Storage: Refrigerated
- Container and Closure System: Vial-clear, (b) (4) glass; Stopper (b) (4) rubber; (b) (4)-aluminum flip-off over seal
- Additional information: Product is to be given by a healthcare professional in an infusion clinic; specialty pharmacy will dispense product

1.2 LABELS AND LABELING

Using the principles of human factors and Failure Mode and Effects Analysis,¹ along with post marketing medication error data, the Division of Medication Error Prevention and Analysis (DMEPA) evaluated the following:

- Container Labels submitted March 29, 2013 (Appendix B)
- Carton Labeling submitted March 29, 2013 (Appendix C)
- Insert Labeling submitted June 11, 2013

2 INTEGRATED SUMMARY OF MEDICATION ERROR RISK ASSESSMENT

Vimizim (elosulfase alfa) is in the same therapeutic category as the approved products, Elapraxe (Idursulfase), BLA 125151 and Naglazyme (Galsulfase), BLA 125117 which were approved July 24, 2006 and May 31, 2005 respectively. All 3 products are dosed by patient weight and they all require further dilution prior to administration.

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

The recommended dose (2 mg/kg) for Vimizim is feasible given the concentration (1 mg/mL). Additionally, given the range in life span and clinical challenges of the target patient population, it is difficult to determine how many vials would be needed to achieve the 'usual' dose, but we do not anticipate difficulty in calculating this information. We also note that the package design (5 mL vial size) and preparation instructions (calculate dose based upon weight with further dilution) are similar to that of the other two drug products in its therapeutic category and, therefore, we do not anticipate confusion in the medical community with the introduction of this drug product.

However, in our review of the dosage and administration section of the insert labeling for Vimizim we note that this section requires revisions to the infusion rate to mitigate dosing errors and requires changes to the organization of this section to better retrieve dosing, preparation and administration information. DMEPA made recommendations to improve the insert labeling for Elaprase (Idursulfase) in OSE Review # 2012-2565 dated June 14, 2013. We will make similar recommendations for improvement (where appropriate) to maintain consistency in the label and labeling among these 3 drug products.

In our review of the container label and carton labeling, we note that the prominence of important drug identifying information (e.g., proprietary name) and the total drug content statement can be improved. Additionally, the dosage form the Applicant proposes (e.g., concentrate for infusion) is inconsistent with other agents in this therapeutic category and is located after the strength statement which is not the traditional location. We discussed this issue with representatives in Chemicals, Manufacturing and Controls (CMC) and the Office of Biotechnology Products (OBP). Based upon our discussion, the appropriate dosage form is "Injection". Our recommendations below address this and other deficiencies.

3 CONCLUSIONS

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

4 RECOMMENDATIONS

4.1 COMMENTS TO THE REVIEW DIVISION

DMEPA provides the following comments for consideration by the review division prior to approval of this BLA:

DMEPA concluded that the dosage and administration section of the insert labeling required revisions to the description of the infusion rate titration schedule to mitigate dosing errors and required changes to the organization of this section to better retrieve dosing, preparation and administration information. These revisions are similar to what was proposed for Elaprase (BLA 125151).

See Appendix D (titled "DMEPA Proposals to Revise the Dosage and Administration Subsection of the Insert Labeling") for our recommendations to the insert labeling.

4.2 COMMENTS TO THE APPLICANT

DMEPA recommends implementing the following prior to approval of this BLA:

- A. General Comments (Container Label and Carton Labeling)
1. Revise the presentation of the proprietary name to title case (e.g., from ‘VIMIZIM’ to ‘Vimizim’) and revise the (b) (4) color on the left side of the letter ‘V’ to the color of the other letters to improve the readability of the proprietary name.
 2. Revise the dosage form (b) (4) (b) (4)
Relocate the dosage form to appear after the active ingredient and just outside of the parenthesis.
 3. Ensure the presentation of the active ingredient (elasulfase alfa) and the dosage form (injection) have a prominence that is at least ½ the size of the proprietary name taking into account all pertinent factors, including typography, layout, contrast, and other printing features per CFR 201.10(g)(2).
 4. Increase the prominence of the total drug statement (5 mg/5 mL) so that it is more prominent than the strength statement (1 mg/mL).
 5. Revise the statement (b) (4)
(b) (4)
- B. Container Label
1. Remove the (b) (4) from around the manufacturer’s name and relocate the manufacturer’s name to the bottom of the principal display panel. Ensure that this information is less prominent than the proprietary, established names, and strength..
 2. If space permits, relocate the statement “For single use only” to the principal display panel and follow it with the statement “Discard unused portions”.

If you have further questions or need clarifications, please contact Phong Do, OSE Project Manager, at 301-796-4795.

APPENDICES

Appendix A. Database Descriptions

FDA Adverse Event Reporting System (FAERS)

The FDA Adverse Event Reporting System (FAERS) is a database that contains information on adverse event and medication error reports submitted to FDA. The database is designed to support the FDA's post-marketing safety surveillance program for drug and therapeutic biologic products. The informatic structure of the database adheres to the international safety reporting guidance issued by the International Conference on Harmonisation. Adverse events and medication errors are coded to terms in the Medical Dictionary for Regulatory Activities (MedDRA) terminology. The suspect products are coded to valid tradenames or active ingredients in the FAERS Product Dictionary (FPD).

FDA implemented FAERS on September 10, 2012, and migrated all the data from the previous reporting system (AERS) to FAERS. Differences may exist when comparing case counts in AERS and FAERS. FDA validated and recoded product information as the AERS reports were migrated to FAERS. In addition, FDA implemented new search functionality based on the date FDA initially received the case to more accurately portray the follow up cases that have multiple receive dates.

FAERS data have limitations. First, there is no certainty that the reported event was actually due to the product. FDA does not require that a causal relationship between a product and event be proven, and reports do not always contain enough detail to properly evaluate an event. Further, FDA does not receive reports for every adverse event or medication error that occurs with a product. Many factors can influence whether or not an event will be reported, such as the time a product has been marketed and publicity about an event. Therefore, FAERS data cannot be used to calculate the incidence of an adverse event or medication error in the U.S. population.

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/s/

DENISE V BAUGH
09/13/2013

LUBNA A MERCHANT
09/16/2013



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

Office of Biotechnology Products

FINAL CARTON AND CONTAINER REVIEW

Date: September 18, 2013

Reviewer: Kimberly Rains, Pharm.D.
Office of Biotechnology Products

Through: Cristina Austin, Ph.D.
Division of Therapeutic Proteins

Emanuela Lacana, Ph.D.
Division of

Application: BLA 125460

Product: Vimizim™ (elosulfase alfa)

Applicant: BioMarin Pharmaceuticals Inc.

Submission Date(s): March 29, 2012

Executive Summary

The carton and container labels for Vimizim™ (elosulfase alfa) were reviewed and found not 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 200.100 and United States Pharmacopeia, 5/1/13-12/31/13, USP 36/NF 31. Labeling deficiencies were identified. Comments are listed in the conclusions section. The carton and container labeling submitted on March 29, 2012 is unacceptable.

Background and Summary Description

BLA 125460 for elosulfase is indicated for patients with Mucopolysaccharidiosis type IV. The product is supplied as 5 mg/5mL (1 mg/mL) solution. The solution must be diluted before use.

Materials Reviewed:

Carton and Container

<<http://cberedrweb.fda.gov:8080/esp/cberedr.jsp?folderObjId=0bbcaea6811d967a>>
Sequence 0000

Start of Sponsor Material



End of Sponsor Material

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:

- (1) The proper name of the product; [see 21 CFR 600.3 (k) and section 351 of the PHS Act] **Conforms**.
- (2) The name, address, and license number of manufacturer; **Conforms**
- (3) The lot number or other lot identification; **Conforms**
- (4) The expiration date; **Conforms**
- (5) The recommended individual dose, for multiple dose containers. **Not applicable**. Single-use vial

(6) The statement: “Rx only” for prescription biologicals.

Conforms

(7) If a Medication Guide is required under part 208 of the chapter, the statement required under §208.24(d) of this chapter instructing the authorized dispenser to provide a Medication Guide to each patient to whom the drug is dispensed and stating how the Medication Guide is provided, except where the container label is too small, the required statement may be placed on the package label. **Not applicable.**

(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. **Not applicable**

(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. – This conforms to the regulation per CMC visual inspection. **Does not conform.**

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]; **Conforms.**

C. 21 CFR 201.5 Drugs; adequate directions for use; **Conforms.**

D. 21 CFR 201.6 Drugs; misleading statements; **Conforms.**

E. 21 CFR 201.10 Drugs; statement of ingredients; [Placement and prominence]. **Does not conform.**

F. 21 CFR 201.15 Drugs; prominence of required label statements; **Conforms.**

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; **Conforms.**
- L. 21 CFR 201.100 Prescription drugs for human use; **Conforms**

Start of Sponsor Material

(b) (4)



End of Sponsor Material

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; **Conforms**
- 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; **Not applicable. Single container**
- 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; **Conforms**
- h) The recommended storage temperature; **Conforms**
- 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; **Not applicable. Single-dose container.**
- 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; Information **provided in prescribing Information. Conforms**
- m) The type and calculated amount of antibiotics added during manufacture; Information **provided in prescribing information. Conforms**

n) The inactive ingredients when a safety factor or reference to enclosed circular containing appropriate information; **Information provided in the prescribing information. Conforms**

o) The adjuvant, if present; **Not applicable**

p) The source of the product when a factor in safe administration; **Conforms. Information provided in prescribing information. Conforms**

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 if no U.S. standard of potency has been prescribed, the words “No U.S. standard of potency”; “No U.S. Standard of Potency” appears on the label. **Conforms**

s) The statement “Rx only” for prescription biologicals; **Conforms**

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)*]

a) Position. The proper name of the product on the package label shall be placed above any trademark or trade name identifying the product and symmetrically arranged with respect to other printing on the label.

b) Prominence. The point size and typeface of the proper name shall be at least as prominent as the point size and typeface used in designating the trademark and trade name. The contrast in color value between the proper name and the background shall be at least as great as the color value between the trademark and trade name and the background. Typography, layout, contrast, and other printing features shall not be used in a manner that will affect adversely the prominence of the proper name.

c) Legible type. All items required to be on the container label and package label shall be in legible type. “Legible type” is type of a size and character which can be read with ease when held in a good light and with normal vision. **Not applicable**

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

- D. 21 CFR 610.64 Name and address of distributor
The name and address of the distributor of a product may appear on the label provided that the name, address, and license number of the manufacturer also appears on the label and the name of the distributor is qualified by one of the following phrases: “Manufactured for _____”. “Distributed by _____”, “Manufactured by _____ for _____”, “Manufactured for _____ by _____”, “Distributor: _____”, or “Marketed by _____”. The qualifying phrases may be abbreviated. **Not applicable**
- E. 21 CFR 610.67 Bar code label requirements
Biological products must comply with the bar code requirements at §201.25 of this chapter; **Conforms**
- 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] **Conforms**
- G. 21 CFR 201.5 Drugs; adequate directions for use; **Conforms**
- H. 21 CFR 201.6 Drugs; misleading statements; **Conforms**
- I. 21 CFR 201.10 Drugs; statement of ingredients;[Placement and Prominence] **Does not conform**
- J. 21 CFR 201.15 Drugs; prominence of required label statements; **Conforms**
- 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**

Conclusions

- I. Container
- a. Please indicate how the label is affixed to the vial and where the visual area of inspection is located per 21 CFR 610.60 (e).

II. Carton and Container

- a. Please revise the dosage form from [REDACTED] (b) (4) (b) (4) to comply with the United States Pharmacopeia 8/1/13-11/30/13, USP 36/NF 31, General Chapter, Injection <1>, Nomenclature and Definitions. * See recommended format below.
- b. Revise the presentation of the Trade name (VIMIZIM) and proper name (elosulfase alfa) to comply with the prominence requirements of 21 CFR 201.10(g)(2). * See recommended format below.

III. Cap and Overseal

- a. Please comment on if there is any text on the ferrule and cap overseal. A revised USP standard will go into effect on December 1, 2010. We refer you to the following address:
http://www.usp.org/sites/default/files/usp_pdf/EN/USPNF/genChapter1Labeling.pdf

*Recommended format:

Vimizim
(elosulfase alfa)
Injection
5 mg/5 mL
1 mg/mL
for Infusion

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/s/

KIMBERLY M RAINS
09/18/2013

CRISTINA AUSIN-MORENO
09/18/2013

EMANUELA LACANA
09/18/2013

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# 125460/0	NDA Supplement #:S- BLA Supplement #	Efficacy Supplement Type SE-
Proprietary Name: Vimizim Established/Proper Name: elosulfase alfa Dosage Form: (b) (4) Strengths: 1 mg per ml concentrate		
Applicant: BioMarin Pharmaceutical Inc. Agent for Applicant (if applicable): Not applicable		
Date of Application: March 29, 2013 Date of Receipt: March 29, 2013 Date clock started after UN:		
PDUFA Goal Date: November 29, 2013		Action Goal Date (if different):
Filing Date: May 28, 2013		Date of Filing Meeting: April 26, 2013
Chemical Classification: (1,2,3 etc.) (original NDAs only)		
Proposed indication(s)/Proposed change(s): Mucopolysaccharidosis type IVA (MPS IVA; Morquio A syndrome).		
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)
<i>If 505(b)(2): Draft the "505(b)(2) Assessment" review found at: http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499 and refer to Appendix A for further information.</i>		
Review Classification: <i>If the application includes a complete response to pediatric WR, review classification is Priority.</i> <i>If a tropical disease priority review voucher was submitted, review classification is Priority.</i>	<input type="checkbox"/> Standard <input checked="" type="checkbox"/> Priority <input type="checkbox"/> Tropical Disease Priority Review Voucher submitted	
Resubmission after withdrawal? <input type="checkbox"/>		Resubmission after refuse to file? <input type="checkbox"/>
Part 3 Combination Product? <input type="checkbox"/> <i>If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults</i>	<input type="checkbox"/> Convenience kit/Co-package <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"/> Breakthrough Therapy Designation <input type="checkbox"/> Rolling Review <input type="checkbox"/> Orphan Designation <input type="checkbox"/> Rx-to-OTC switch, Full <input type="checkbox"/> Rx-to-OTC switch, Partial <input type="checkbox"/> Direct-to-OTC Other:	<input type="checkbox"/> PMC response <input type="checkbox"/> PMR response: <input type="checkbox"/> FDAAA [505(o)] <input type="checkbox"/> PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] <input type="checkbox"/> Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) <input type="checkbox"/> Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)
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Collaborative Review Division (*if OTC product*):

List referenced IND Number(s): 101234

Goal Dates/Product Names/Classification Properties	YES	NO	NA	Comment
PDUFA and Action Goal dates correct in tracking system? <i>If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.</i>	X			
Are the proprietary, established/proper, and applicant names correct in tracking system? <i>If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into tracking system.</i>	X			
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug)? <i>For NDAs/NDA supplements, check the New Application and New Supplement Notification Checklists for a list of all classifications/properties at: http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm</i> <i>If no, ask the document room staff to make the appropriate entries.</i>	X			
Application Integrity Policy	YES	NO	NA	Comment
Is the application affected by the Application Integrity Policy (AIP)? <i>Check the AIP list at: http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</i>		X		
If yes , explain in comment column.				
If affected by AIP , has OC/OMPQ been notified of the submission? If yes , date notified:				
User Fees	YES	NO	NA	Comment
Is Form 3397 (User Fee Cover Sheet) included with authorized signature?	X			

<p><u>User Fee Status</u></p> <p><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></p>	<p>Payment for this application:</p> <p><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</p>			
<p><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></p>	<p>Payment of other user fees:</p> <p><input checked="" type="checkbox"/> Not in arrears <input type="checkbox"/> In arrears</p>			
<p>505(b)(2) (NDAs/NDA Efficacy Supplements only)</p>	<p>YES</p>	<p>NO</p>	<p>NA</p>	<p>Comment</p>
<p>Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?</p>			X	
<p>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)].</p>			X	
<p>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)]?</p> <p><i>If you answered yes to any of the above 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</i></p>			X	
<p>Is there unexpired exclusivity on any drug product containing the active moiety (e.g., 5-year, 3-year, orphan, or pediatric exclusivity)?</p> <p>Check the Electronic Orange Book at: http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm If yes, please list below:</p>			X	
<p>Application No.</p>	<p>Drug Name</p>	<p>Exclusivity Code</p>	<p>Exclusivity Expiration</p>	
<p><i>If there is unexpired, 5-year exclusivity remaining on the active moiety for the proposed drug product, 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></p>				
<p>Exclusivity</p>	<p>YES</p>	<p>NO</p>	<p>NA</p>	<p>Comment</p>
<p>Does another product (same active moiety) have orphan exclusivity for the same indication? Check the Orphan Drug Designations and Approvals list at: http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm</p>		X		

<p>If another product has orphan exclusivity, is the product considered to be the same product according to the orphan drug definition of sameness [see 21 CFR 316.3(b)(13)]?</p> <p><i>If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy</i></p>			X	
<p>Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? (<i>NDA/NDA efficacy supplements only</i>)</p> <p>If yes, # years requested:</p> <p><i>Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i></p>			X	
<p>Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use (<i>NDA only</i>)?</p>			X	
<p>If yes, did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)?</p> <p><i>If yes, contact Mary Ann Holovac, Director of Drug Information, OGD/DLPS/LRB.</i></p>			X	

Format and Content				
<p><i>Do not check mixed submission if the only electronic component is the content of labeling (COL).</i></p>	<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)			
<p>If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?</p>				
Overall Format/Content	YES	NO	NA	Comment
<p>If electronic submission, does it follow the eCTD guidance?¹ If not, explain (e.g., waiver granted).</p>	X			
<p>Index: Does the submission contain an accurate comprehensive index?</p>	X			
<p>Is the submission complete as required under 21 CFR 314.50 (<i>NDA/NDA efficacy supplements</i>) or under 21 CFR 601.2 (<i>BLAs/BLA efficacy supplements</i>) including:</p>	X			

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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)				
If no , explain.				
BLAs only : Companion application received if a shared or divided manufacturing arrangement?			X	
If yes , BLA #				
Forms and Certifications				
<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), 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>				
Application Form	YES	NO	NA	Comment
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)?	X			
<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?	X			
Patent Information (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?			X	
Financial Disclosure	YES	NO	NA	Comment
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)?	X			
<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>				
Clinical Trials Database	YES	NO	NA	Comment
Is form FDA 3674 included with authorized signature?	X			
<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>				
Debarment Certification	YES	NO	NA	Comment
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, <u>both</u> 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&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>	X			
Field Copy Certification (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included? <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>			X	
Controlled Substance/Product with Abuse Potential	YES	NO	NA	Comment
<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>			X	
Pediatrics	YES	NO	NA	Comment
<u>PREA</u> Does the application trigger PREA? <i>If yes, notify PeRC RPM (PeRC meeting is required)²</i> <i>Note: NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage 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.</i>		X		Orphan Designation

² <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027829.htm>

If the application triggers PREA , are the required pediatric assessment studies or a full waiver of pediatric studies included?			X	
If studies or full waiver not included , is a request for full waiver of pediatric studies OR a request for partial waiver and/or deferral with a pediatric plan included? <i>If no, request in 74-day letter</i>			X	
If a request for full waiver/partial waiver/deferral is included , does the application contain the certification(s) required by FDCA Section 505B(a)(3) and (4)? <i>If no, request in 74-day letter</i>			X	
BPCA (NDAs/NDA efficacy supplements only): Is this submission a complete response to a pediatric Written Request? <i>If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)³</i>		X		
Proprietary Name	YES	NO	NA	Comment
Is a proposed proprietary name submitted? <i>If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."</i>	X			Submitted 4/30/2013
REMS	YES	NO	NA	Comment
Is a REMS submitted? <i>If yes, send consult to OSE/DRISK and notify OC/OSI/DSC/PMSB via the CDER OSI RMP mailbox</i>	X			
Prescription Labeling	<input type="checkbox"/> Not applicable			
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 type="checkbox"/> Medication Guide (MedGuide) <input checked="" type="checkbox"/> Carton labels <input checked="" type="checkbox"/> Immediate container labels <input type="checkbox"/> Diluent <input type="checkbox"/> Other (specify)			
	YES	NO	NA	Comment
Is Electronic Content of Labeling (COL) submitted in SPL format? <i>If no, request applicant to submit SPL before the filing date.</i>	X			
Is the PI submitted in PLR format? ⁴	X			

³ <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027837.htm>

⁴ <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/StudyEndpointsandLabelingDevelopmentTeam/ucm025576.htm>

If PI not submitted in PLR format , was a waiver or deferral requested before the application was received or in the submission? If requested before application was submitted , what is the status of the request? <i>If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.</i>			X	
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to OPDP?		X		To be sent after filing meeting
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (send WORD version if available)			X	
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office (OBP or ONDQA)?	X			
OTC Labeling	<input checked="" type="checkbox"/> Not Applicable			
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)			
	YES	NO	NA	Comment
Is electronic content of labeling (COL) submitted? <i>If no, request in 74-day letter.</i>				
Are annotated specifications submitted for all stock keeping units (SKUs)? <i>If no, request in 74-day letter.</i>				
If representative labeling is submitted, are all represented SKUs defined? <i>If no, request in 74-day letter.</i>				
All labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEPA?				
Other Consults	YES	NO	NA	Comment
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team) <i>If yes, specify consult(s) and date(s) sent:</i>		X		
Meeting Minutes/SPAs	YES	NO	NA	Comment
End-of Phase 2 meeting(s) Date(s): 7/28/2010 <i>If yes, distribute minutes before filing meeting</i>	X			PIND/EOP2

Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? Date(s): 11/13/2012 (CMC), 12/11/2012 <i>If yes, distribute minutes before filing meeting</i>	X			
Any Special Protocol Assessments (SPAs)? Date(s): 1/20/2011 <i>If yes, distribute letter and/or relevant minutes before filing meeting</i>	X			

ATTACHMENT

MEMO OF FILING MEETING

DATE: April 26, 2013

BLA/NDA/Supp #: 125460/0

PROPRIETARY NAME: Vimizim

ESTABLISHED/PROPER NAME: elosulfase alfa

DOSAGE FORM/STRENGTH: [REDACTED] (b) (4) /1mg per ml concentration

APPLICANT: BioMarin Pharmaceutical Inc.

PROPOSED INDICATION(S)/PROPOSED CHANGE(S): Mucopolysaccharidosis type IVA (MPS IVA; Morquio A syndrome).

BACKGROUND: BioMarin is developing Recombinant N-acetylgalactosamine-6-sulfatase (BMN 110) as an enzyme replacement therapy (ERT) for the treatment of mucopolysaccharidosis IV Type A (Morquio A syndrome, MPS IVA). BMN 110 is produced in a genetically engineered Chinese Hamster Ovary mutant cell line that overexpresses the cDNA encoding for the full human GALNS protein.

On July 28, 2010, FDA and BioMarin met at a Pre-IND meeting to discuss a proposed phase 3 clinical study design and the adequacy of the clinical, nonclinical, and CMC programs for BMN 110. FDA provided comments regarding BioMarin's proposed study design and endpoints, including specific information that would be necessary to justify the use of the 6 Minute Walk Test (6MWT) as an acceptable clinical endpoint in clinical trials for MPS IVA.

As recommended by FDA at the Pre-IND meeting, BioMarin submitted a request for a special protocol assessment (SPA) of clinical protocol MOR-004 on December 3, 2010. FDA issued a SPA No-Agreement Letter on January 20, 2011. FDA agreed that the 6MWT could be used as a primary endpoint for the pivotal study in MPS IVA patients but did not agree with the proposed null hypothesis for the primary statistical analysis. BioMarin submitted a Type C meeting request on April 11, 2012, seeking agreement with the Agency on clinical and statistical aspects of the clinical development plan. The preliminary comments outlined FDA concerns regarding dosing, endpoints, trial duration, patient population, statistical issues, Following acceptance of the preliminary comments, the meeting was cancelled.

Two pre-BLA meetings were held in advance of the BLA submission, December 4, 2012, and November 13, 2012 (CMC only).

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Elizabeth Ford	Y
	CPMS/TL:	Brian Strongin	N
Cross-Discipline Team Leader (CDTL)	Jessica Lee		Y
Clinical	Reviewer:	Tamara Johnson	Y
	TL:	Jessica Lee	Y
Social Scientist Review (<i>for OTC products</i>)	Reviewer:	N/A	
	TL:	N/A	
OTC Labeling Review (<i>for OTC products</i>)	Reviewer:	N/A	
	TL:	N/A	
Clinical Microbiology (<i>for antimicrobial products</i>)	Reviewer:	N/A	
	TL:		

Clinical Pharmacology	Reviewer:	Christine Hon	Y
	TL:	Yow-Ming Wang	Y
Biostatistics	Reviewer:	Behrang Vali	Y
	TL:	Freda Cooner	Y
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Fang Cai	Y
	TL:	David Joseph	N
Statistics (carcinogenicity)	Reviewer:	N/A	
	TL:		
Immunogenicity (assay/assay validation) (<i>for BLAs/BLA efficacy supplements</i>)	Reviewer:	Jinhai Wang	Y
	TL:	Susan Kirshner	N
Product Quality (CMC)	Reviewer:	Cristina Ausin (DS) Richard Ledwidge (DP)	Y
	TL:	Emanuela Lacana (secondary) Susan Kirshner (tertiary)	N
Quality Microbiology (<i>for sterile products</i>)	Reviewer:	Candace Gomez (DS) Colleen Thomas (DP)	Y
	TL:	Patricia Hughes	Y
CMC Labeling Review	Reviewer:	Kimberly Rains	N
	TL:		
Facility Review/Inspection	Reviewer:	Cristina Ausin, Colleen Thomas, Candace Gomez	Y
	TL:	Patricia Hughes, Emanuela Lacana	Y
OSE/DMEPA (proprietary name)	Reviewer:	Denise Baugh	Y
	TL:	Lubna Merchant	Y
OSE/DRISK (REMS)	Reviewer:	George Neyarapally	Y
	TL:	Kendra Worthy	Y
OSE/DPV	Reviewer:	Thang La	N
	TL:	Eileen Wu	Y

OSE/DEPI	Reviewer:	David Shih	
	TL:	David Shih	
OC/OSI/DSC/PMSB (REMS)	Reviewer:	Khairy Malek (OSI)	Y
	TL:	Susan Leibenhaut	N
Other reviewers	Reviewer:		
	TL:		
Other attendees			

FILING MEETING DISCUSSION:

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

If no, explain:	
<ul style="list-style-type: none"> Advisory Committee Meeting needed? <p>Comments:</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"> <i>this drug/biologic is not the first in its class</i> <i>the clinical study design was acceptable</i> <i>the application did not raise significant safety or efficacy issues</i> <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> 	<input type="checkbox"/> YES Date if known: <input type="checkbox"/> NO <input checked="" type="checkbox"/> To be determined Reason:
<ul style="list-style-type: none"> Abuse Liability/Potential <p>Comments:</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
<ul style="list-style-type: none"> 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? <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<p>CLINICAL MICROBIOLOGY</p> <p>Comments:</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>CLINICAL PHARMACOLOGY</p> <p>Comments:</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"> Clinical pharmacology study site(s) inspections(s) needed? 	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<p>BIostatISTICS</p> <p>Comments:</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>NONCLINICAL (PHARMACOLOGY/TOXICOLOGY)</p> <p>Comments:</p>	<p><input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE</p> <p><input type="checkbox"/> Review issues for 74-day letter</p>
<p>IMMUNOGENICITY (BLAs/BLA efficacy supplements only)</p> <p>Comments:</p>	<p><input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE</p> <p><input type="checkbox"/> Review issues for 74-day letter</p>
<p>PRODUCT QUALITY (CMC)</p> <p>Comments:</p>	<p><input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE</p> <p><input checked="" type="checkbox"/> Review issues for 74-day letter</p>
<p><u>Environmental Assessment</u></p> <ul style="list-style-type: none"> • Categorical exclusion for environmental assessment (EA) requested? <p style="padding-left: 40px;">If no, was a complete EA submitted?</p> <p style="padding-left: 40px;">If EA submitted, consulted to EA officer (OPS)?</p> <p>Comments:</p>	<p><input type="checkbox"/> Not Applicable</p> <p><input checked="" type="checkbox"/> YES <input type="checkbox"/> NO</p> <p><input type="checkbox"/> YES <input type="checkbox"/> NO</p> <p><input type="checkbox"/> YES <input type="checkbox"/> NO</p>
<p><u>Quality Microbiology (for sterile products)</u></p> <ul style="list-style-type: none"> • Was the Microbiology Team consulted for validation of sterilization? (NDAs/NDA supplements only) <p>Comments:</p>	<p><input type="checkbox"/> Not Applicable</p> <p><input type="checkbox"/> YES <input type="checkbox"/> NO</p>
<p><u>Facility Inspection</u></p> <ul style="list-style-type: none"> • Establishment(s) ready for inspection? ▪ Establishment Evaluation Request (EER/TBP-EER) submitted to OMPQ? <p>Comments:</p>	<p><input type="checkbox"/> Not Applicable</p> <p><input checked="" type="checkbox"/> YES <input type="checkbox"/> NO</p> <p><input checked="" type="checkbox"/> YES <input type="checkbox"/> NO</p>

<p><u>Facility/Microbiology Review (BLAs only)</u></p> <p>Comments: Applicant provided deficient items in submission dated May 10, 2013. BMAB indicated application can be filed.</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><u>CMC Labeling Review</u></p> <p>Comments:</p>	<input type="checkbox"/> Review issues for 74-day letter
<p><u>APPLICATIONS IN THE PROGRAM (PDUFA V) (NME NDAs/Original BLAs)</u></p> <ul style="list-style-type: none"> • Were there agreements made at the application's pre-submission meeting (and documented in the minutes) regarding certain late submission components that could be submitted within 30 days after receipt of the original application? • If so, were the late submission components all submitted within 30 days? 	<input type="checkbox"/> N/A <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> • What late submission components, if any, arrived after 30 days? 	<p>Filing deficiencies identified by BMAB submitted on May 10, 2013. Clinical Pharmacology filing deficiencies submitted May 10, 2013.</p>
<ul style="list-style-type: none"> • Was the application otherwise complete upon submission, including those applications where there were no agreements regarding late submission components? 	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
<ul style="list-style-type: none"> • Is a comprehensive and readily located list of all clinical sites included or referenced in the application? 	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> • Is a comprehensive and readily located list of all manufacturing facilities included or referenced in the application? 	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO

REGULATORY PROJECT MANAGEMENT	
Signatory Authority: Julie Beitz, M.D., Director, Office of Drug Evaluation III	
Date of Mid-Cycle Meeting (for NME NDAs/BLAs in “the Program” PDUFA V): 7/18/2013	
21st Century Review Milestones (see attached) (listing review milestones in this document is optional):	
Comments:	
REGULATORY CONCLUSIONS/DEFICIENCIES	
<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. List (optional): <u>Review Classification:</u> <input type="checkbox"/> Standard Review <input checked="" type="checkbox"/> Priority Review
ACTIONS ITEMS	
<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, 505(b)(2), orphan drug).
<input type="checkbox"/>	If RTF, notify everybody 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 checked="" type="checkbox"/>	BLA/BLA supplements: If filed, send 60-day filing letter
<input checked="" type="checkbox"/>	If priority review: <ul style="list-style-type: none"> • notify sponsor in writing by day 60 (For BLAs/BLA supplements: include in 60-day filing letter; For NDAs/NDA supplements: see CST for choices) • notify OMPQ (so facility inspections can be scheduled earlier)
<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 NME NDAs in the Program)
<input checked="" type="checkbox"/>	BLA/BLA supplements: Send the Product Information Sheet to the product reviewer and the Facility Information Sheet to the facility reviewer for completion. Ensure that the completed forms are forwarded to the CDER RMS-BLA Superuser for data entry into RMS-BLA one month prior to taking an action [These sheets may be found in the CST eRoom at: http://eroom.fda.gov/eRoom/CDER2/CDERStandardLettersCommittee/0_1685f]
<input type="checkbox"/>	Other

Appendix A (NDA and NDA Supplements only)

NOTE: The term "original application" or "original NDA" as used in this appendix denotes the NDA submitted. It does not refer to the reference drug product or "reference listed drug."

An original application is likely to be a 505(b)(2) application if:

- (1) it relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application,
- (2) it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval, or
- (3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

- (1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies),
- (2) No additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application, and.
- (3) All other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely

for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

- (1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2),
- (2) The applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement, or
- (3) The applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your OND ADRA or OND IO.

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

/s/

ELIZABETH A FORD
05/23/2013

BRIAN K STRONGIN
05/23/2013

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

To be completed for all new NDAs, BLAs, Efficacy Supplements, and PLR Conversion Supplements

Application: BLA 125460

Application Type: New BLA

Name of Drug: Vimizim (elosulfase alfa)

Applicant: BioMarin

Submission Date: March 29, 2013

Receipt Date: March 29, 2013

1.0 Regulatory History and Applicant's Main Proposals

BLA 125460/0, Vimizim (elosulfase alfa), was received on March 29, 2013 and is proposed for use in patients with Mucopolysaccharidosis type IVA (MPS IVA; Morquio A syndrome). Vimizim is to be administered once every week as an intravenous (IV) infusion.

2.0 Review of the Prescribing Information (PI)

This review is based on the applicant's submitted Microsoft Word format of the 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).

3.0 Conclusions/Recommendations

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

All SRPI format deficiencies of the PI will be conveyed to the applicant in the 60-day letter. The applicant will be asked to correct these deficiencies and resubmit the PI in Word format by June 10, 2013. The resubmitted PI will be used for further labeling review.

4.0 Appendix

Selected Requirements of Prescribing Information (SRPI)

The Selected Requirement of Prescribing Information (SRPI) version 2 is a 48-item, drop-down checklist of critical format elements of the prescribing information (PI) based on labeling regulations (21 CFR 201.56 and 201.57) and labeling guidances.

Highlights (HL)

GENERAL FORMAT

- YES** 1. Highlights (HL) must be in two-column format, with ½ inch margins on all sides and in a minimum of 8-point font.
- YES** 2. The length of HL must be less than or equal to one-half page (the HL Boxed Warning does not count against the one-half page requirement) unless a waiver has been granted in a previous submission (i.e., the application being reviewed is an efficacy supplement).
- YES** 3. All headings in HL must be presented in the center of a horizontal line, in UPPER-CASE letters and **bolded**.
- NO** 4. White space must be present before each major heading in HL.
***Comment:** The applicant must add white space before each major heading in HL.*
- YES** 5. Each summarized statement in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contains more detailed information. The preferred format is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each information summary (e.g. end of each bullet).
- YES** 6. Section headings are 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*
• Indications and Usage	Required
• Dosage and Administration	Required
• Dosage Forms and Strengths	Required
• Contraindications	Required (if no contraindications must state “None.”)
• Warnings and Precautions	Not required by regulation, but should be present
• Adverse Reactions	Required
• Drug Interactions	Optional

Selected Requirements of Prescribing Information (SRPI)

• Use in Specific Populations	Optional
• Patient Counseling Information Statement	Required
• Revision Date	Required

* RMC only applies to the Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions sections.

- YES** 7. A horizontal line must separate HL and Table of Contents (TOC).

HIGHLIGHTS DETAILS

Highlights Heading

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

Highlights Limitation Statement

- YES** 9. The **bolded** HL Limitation Statement must be on the line immediately beneath the HL heading and must state: “**These highlights do not include all the information needed to use (insert name of drug product in UPPER CASE) safely and effectively. See full prescribing information for (insert name of drug product in UPPER CASE).**”

Product Title

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

Initial U.S. Approval

- NO** 11. Initial U.S. Approval in HL must be placed immediately beneath the product title, **bolded**, and include the verbatim statement “**Initial U.S. Approval:**” followed by the **4-digit year**.

***Comment:** The Initial U.S. Approval must be in bold type and placed on the line immediately beneath established name or, for biological products, proper name of the product. Therefore, there must NOT be a space between the product title and initial U.S. approval lines.*

Boxed Warning

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

- N/A** 13. Must have a centered 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**”).

- N/A** 14. Must always have the verbatim statement “*See full prescribing information for complete boxed warning.*” centered immediately beneath the heading.

Selected Requirements of Prescribing Information (SRPI)

N/A 15. Must be limited in length to 20 lines (this does not include the heading and statement “*See full prescribing information for complete boxed warning.*”)

N/A 16. Use sentence case for summary (combination of uppercase and lowercase letters typical of that used in a sentence).

Recent Major Changes (RMC)

N/A 17. Pertains to only the following five sections of the FPI: Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions.

N/A 18. Must be listed in the same order in HL as they appear in FPI.

N/A 19. Includes heading(s) and, if appropriate, subheading(s) of labeling section(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, “Dosage and Administration, Coronary Stenting (2.2) --- 3/2012”.

N/A 20. 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).

Indications and Usage

N/A 21. If a product belongs to an established pharmacologic class, the following statement is required in the Indications and Usage section of HL: [(Product) is a (name of class) indicated for (indication)].”

Dosage Forms and Strengths

N/A 22. For a product that has several dosage forms, bulleted subheadings (e.g., capsules, tablets, injection, suspension) or tabular presentations of information is used.

Contraindications

YES 23. All contraindications listed in the FPI must also be listed in HL or must include the statement “None” if no contraindications are known.

N/A 24. Each contraindication is bulleted when there is more than one contraindication.

Selected Requirements of Prescribing Information (SRPI)

Adverse Reactions

- NO** 25. 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:** For manufacturers with a Web site for voluntary reporting of AR, the Web address of the direct link to the site may be included. An email address, fax number, or general link to a company’s website does not meet the requirement to have AR reporting contact information in HL. It would not provide a structured process for reporting AR. The applicant should ^{(b) (4)} inserted into this statement, or provide the web address of the direct link to the site.*

Patient Counseling Information Statement

- YES** 26. Must include one of the following three **bolded** verbatim statements (without quotation marks):

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.**”

Revision Date

- NO** 27. **Bolded** revision date (i.e., “**Revised: MM/YYYY or Month Year**”) must be at the end of HL.

***Comment:** The applicant should change the revision date from MM/2013 to MM/YYYY*

Contents: Table of Contents (TOC)

GENERAL FORMAT

- YES** 28. A horizontal line must separate TOC from the FPI.
- YES** 29. The following **bolded** heading in all UPPER CASE letters must appear at the beginning of TOC: “**FULL PRESCRIBING INFORMATION: CONTENTS**”.
- YES** 30. The section headings and subheadings (including title of the Boxed Warning) in the TOC must match the headings and subheadings in the FPI.
- N/A** 31. The same title for the Boxed Warning that appears in the HL and FPI must also appear at the beginning of the TOC in UPPER-CASE letters and **bolded**.

Selected Requirements of Prescribing Information (SRPI)

- NO** 32. All section headings must be **bolded** and in UPPER CASE.
Comment: Section headings must be bolded.
- YES** 33. All subsection headings must be indented, not bolded, and in title case.
- YES** 34. When a section or subsection is omitted, the numbering does not change.
- YES** 35. 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.”

Full Prescribing Information (FPI)

GENERAL FORMAT

- YES** 36. The following heading must appear at the beginning of the FPI in UPPER CASE and **bolded**: “**FULL PRESCRIBING INFORMATION**”.
- YES** 37. All section and subsection headings and numbers must be **bolded**.
- YES** 38. The **bolded** section and subsection headings must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below. If a section/subsection is omitted, the numbering does not change.

Boxed Warning
1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
6 ADVERSE REACTIONS
7 DRUG INTERACTIONS
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

Selected Requirements of Prescribing Information (SRPI)

12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
12.4 Microbiology (by guidance)
12.5 Pharmacogenomics (by guidance)
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology
14 CLINICAL STUDIES
15 REFERENCES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

- N/A** 39. 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 patient labeling must appear at the end of the PI upon approval.
- YES** 40. The preferred presentation for cross-references in the FPI is the section heading (not subsection heading) followed by the numerical identifier in italics. For example, [*see Warnings and Precautions (5.2)*].
- N/A** 41. 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.

FULL PRESCRIBING INFORMATION DETAILS

Boxed Warning

- N/A** 42. All text is **bolded**.
- N/A** 43. 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**”).
- N/A** 44. Use sentence case (combination of uppercase and lowercase letters typical of that used in a sentence) for the information in the Boxed Warning.

Contraindications

- YES** 45. If no Contraindications are known, this section must state “None”.

Adverse Reactions

- NO** 46. When clinical trials adverse reactions data is 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:

Selected Requirements of Prescribing Information (SRPI)

“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 clinical practice.”

Comment: The applicant should correct their statement from [REDACTED] (b) (4) to “...the rates observed in clinical [REDACTED] (b) (4)”

N/A

47. When postmarketing adverse reaction data is 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.”

Patient Counseling Information

N/A

48. Must reference any FDA-approved patient labeling, include the type of patient labeling, and use one of the following statements at the beginning of Section 17:
- “See FDA-approved patient labeling (Medication Guide)”
 - “See FDA-approved patient labeling (Medication Guide and Instructions for Use)”
 - “See FDA-approved patient labeling (Patient Information)”
 - “See FDA-approved patient labeling (Instructions for Use)”
 - “See FDA-approved patient labeling (Patient Information and Instructions for Use)”
-

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/s/

ELIZABETH A FORD
05/22/2013

BRIAN K STRONGIN
05/22/2013