CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

202535Orig1s000

<u>OTHER REVIEW(S)</u>

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 # NDA 202535
Product Name: Prepopik

PMR/PMC Description: 1902-4
A retrospective study to identify the risk factors associated with development of persistent deterioration of renal function in patients undergoing colon cleansing in preparation for colonoscopy.

PMR/PMC Schedule Milestones:		
	Final Protocol Submission:	03/2013
	Study/Trial Completion:	06/2014
	Final Report Submission:	12/2014
	Other:	MM/DD/YYYY

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
   x Long-term data needed
   ☐ Only feasible to conduct post-approval
   ☐ Prior clinical experience indicates safety
   ☐ Small subpopulation affected
   ☐ Theoretical concern
   Other

   It is important to further evaluate the risk factors associated with the development of persistent deterioration of renal function in patients undergoing colon cleansing in preparation for colonoscopy.

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."

Reference ID: 3159462

The study will identify those patients with a decrease in renal function and compare any difference in risk factors or clinical status with those patients who did not have renal dysfunction.

This study should evaluate all available data for all patients at any point during studies FE2009-01 and FE2009-02, including relevant clinical data not recorded in the CRF such as volume of fluid administered during the colonoscopy and vital signs recorded during the colonoscopy. Identify those patients with a decrease in renal function and compare any difference in risk factors or clinical status with those patients who did not have renal dysfunction.

Evaluate any patient who had a decline in renal function as measured by a decline in eGFR at the Day 30 assessment by collecting additional information with regard to renal function beyond the Day 30 assessment including concomitant medication use, additional procedures, and inter-current illness.

The application for the adult usage of Prepopik has suggested a potential signal for renal dysfunction. Additional information regarding the outcomes on the patients identified in the clinical trials will need to be gathered. The rates are similar to the comparator, HalfLytely.

It should be noted that available data for other drugs in the same pharmacological class indicate a potential for adverse events including fluid and electrolyte disturbances, cardiac arrhythmia, and renal impairment. (see labeling)

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
     x 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?
     X 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

Reference ID: 3159462

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

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

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

A retrospective study to identify the risk factors associated with development of persistent deterioration of renal function in patients undergoing colon cleansing in preparation for colonoscopy.

- **This study should evaluate all available data for all patients at any point during studies FE2009-01 and FE2009-02, including relevant clinical data not recorded in the CRF such as volume of fluid administered during the colonoscopy and vital signs recorded during the colonoscopy. Identify those patients with a decrease in renal function and compare any difference in risk factors or clinical status with those patients who did not have renal dysfunction.**

- **Evaluate any patients who had a decline in renal function as measured by a decline in eGFR at the Day 30 assessment by collecting additional information with regard to renal function beyond the Day 30 assessment including concomitant medication use, additional procedures, and inter-current illness**

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
☐ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

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

Reference ID: 3159462

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?

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

PMR/PMC Development Coordinator:

X *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.*

Reference ID: 3159462

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/s/

ZANA H MARKS
07/16/2012

ROBERT FIORENTINO
07/16/2012

JOYCE A KORVICK
07/16/2012

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 #	NDA 202535
Product Name:	Prepopik

PMR/PMC Description: 1902-3 PREA Study 3	A randomized, single-blind, multicenter dose ranging study comparing the safety and efficacy of Prepopik to community standard of care in children (ages 12 months to <2 years). This study will include PK assessments.

PMR/PMC Schedule Milestones:	Final Protocol Submission:	02/28/2018
	Study/Trial Completion:	08/31/ 2019
	Final Report Submission:	02/28/2020
	Other: _____	MM/DD/YYYY

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
   x Other

   The Division met with the Pediatric Review Committee (PeRC) 7/11/2012. The PeRC agreed that post marketing studies for the pediatric population using this drug should include a study designed to assess efficacy, safety and PK in pediatric subjects ages 12months to <2 years old. They also agreed that the sponsor will need to conduct dose ranging studies across all age groups;12 months - <2 years; 2-<9years; >9 years. The sponsor should include an analysis of available data originating from controlled clinical studies of Prepopik (or identical formulations) in pediatric patients, as well as post marketing safety data from countries where Prepopik (or identical formulations) is approved for pediatric use.

   While no safety signals have emerged from review of the application for adult usage, there are some class effects that may be experienced with osmotic bowel cleansing preparations such as Prepopik. These include but are not limited to fluid shifts (dehydration) and electrolyte imbalances. This product is approved for pediatric usage in the UK and Canada.

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."

Reference ID: 3159533

Prepopik is an approved bowel cleansing agent in pediatric patients in the UK and Canada. This drug was not studied for pediatric usage in the United States. The application for the adult usage of Prepopik has revealed no safety signals. Review of similar osmotic bowel cleansing agents demonstrates class effects from usage may exist . Some possible class effect safety concerns include fluid shifts (dehydration), electrolyte imbalances, renal impairment and cardiac arrhythmias.

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
     x Pediatric Research Equity Act
     ☐ FDAAA required safety study/clinical trial

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

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

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

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

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

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

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

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

A randomized, single-blind, multicenter dose ranging study comparing the safety and efficacy of Prepopik to community standard of care in children (ages 12 months to <2 years). This study will include PK assessments.

Reference ID: 3159533

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
☐ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
x Pharmacokinetic studies or clinical trials
☐ Drug interaction or bioavailability studies or clinical trials
☐ Dosing trials
☐ 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)

x Other

A randomized, single-blind, multicenter dose ranging study comparing the safety and efficacy of Prepopik to community standard of care in children (ages 12 months to <2 years). This study will include PK assessments.

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

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

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)

Reference ID: 3159533

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/s/

ZANA H MARKS
07/16/2012

ROBERT FIORENTINO
07/16/2012

JOYCE A KORVICK
07/16/2012

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 #	NDA 202535
Product Name:	Prepopik
PMR/PMC Description: 1902-2 PREA Study 2	A randomized, single-blind, multicenter dose ranging study comparing the safety and efficacy of Prepopik to community standard of care in children (ages 2 years to <9 years). This study will include PK assessments.

PMR/PMC Schedule Milestones:	Final Protocol Submission:	02/28/2016
	Study/Trial Completion:	02/28/ 2019
	Final Report Submission:	08/31/2019
	Other: _____	MM/DD/YYYY

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
   x Other

   The Division met with the Pediatric Review Committee (PeRC) 7/11/2012. The PeRC agreed that post marketing studies for the pediatric population using this drug should include a study designed to assess efficacy, safety and PK in pediatric subjects ages 2-<9 years old. They also agreed that the sponsor will need to conduct dose ranging studies across all age groups; 1-<2 years; 2- <9years; >9 years. The sponsor should include an analysis of available data originating from controlled clinical studies of Prepopik (or identical formulations) in pediatric patients, as well as post marketing safety data from countries where Prepopik (or identical formulations) is approved for pediatric use.

   While no safety signals have emerged from review of the application for adult usage, there are some class effects that may be experienced with osmotic bowel cleansing preparations such as Prepopik. These include but are not limited to fluid shifts (dehydration) and electrolyte imbalances. This product is approved for pediatric usage in the UK and Canada.

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."

Reference ID: 3159526

Prepopik is an approved bowel cleansing agent in pediatric patients in the UK and Canada. This drug was not studied for pediatric usage in the United States. The application for the adult usage of Prepopik has revealed no safety signals. Review of similar osmotic bowel cleansing agents demonstrates class effects from usage may exist . Some possible class effect safety concerns include fluid shifts (dehydration), electrolyte imbalances, renal impairment and cardiac arrhythmias.

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
     x Pediatric Research Equity Act
     ☐ FDAAA required safety study/clinical trial

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

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

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

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

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

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

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

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

A randomized, single-blind, multicenter dose ranging study comparing the safety and efficacy of Prepopik to community standard of care in children (ages 2 years to <9 years). This study will include PK assessments.

Reference ID: 3159526

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
☐ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
x Pharmacokinetic studies or clinical trials
☐ Drug interaction or bioavailability studies or clinical trials
☐ Dosing trials
☐ 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)

x Other

A randomized, single-blind, multicenter dose ranging study comparing the safety and efficacy of Prepopik to community standard of care. in children (ages 2 years to <9 years). This study will include PK assessments.

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

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

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)

Reference ID: 3159526

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/s/

ZANA H MARKS
07/16/2012

ROBERT FIORENTINO
07/16/2012

JOYCE A KORVICK
07/16/2012

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 # NDA 202535
Product Name: Prepopik

PMR/PMC Description: 1902-1 PREA Study 1
A randomized, single-blind, multicenter, dose ranging study comparing the safety and efficacy of Prepopik to community standard of care in children (ages 9 years to 16 years). This study will include PK assessments.

PMR/PMC Schedule Milestones:		
	Final Protocol Submission:	02/28/2013
	Study/Trial Completion:	02/28/ 2016
	Final Report Submission:	08/31/2016
	Other: _____	MM/DD/YYYY

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
   x Other

   The Division met with the Pediatric Review Committee (PeRC) 7/11/2012. The PeRC agreed that post marketing studies for the pediatric population using this drug should include a study designed to assess efficacy, safety and PK in pediatric subjects ages 9-16 years old. They also agreed that the sponsor will need to conduct dose ranging studies across all age groups; 1- <2 years; 2-<9years; >9 years. The sponsor should include an analysis of available data originating from controlled clinical studies of Prepopik (or identical formulations) in pediatric patients, as well as post marketing safety data from countries where Prepopik (or identical formulations) is approved for pediatric use.
   While no safety signals have emerged from review of the application for adult usage, there are some class effects that may be experienced with osmotic bowel cleansing preparations such as Prepopik. These include but are not limited to fluid shifts (dehydration) and electrolyte imbalances. This product is approved for pediatric usage in the UK and Canada.

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."

Reference ID: 3159517

Prepopik is an approved bowel cleansing agent in pediatric patients in the UK and Canada. This drug was not studied for pediatric usage in the United States. The application for the adult usage of Prepopik has revealed no safety signals. Review of similar osmotic bowel cleansing agents demonstrates class effects from usage may exist . Some possible class effect safety concerns include fluid shifts (dehydration), electrolyte imbalances, renal impairment and cardiac arrhythmias.

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
     x Pediatric Research Equity Act
     ☐ FDAAA required safety study/clinical trial

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

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

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

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

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

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

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

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

A randomized, single-blind, multicenter, dose ranging study comparing the safety and efficacy of Prepopik community standard of care in children (ages 9 years to 16 years). This study will include PK assessments.

Reference ID: 3159517

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
☐ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
x Pharmacokinetic studies or clinical trials
☐ Drug interaction or bioavailability studies or clinical trials
☐ Dosing trials
☐ 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)

x Other

A randomized, single-blind, multicenter, dose ranging study comparing the safety and efficacy of Prepopik to community standard of care in children (ages 9 years to 16 years). This study will include PK assessments.

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

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

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)

Reference ID: 3159517

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/s/

ZANA H MARKS
07/16/2012

ROBERT FIORENTINO
07/16/2012

JOYCE A KORVICK
07/16/2012

505(b)(2) ASSESSMENT

Application Information		
NDA # 202535	NDA Supplement #: S-	Efficacy Supplement Type SE-
Proprietary Name: Prepopik Established/Proper Name: sodium picosulfate, magnesium oxide and anhydrous citric acid Dosage Form: powder for oral solution Strengths: 10 mg/3,5 g/12 g		
Applicant: Ferring Pharmaceuticals		
Date of Receipt: 09/16/2011		
PDUFA Goal Date: 07/16/2012	Action Goal Date (if different):	
Proposed Indication(s): cleansing of the colon as a preparation for colonoscopy in adults.		

GENERAL INFORMATION

1) Is this application for a recombinant or biologically-derived product and/or protein or peptide product *OR* is the applicant relying on a recombinant or biologically-derived product and/or protein or peptide product to support approval of the proposed product?

YES ☐ NO ☒

*If "**YES** "contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

INFORMATION PROVIDED VIA RELIANCE (LISTED DRUG OR LITERATURE)

2) List the information essential to the approval of the proposed drug that is provided by reliance on our previous finding of safety and efficacy for a listed drug or by reliance on published literature. *(If not clearly identified by the applicant, this information can usually be derived from annotated labeling.)*

Source of information* (e.g., published literature, name of referenced product)	Information provided (e.g., pharmacokinetic data, or specific sections of labeling)
Published literature	**Clinical information to address combination rule**

*each source of information should be listed on separate rows

3) Reliance on information regarding another product (whether a previously approved product or from published literature) must be scientifically appropriate. An applicant needs to provide a scientific "bridge" to demonstrate the relationship of the referenced and proposed products. Describe how the applicant bridged the proposed product to the referenced product(s). (Example: BA/BE studies)

The requirements for fixed combination prescription drugs found in 21 CFR 300.50 apply to NDA 202535 Prepopik (sodium picosulfate, magnesium oxide, and anhydrous citric acid). The review division examined literature for evidence regarding the adequacy of each component of Prepopik as single agents and identified literature studies with bisacodyl and magnesium citrate. Sodium picosulfate and bisacodyl are prodrugs that have the same active metabolite. Magnesium oxide and anhydrous citric acid when mixed in water form magnesium citrate.

FDA has typically interpreted the regulations at 21 CFR 300.50 to require a factorial analysis of proposed combination ingredients that demonstrates that the combination is more effective than each component of the combination alone. Although FDA may require sponsors to conduct a factorial analysis of proposed combination ingredients, sponsors may meet the requirements of 21 CFR 300.50 in other ways. Factorial studies may not be necessary or ethical in certain cases, and FDA may exercise its discretion and need not require an applicant to conduct a clinical study with a factorial design if the Agency deems it unnecessary.

RELIANCE ON PUBLISHED LITERATURE

4) (a) Regardless of whether the applicant has explicitly stated a reliance on published literature to support their application, is reliance on published literature necessary to support the approval of the proposed drug product (i.e., the application *cannot* be approved without the published literature)?

YES ☒ NO ☐

*If "**NO**," proceed to question #5.*

(b) Does any of the published literature necessary to support approval identify a specific (e.g., brand name) *listed* drug product?

YES ☐ NO ☒

*If "**NO**", proceed to question #5.*
*If "**YES**", list the listed drug(s) identified by name and answer question #4(c).*

(c) Are the drug product(s) listed in (b) identified by the applicant as the listed drug(s)?

YES ☐ NO ☐

RELIANCE ON LISTED DRUG(S)

Reliance on published literature which identifies a specific approved (listed) drug constitutes reliance on that listed drug. Please answer questions #5-9 accordingly.

5) Regardless of whether the applicant has explicitly referenced the listed drug(s), does the application **rely** on the finding of safety and effectiveness for one or more listed drugs (approved drugs) to support the approval of the proposed drug product (i.e., the application cannot be approved without this reliance)?

YES ☐ NO ☒

*If "**NO**," proceed to question #10.*

6) Name of listed drug(s) relied upon, and the NDA/ANDA #(s). Please indicate if the applicant explicitly identified the product as being relied upon (see note below):

Name of Drug	NDA/ANDA #	Did applicant specify reliance on the product? (Y/N)

Applicants should specify reliance on the 356h, in the cover letter, and/or with their patent certification/statement. If you believe there is reliance on a listed product that has not been explicitly identified as such by the applicant, please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

7) If this is a (b)(2) supplement to an original (b)(2) application, does the supplement rely upon the same listed drug(s) as the original (b)(2) application?

N/A ☐ YES ☐ NO ☐

*If this application is a (b)(2) supplement to an original (b)(1) application or not a supplemental application, answer "**N/A**".*
*If "**NO**", please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

8) Were any of the listed drug(s) relied upon for this application:
   a) Approved in a 505(b)(2) application?

YES ☐ NO ☐

*If "**YES**", please list which drug(s).*

Name of drug(s) approved in a 505(b)(2) application:

b) Approved by the DESI process?

YES ☐ NO ☐

*If "**YES**", please list which drug(s).*

Name of drug(s) approved via the DESI process:

c) Described in a monograph?

YES ☐ NO ☐

*If "**YES**", please list which drug(s).*

Name of drug(s) described in a monograph:

d) Discontinued from marketing?

YES ☐ NO ☐

*If "**YES**", please list which drug(s) and answer question d) i. below.*
*If "**NO**", proceed to question #9.*

Name of drug(s) discontinued from marketing:

i) Were the products discontinued for reasons related to safety or effectiveness?

YES ☐ NO ☐

(Information regarding whether a drug has been discontinued from marketing for reasons of safety or effectiveness may be available in the Orange Book. Refer to section 1.11 for an explanation, and section 6.1 for the list of discontinued drugs. If a determination of the reason for discontinuation has not been published in the Federal Register (and noted in the Orange Book), you will need to research the archive file and/or consult with the review team. Do not rely solely on any statements made by the sponsor.)

9) Describe the change from the listed drug(s) relied upon to support this (b)(2) application (for example, "This application provides for a new indication, otitis media" or "This application provides for a change in dosage form, from capsule to solution").

The purpose of the following two questions is to determine if there is an approved drug product that is equivalent or very similar to the product proposed for approval that should be referenced as a listed drug in the pending application.

*The assessment of pharmaceutical equivalence for a recombinant or biologically-derived product and/or protein or peptide product is complex. If you answered **YES to question #1**, proceed to question #12; if you answered **NO to question #1**, proceed to question #10 below.*

10) (a) Is there a pharmaceutical equivalent(s) to the product proposed in the 505(b)(2) application that is already approved (via an NDA or ANDA)?

*(**Pharmaceutical equivalents** are drug products in identical dosage forms that: **(1)** contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; **(2)** do not necessarily contain the same inactive ingredients; **and (3)** meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including*

potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates. (21 CFR 320.1(c)).

***Note** that for proposed combinations of one or more previously approved drugs, a pharmaceutical equivalent must also be a combination of the same drugs.*

YES ☐ NO ☒

*If "**NO**" to (a) proceed to question #11.*
*If "**YES**" to (a), answer (b) and (c) then proceed to question #12.*

(b) Is the pharmaceutical equivalent approved for the same indication for which the 505(b)(2) application is seeking approval?

YES ☐ NO ☐

(c) Is the listed drug(s) referenced by the application a pharmaceutical equivalent?

YES ☐ NO ☐

*If "**YES**" to (c) <u>and</u> there are no additional pharmaceutical equivalents listed, proceed to question #12.*
*If "**NO**" <u>or</u> if there are additional pharmaceutical equivalents that are not referenced by the application, list the NDA pharmaceutical equivalent(s); you do <u>not</u> have to individually list all of the products approved as ANDAs, but please note below if approved approved generics are listed in the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

Pharmaceutical equivalent(s):

11) (a) Is there a pharmaceutical alternative(s) already approved (via an NDA or ANDA)?

*(**Pharmaceutical alternatives** are drug products that contain the identical therapeutic moiety, or its precursor, but not necessarily in the same amount or dosage form or as the same salt or ester. Each such drug product individually meets either the identical or its own respective compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times and/or dissolution rates. (21 CFR 320.1(d)) Different dosage forms and strengths within a product line by a single manufacturer are thus pharmaceutical alternatives, as are extended-release products when compared with immediate- or standard-release formulations of the same active ingredient.)*

***Note** that for proposed combinations of one or more previously approved drugs, a pharmaceutical alternative must also be a combination of the same drugs.*

YES ☐ NO ☒

*If "**NO**", proceed to question #12.*

(b) Is the pharmaceutical alternative approved for the same indication for which the 505(b)(2) application is seeking approval?

YES ☐ NO ☐

(c) Is the approved pharmaceutical alternative(s) referenced as the listed drug(s)?

YES ☐ NO ☐

*If "**YES**" and there are no additional pharmaceutical alternatives listed, proceed to question #12.*
*If "**NO**" or if there are additional pharmaceutical alternatives that are not referenced by the application, list the NDA pharmaceutical alternative(s); you do not have to individually list all of the products approved as ANDAs, but please note below if approved generics are listed in the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

Pharmaceutical alternative(s):

PATENT CERTIFICATION/STATEMENTS

12) List the patent numbers of all unexpired patents listed in the Orange Book for the listed drug(s) for which our finding of safety and effectiveness is relied upon to support approval of the (b)(2) product.

Listed drug/Patent number(s):

No patents listed ☐ *proceed to question #14*

13) Did the applicant address (with an appropriate certification or statement) all of the unexpired patents listed in the Orange Book for the listed drug(s) relied upon to support approval of the (b)(2) product?

YES ☐ NO ☐

*If "**NO**", list which patents (and which listed drugs) were not addressed by the applicant.*

Listed drug/Patent number(s):

14) Which of the following patent certifications does the application contain? *(Check all that apply and identify the patents to which each type of certification was made, as appropriate.)*

☒ No patent certifications are required (e.g., because application is based solely on published literature that does not cite a specific innovator product)

☐ 21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA. (Paragraph I certification)

☐ 21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired. (Paragraph II certification)

Patent number(s):

☐ 21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire. (Paragraph III certification)

Patent number(s): Expiry date(s):

☐ 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be

infringed by the manufacture, use, or sale of the drug product for which the application is submitted. (Paragraph IV certification). *If Paragraph IV certification was submitted, proceed to question #15.*

☐ 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the NDA holder/patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above). *If the applicant has a licensing agreement with the NDA holder/patent owner, proceed to question #15.*

☐ 21 CFR 314.50(i)(1)(ii): No relevant patents.

☐ 21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent as described in the corresponding use code in the Orange Book. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications. (Section viii statement)

Patent number(s):
Method(s) of Use/Code(s):

15) Complete the following checklist ***ONLY*** for applications containing Paragraph IV certification and/or applications in which the applicant and patent holder have a licensing agreement:

(a) Patent number(s):
(b) Did the applicant submit a signed certification stating that the NDA holder and patent owner(s) were notified that this b(2) application was filed [21 CFR 314.52(b)]?

YES ☐ NO ☐

*If "**NO**", please contact the applicant and request the signed certification.*

(c) Did the applicant submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)]? This is generally provided in the form of a registered mail receipt.

YES ☐ NO ☐

*If "**NO**", please contact the applicant and request the documentation.*

(d) What is/are the date(s) on the registered mail receipt(s) (i.e., the date(s) the NDA holder and patent owner(s) received notification):

Date(s):

(e) Has the applicant been sued for patent infringement within 45-days of receipt of the notification listed above?

***Note** that you may need to call the applicant (after 45 days of receipt of the notification) to verify this information **UNLESS** the applicant provided a written statement from the notified patent owner(s) that it consents to an immediate effective date of approval.*

YES ☐ NO ☐ Patent owner(s) consent(s) to an immediate effective date of ☐

approval

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/s/

MAUREEN D DEWEY
07/09/2012

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

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

Memorandum

Date: July 5, 2012

To: Maureen Dewey, M.P.H.
Senior Regulatory Project Manager
Division Gastroenterology and Inborn Error Products (DGIEP)

From: Eunice Chung-Davies, PharmD., Regulatory Review Officer
Division of Consumer Drug Promotion (DCDP)

CC: Kathleen Klemm, Pharm.D., Regulatory Review Officer
Division of Professional Drug Promotion (DPDP)

Subject: DCDP's comments for NDA 202535
PICOPREP (sodium picosulfate, magnesium oxide, and anhydrous citric acid) powder for oral solution

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On January 6, 2012, DCDP received a consult request from DGIEP to review the proposed medication guide for PICOPREP (sodium picosulfate, magnesium oxide, and anhydrous citric acid) powder for oral solution.

DCDP has reviewed the proposed labeling using the following version of the proposed label:

- sodium picosulfate magnesium oxide and anhydrous citric acid (PICOPREP) NDA 202535 DMPP MG review clean copy.doc (received July 5, 2012)
- PICOPREP draft PI w Med Guide 2012-06-18.doc (Version 31 accessed in e-room on June 29, 2012)

Upon review of the proposed labeling, DCDP offers the following comments.

If you have any questions regarding the patient labeling, please contact Eunice Chung-Davies at 301-796-4006 or eunice.chung-davies@fda.hhs.gov .

Enclosure:
Marked up Medication Guide

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

Reference ID: 3155063

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/s/

EUNICE H CHUNG-DAVIES
07/05/2012

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

PATIENT LABELING REVIEW

Date:	July 3, 2012
To:	Donna Griebel, MD Director **Division of Gastroenterology and Inborn Errors Products (DGIEP)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)** Barbara Fuller, RN, MSN, CWOCN Team Leader, Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Latonia M. Ford, RN, BSN, MBA Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)**
Subject:	DMPP Review of Patient Labeling: Medication Guide (MG)
Drug Name (established name):	PICOPREP (sodium picosulfate, magnesium oxide and anhydrous citric acid)
Dosage Form and Route:	powder for oral solution
Application Type/Number:	NDA 202535
Applicant:	Ferring Pharmaceuticals Inc.

1 INTRODUCTION

On September 16, 2011, Ferring Pharmaceuticals Inc. submitted an Original New Drug Application (NDA) 202535 under Section 505(b) of the Food, Drug and Cosmetic Act for PICOPREP (sodium picosulfate, magnesium oxide and anhydrous citric acid) powder for oral solution. The Applicant's proposed indication for PICOPREP (sodium picosulfate, magnesium oxide and anhydrous citric acid) powder for oral solution is for cleansing of the colon as a preparation for colonoscopy in adults.

On January 10, 2012, the Division of Gastroenterology and Inborn Error Products (DGIEP) requested that the Division of Medical Policy Programs (DMPP) review the Applicant's proposed Medication Guide (MG) for PICOPREP (sodium picosulfate, magnesium oxide and anhydrous citric acid) powder for oral solution.

This review is written in response to a request by DGIEP for DMPP to review the Applicant's proposed Medication Guide (MG) for PICOPREP (sodium picosulfate, magnesium oxide and anhydrous citric acid) powder for oral solution.

2 MATERIAL REVIEWED

- Draft PICOPREP (sodium picosulfate, magnesium oxide and anhydrous citric acid) powder for oral solution Medication Guide (MG) received on September 16, 2011, revised by the Review Division throughout the review cycle, and received by DMPP on June 28, 2012.
- Draft PICOPREP (sodium picosulfate, magnesium oxide and anhydrous citric acid) powder for oral solution Prescribing Information (PI) received on September 16, 2011, revised by the Review Division throughout the review cycle, and received by DMPP on June 28, 2012.
- Approved SUPREP Bowel Prep Kit (sodium sulfate, potassium sulfate, and magnesium sulfate) Oral Solution comparator labeling dated August 10, 2010.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level. In our review of the MG the target reading level is at or below an 8th grade level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss. We have reformatted the MG document using the Verdana font, size 11.

In our review of the MG we have:

- simplified wording and clarified concepts where possible
- ensured that the MG is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20
- ensured that the MG meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)
- ensured that the MG is consistent with the approved comparator labeling where applicable.

4 CONCLUSIONS

The MG is acceptable with our recommended changes.

5 RECOMMENDATIONS

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

Please let us know if you have any questions.

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

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/s/

LATONIA M FORD
07/03/2012

BARBARA A FULLER
07/03/2012

LASHAWN M GRIFFITHS
07/03/2012

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

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

Memorandum

Date: July 3, 2012

To: Maureen Dewey, Senior Regulatory Project Manager
Division of Gastroenterology and Inborn Errors Products (DGIEP)

From: Kathleen Klemm, Regulatory Review Officer
Division of Professional Drug Promotion (DPDP)
Office of Prescription Drug Promotion (OPDP)

CC: Lisa Hubbard, Group Leader, DPDP, OPDP

Eunice Chung-Davies, Regulatory Review Officer
Division of Consumer Drug Promotion (DCDP), OPDP

Subject: NDA 202535
OPDP labeling comments for PICOPREP (sodium picosulfate, magnesium oxide, and anhydrous citric acid) powder for oral solution (Picoprep)

OPDP has reviewed the proposed Package Insert (PI) for PICOPREP (sodium picosulfate, magnesium oxide, and anhydrous citric acid) power for oral solution (Picoprep) submitted for consult on January 6, 2012, and offers the following comments.

OPDP's comments on the PI are based on Version 32 of the proposed draft marked-up labeling titled, "PICOPREP draft PI w Med Guide 2012-06-18.doc" accessed via the eRoom.

OPDP's comments on the PI are provided directly in the marked-up document attached below. (Please note that we hid previous track changes in order for our comments to be more easily viewed.)

OPDP's comments on the proposed patient labeling will follow under separate cover at a later date.

Thank you for the opportunity to comment on the proposed labeling. If you have any questions regarding the PI, please contact Katie Klemm at 301-796-3946 or Kathleen.klemm@fda.hhs.gov.

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

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/s/

KATHLEEN KLEMM
07/03/2012

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

Product Title	**PICOPREP (sodium picosulfate, magnesium oxide, and anhydrous citric acid) powder for oral solution**
Applicant	Ferring Pharmaceuticals Inc.
Application/Supplement Number	NDA 202535
Type of Application	Original NDA
Indication	PICOPREP™ is indicated for cleansing of the colon as a preparation for colonoscopy in adults.
Established Pharmacologic Class[1]	Stimulant laxative and osmotic laxative
Office/Division	Office of New Drugs/Division of Gastroenterology and Inborn Errors Products (OND/DGIEP)
Division Project Manager	Maureen Dewey, M.P.H.
Receipt Date	September 16th, 2011
PDUFA Goal Date	July 16th, 2012
SEALD Review Date	June 29th, 2012
SEALD Labeling Reviewer	Abimbola Adebowale
SEALD Team Leader	Eric Brodsky
SEALD Division Director	Laurie Burke

[1] The established pharmacologic class (EPC) that appears in the final draft PI.

This Study Endpoints and Labeling Development (SEALD) Director Sign-Off review of the end-of-cycle, draft prescribing information (PI) for critical format elements reveals **outstanding labeling format deficiencies that must be corrected** before the final PI is approved. After these outstanding labeling format deficiencies are corrected, the SEALD Director will have no objection to the approval of this PI.

The critical format elements include labeling regulation (21 CFR 201.56 and 201.57), labeling guidance, and best labeling practices (see list below). This review does not include every regulation or guidance that pertains to PI format.

Guide to the Selected Requirements for Prescribing Information (SRPI) Checklist: For each SRPI item, one of the following 3 response options is selected:

- **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** (not applicable): This item does not apply to the specific PI under review.

Reference ID: 3153227

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.

Comment:

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 is granted in a previous submission (i.e., the application being reviewed is an efficacy supplement).

Instructions to complete this item: If the length of the HL is less than or equal to one-half page 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 RPMs)**
  - *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**" in the drop-down menu 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 (for SEALD reviewers)**
  - The SEALD reviewer documents (based on information received from the RPM) that a waiver has been previously granted or will be granted by the review division in the approval letter.

Comment:

YES 3. All headings in HL must be presented in the center of a horizontal line, in UPPER-CASE letters and **bolded**.

Comment:

NO 4. White space must be present before each major heading in HL.

Comment:

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).

Comment: *Consider adding an additional reference to "Gastrointestinal (GI) obstruction" and "Bowel perforation" in Contraindication: Gastrointestinal(GI) obstruction (4, 5.6) and Bowel perforation (4, 5.6).*

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

Reference ID: 3153227

• **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:

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

Comment:

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"**.

Comment:

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)**."

Comment:

Product Title

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

Comment:

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: *Delete white space between "Product Title" and "Initial U.S. Approval" Date. Include the year "2012".*

Boxed Warning

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

Comment:

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**").

Comment:

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

Comment:

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.***")

Comment:

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

Comment:

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.

Comment:

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

Comment:

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".

Comment:

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).

Comment:

Indications and Usage

NO 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 established pharmacologic class) indicated for (indication)".

Comment: *The proposed labeling language (see below) does not differentiate the established pharmacological class (EPC) for each individual component of the combination:*

> *PICOPREP™ (sodium picosulfate, magnesium oxide and citric acid) powder for oral solution is a stimulant laxative and osmotic laxative indicated for cleansing of the colon as a preparation for colonoscopy in adults.*

See the 2009 "Labeling for Human Prescription Drug and Biological Products - Determining Established Pharmacologic Class for Use in the Highlights of Prescribing Information" Guidance (EPC Guidance) at

Selected Requirements of Prescribing Information (SRPI) Revised

http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM186607.pdf. We recommend the following language as per the EPC guidance:

PICOPREP is a combination of sodium picosulfate, a stimulant laxative, and magnesium oxide and citric acid, both osmotic laxatives, indicated for cleansing of the colon as a preparation for colonoscopy in adults.

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.

Comment:

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.

Comment:

YES 24. Each contraindication is bulleted when there is more than one contraindication.

Comment:

Adverse Reactions

YES 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:

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."**

Comment:

Revision Date

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

Comment: *Must include "Revised: July 2012" in the approval letter or appropriate month year when approved.*

Contents: Table of Contents (TOC)

Reference ID: 3153227

Selected Requirements of Prescribing Information (SRPI) Revised

GENERAL FORMAT

NO 28. A horizontal line must separate TOC from the FPI.

Comment:

YES 29. The following **bolded** heading in all UPPER CASE letters must appear at the beginning of TOC: **"FULL PRESCRIBING INFORMATION: CONTENTS"**.

Comment:

NO 30. The section headings and subheadings (including title of the Boxed Warning) in the TOC must match the headings and subheadings in the FPI.

Comment: *In the TOC, change section heading* (b) (4) *to "PATIENT COUNSELING INFORMATION." In the TOC change "7.3 Antiobiotics" to "7.3 Antibiotics".*

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**.

Comment:

YES 32. All section headings must be **bolded** and in UPPER CASE.

Comment:

YES 33. All subsection headings must be indented, not bolded, and in title case.

Comment:

YES 34. When a section or subsection is omitted, the numbering does not change.

Comment:

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."

Comment:

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".**

Comment:

YES 37. All section and subsection headings and numbers must be **bolded**.

Comment:

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

Reference ID: 3153227

Selected Requirements of Prescribing Information (SRPI) Revised

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 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.

Comment:

NO 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)]*".

Comment: *The following need additional cross-referencing:*

1. Bulleted items under Contraindication: Gastrointestinal(GI) obstruction and Bowel perforation must include the following cross-reference [see Warnings and Precautions (5.6)]

2. Section 5.1 must cross-reference Adverse Reactions (6.1, 6.2) and Section 7.1 because there is additional electrolyte data in these subsections.

3. Recommend that you move information from Section 6.2 (There have been isolated reports of (b) (4) *reversible aphthoid ileal ulcers. Ischemic colitis has been reported with the use of PICOPREP for colon preparation prior to colonoscopy. However, a causal relationship between these ischemic colitis cases and the use of PICOPREP has not been established.) to*

Section 5.5. Alternatively, cross-reference Section 5.5 to Adverse Reactions (6.2) because there is additional information about ischemic colitis and colonic ulcers.

4. Section 5.2 must cross-reference Adverse Reactions (6.2) because there is additional information about seizures in this subsection.

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.

Comment:

FULL PRESCRIBING INFORMATION DETAILS

Boxed Warning

N/A 42. All text is **bolded**.

Comment:

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**").

Comment:

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.

Comment:

Contraindications

N/A 45. If no Contraindications are known, this section must state "None".

Comment:

Adverse Reactions

YES 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:

"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:

NO 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."

Comment: *The following are proposed changes to the verbatim statement:*

(b) (4)

This statement is not consistent with the 2006 "Adverse Reactions Section of Labeling for Human Prescription Drug and Biological Products - Content and Format" Guidance http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075057.pdf and is not consistent with best labeling practices because it may be promotional to include the post-marketing exposure in this subsection. We recommend the following statement or appropriate modification:

*"**The following foreign spontaneous reports have been identified during use of formulations similar to*** (b) (4) *-Because these events 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

YES 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)"

Comment:

Reference ID: 3153227

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/s/

ABIMBOLA O ADEBOWALE
06/29/2012

ERIC R BRODSKY
06/29/2012
I agree. Eric Brodsky, signing for Laurie Burke, Director of SEALD.

M E M O R A N D U M

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

CLINICAL INSPECTION SUMMARY

DATE: June 19, 2012

TO: Maureen Dewey, Project Manager
Division of Gastroenterology and Inborn Errors Products

FROM: Khairy W. Malek, M.D., Ph.D.
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

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

SUBJECT: Evaluation of Clinical Inspections

NDA: 202-535

APPLICANT: Ferring Pharmaceuticals Inc

DRUG: Prepopik (Picoprep)

NME: No

THERAPEUTIC CLASSIFICATION: Standard

INDICATIONS: Colon Cleansing in Preparation of Colonoscopy.

CONSULTATION REQUEST DATE: January 4, 12

Inspection Summary Goal Date: June 1, 2012

PDUFA DATE: July 16, 2012

I. BACKGROUND:

NDA 202-535 was submitted by the sponsor, Ferring Pharmaceuticals Inc. for the indication of use of a colon cleansing agent in the preparation for colonoscopy in adults.
A preferable colon cleansing preparation should be:

- Consistently and reliably emptying the colon of all fecal material rapidly with no gross or histological alteration of the colonic mucosa
- Not causing any patient discomfort or clinically relevant shifts in fluids and electrolytes
- Requiring a short period for ingestion and evacuation.

The sponsor claims that the new preparation fulfills these elements. The active ingredients of this product, sodium picosulfate and magnesium citrate have been on the market in Europe, Australia and New Zealand for many years with excellent safety profile according to the sponsor.

The protocol inspected was Protocol # FE2009-01, entitled "A Randomized, Assessor-Blinded, Multi-Center Study Investigating the Efficacy, Safety and Tolerability of Split-Dose PICOPREP for Oral Administration Versus Half-Lytely for Colon Cleansing in Preparation for Colonoscopy." The results of this study were considered critical in the review of this NDA.

II. RESULTS (by Site):

Name of CI/Site #	Protocol # and # of Subjects Randomized	Inspection Date	Final Classification
Gerald Bertiger, M.D. Site 101	FE2009-01/124 subjects	March 19 to 23, 2012	NAI
John Lowe, M.D. Site 106	FE2009-01/111 subjects	May 7 to 11, 2012	Pending (Preliminary classification VAI)
Arthur Poch, M.D Site 107	FE2009-01/89 subjects	March 12-14	NAI

<u>Key to Classifications</u>

NAI = No deviation from regulations.
VAI = Deviation(s) from regulations.
OAI = Significant deviations from regulations. Data unreliable.
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. Gerald Bertiger, M.D., Hillmont GI, PC
   1811 Bethlehem Pike, Building C
   Flourtown, PA 19031-1111

a. What was inspected: At this site, total of 127 subjects were screened and 124 subjects were randomized. All randomized subjects completed the study. All subjects' records were examined to verify the existence of the subjects. A detailed audit of 40 subject records was conducted. This included comparison of subject's charts with CRFs and data listings. Source documents were reviewed for primary and secondary endpoints as well as adverse reactions

b. General observations/commentary: No significant violations were noted, and no Form FDA 483 was issued.

c. Assessment of data integrity: The data from this site appears to be reliable and can be used in support of the NDA.

2. John Lowe, M.D; Advanced Research Associates, LLC
   5896 S. Ridgeline Drive, Ogden, UT 84405

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

a. What was inspected: At this site, 118 subjects were screened. A total of 111 subjects were randomized and completed the study. The FDA investigator reviewed the records of 35 subjects. The Investigator reviewed the primary and secondary endpoints. Source documents and CRFs were found to be consistent with the data listings provided.

b. General observations/commentary: No Form FDA 483 was issued at the time of inspection. However, a preliminary review of the Establishment Inspection Report (EIR) by the OSI reviewer notes that the protocol required diabetics to be provided with guidelines for diabetes management (Appendix III of the protocol) on the day before colonoscopy. According to the EIR, these guidelines were not provided for three diabetic subjects # 106037, 106046 and 106117. This inspection has the preliminary classification of VAI because of this assessment. This possible violation does not impact data reliability.

c. Assessment of data integrity: The possible violation noted above does not impact data reliability. The data from this site appear reliable and can be used in support of the NDA.

3. Arthur Poch, M.D.
   3217 Mabel Street, Shreveport, LA 71103

a. What was inspected: At this site, 95 subjects were screened, and 89 were randomized and completed the study. The FDA investigator reviewed the records of all screened subjects. The field investigator reviewed clinical investigators' financial disclosures, all informed consents and inclusion/exclusion criteria. The primary and secondary endpoints and adverse events were compared with the data listings provided and no discrepancies were noted.

b. General observations/commentary: No significant regulatory violations were observed and no Form FDA 483 was issued. There was one subject who experienced a serious adverse event (SAE). Subject # 019 experienced chest pain, 10 days after colonoscopy. The subject was hospitalized and released on the same day. The AE was described as non-cardiac and non-related to the study medication.

c. Assessment of data integrity: The data obtained from this site appear reliable and can be used in support of the NDA.

III. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Three clinical sites that participated in the clinical trial were inspected. The data from the 3 sites inspected appear reliable and can be used in support of the NDA. Observations noted for Dr. Lowe's site are based on preliminary review of the EIR. An inspection summary addendum will be issued if conclusions change upon further review of the EIR.

{See appended electronic signature page}
Khairy Malek, M.D.
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}
Susan Leibenhaut, M.D.
Acting Team Leader
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Lauren Iacono-Connors, Ph. D.
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Office of Scientific Investigations

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/s/

KHAIRY W MALEK
06/19/2012

SUSAN LEIBENHAUT
06/19/2012

LAUREN C IACONO-CONNORS
06/20/2012

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 Review

Date:	May 1, 2012
Reviewer:	Manizheh Siahpoushan, PharmD Division of Medication Error Prevention and Analysis
Team Leader:	Zachary Oleszczuk, PharmD Division of Medication Error Prevention and Analysis
Division Director:	Carol A. Holquist, RPh Division of Medication Error Prevention and Analysis
Drug Name and Strength(s):	Picoprep (Sodium Picosulfate, 10 mg Magnesium Oxide, 3.5 gram Citric Acid, 12 gram) Powder for Oral Solution
Application Type/Number:	NDA 202535
Applicant/sponsor:	Ferring Pharmaceuticals
OSE RCM #:	2012-55

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

1 INTRODUCTION

This review summarizes the Division of Medication Error Prevention and Analysis's evaluation of the proposed container labels, carton labeling, Prescribing Information, and Medication Guide for Picoprep for areas of vulnerability that could lead to medication errors.

1.1 REGULATORY HISTORY

The Applicant submitted the proposed labels and labeling for Picoprep (NDA 202535) on Januray 31, 2012.

1.2 PRODUCT INFORMATION

The following product information is provided in the January 31, 2012 proprietary name submission.

- Active Ingredients: Sodium Picosulfate, Magnesium Oxide, and Citric Acid
- Indication of Use: Cleansing of the colon as a preparation for colonoscopy in adults
- Route of administration: Oral
- Dosage form: Solution
- Strength: 10 mg/ 3.5 gram/12 gram
- Dose and Frequency: One dose of Picoprep consists of 2 pouches of powder for oral solution, each dissolved in 5 ounces of cold water and administered at separate times. Additional fluids must be consumed.

  1. Split-Dose regimen: The first Picoprep pouch is taken the night before the colonoscopy, and the second is taken the next day, in the morning of colonoscopy.

  2. Day-Before regimen: The first Picoprep pouch is taken in the afternoon or early evening and the second is taken approximately 6 hours later, the night before the colonoscopy.
- How Supplied: Supplied in cartons containing 2 pouches of powder for oral solution, along with a pre-marked dosing cup.
- Storage: 25ºC (77ºF). Excursions permitted at 15ºC to 30ºC (59ºF to 86ºF)
- Container and Closure Systems: Picoprep is filled in a sachet (b) (4)

Reference ID: 3124344

2 METHODS AND MATERIALS REVIEWED

Using Failure Mode and Effects Analysis[1], principals of human factors, and postmarketing medication error data, the Division of Medication Error Prevention and Analysis (DMEPA) evaluated the following:

- Prescribing Information and Medication Guide submitted January 31, 2012 (no image)
- Container label, carton labeling, and dose cup submitted January 31, 2012 (Appendices A through D)

3 DISCUSSION OF DEFICIENCIES IDENTIFIED

3.1 PRESCRIBING INFORMATION AND MEDICATION GUIDE

- [redacted] (b) (4) appear in the *Dosage Forms and Strengths* section of the Highlights and the full Prescribing Information.
- The statement [redacted] (b) (4) in the *Dosage and Administration* section of the Full Prescribing Information (under 'Additional fluids must be consumed:') is ambiguous and nonspecific.
- The presentation of information for the Split-Dose regimen in the Dosage and Administration Section of the Highlights and the Full Prescribing Information may be confusing.
- The [redacted] (b) (4) in the [redacted] (b) (4) in the Dosage and Administration Section of the Full Prescribing Information is duplicative and may be confusing.
- The presentation of 'Medication Guide', the proprietary, and the established names on the first page of the Medication Guide are not in accordance with 21 CFR 208.20.

3.2 CONTAINER LABELS AND CARTON LABELING

- The proprietary name, Picoprep appears on the container labels and carton labeling (DMEPA found the proposed proprietary name, Picoprep unacceptable).
- The proprietary name is presented in upper case letters making this information difficult to read. Additionally part of the name (i.e. 'prep') appears in bold letters, providing more emphasis on the suffix 'prep'.
- Although the established name is at least half the size of the proprietary name, the proprietary name is presented in light gray font and lacks prominence.
- The dosage form appears more prominent than the established name.

---

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

Reference ID: 3124344

- The product strength does not appear on the principal display panel of the outer carton labeling and the pouch label.
- The round graphic directly adjacent to the proprietary name is too prominent and distracts from the proprietary name and the established name.
- The Medication Guide statement does not appear on the principal display panel.
- The [redacted] (b) (4) in the preparation instructions may be confusing.

Additionally, the Applicant requested DMEPA's advice on whether the final mock up of the [redacted] (b) (4) while the carton labeling (which will be printed after approval) will be printed with the proprietary name. DMEPA informed the Division via email dated March 6, 2012, that from a medication error perspective, the container label may contain the established name, strength, and quantity, without the proprietary name (the proprietary name would only appear on the carton labeling). However, because this issue involves the labels, DMEPA defers to the Division for the final decision.

4 CONCLUSIONS AND RECOMMENDATIONS

DMEPA concludes that the proposed labels and labeling introduce vulnerability that can lead to medication error. We recommend the following:

A. Prescribing Information and Medication Guide

1. Dosage Forms and Strengths (Highlights and Full Prescribing Information: [redacted] (b) (4)

2. Dosage and Administration (Highlights and Full Prescribing Information: For clarity, revise the statemen [redacted] (b) (4) (b) (4)

Reference ID: 3124344

3. Dosage and Administration (Highlights and Full Prescribing Information): Revise the 'Split-Dose regimen' section (i.e. Split-Dose regiment: (b) (4) to read: 'Split-Dose regiment: (b) (4)

4. Dosage and Administration (Full Prescribing Information): To increase the clarity of the (b) (4) solution sections, (b) (4) The revised statements should appear as follows: 'three 8-ounce' or 'five 8-ounce'. (b) (4)

5. Medication Guide: Revise the presentation of the title 'Medication Guide' at the top of the first page, to appear more prominent and to appear in a larger font size than that of the proprietary name, per 21 CFR 208.20.

B. All Container Labels and Carton Labeling

1. Remove the proprietary name, Picoprep from all container labels and carton labeling.

2. Although the proposed proprietary was found unacceptable, the proprietary name is presented in upper case letters (PICOPREP). To increase its readability, revise the presentation of your future proprietary name so that it is presented in title case (Picoprep). Additionally, part of the name is presented in bold letters (i.e. PICO**PREP**), giving more emphasis to the suffix 'prep'. Revise the presentation of the future proprietary name so that the entire name is presented in one type and one color font (i.e. Picoprep or **Picoprep**). Highlighting sections of drug names by using heavier font type or using tall man letters are utilized to help distinguish similar drug names and making them less prone to mix ups.

3. We acknowledge that the established name is at least half as large as the proprietary name, however, in accordance with 21 CFR 201.10(g)(2), the presentation of the established name should also "… have a prominence commensurate with the prominence with which such proprietary name or designation appears, taking into account all pertinent factors, including typography, layout, contrast and other printing features'. Therefore, we request you revise the established name accordingly (i.e. using a darker color font).

4. Remove or decrease the prominence of the round shaped graphic directly adjacent to the proprietary name. As currently presented, the graphic distracts from the proprietary and the established names.

C. Container Label (pouch)

1. Include the product strength on the principal display panel of the container label (pouch). As currently presented this information does not appear on the principal display panel of the pouch label. The product strength should appear on the principal display panel, below the dosage for [redacted] (b) (4) The revised presentation may appear as follows:

[redacted] (b) (4)

2. From a medication error perspective, we find your proposal to include only the established name, strength, and quantity, without the proprietary name (the proprietary name would only appear on the carton labeling) on the container label acceptbale. However, because this issue involves the labels, DMEPA defers to the Division for the final decision.

D. Carton Labeling

1. Include the product strength on the principal display panel of the inner and outer carton labeling. As currently presented this information does not appear on the outer carton labeling, and appears only on the back panel of the inner carton labeling. The product strength should appear on the principal display panel, below the dosage form (b) (4) The revised presentation of the proprietary name, established name, dosage form, and strength statement may appear as follows (note the use of the words 'Proprietary Name' as a place holder for future proprietary name):

   (b) (4)

2. Repeat the Medication Guide statement on the principal display panel between the statement, (b) (4) and the storage information statement. Additionally ensure the statement is presented in a prominent manner per 21 CFR 208.24 (d) which states 'These statements shall appear on the label in a prominent and conspicuous manner.', and begins with 'ATTENTION PHARMACIST:' As currently presented, the Medication Guide statement appears on the top panel of the carton labeling and lacks prominence. The revised Medication Guide statement may appear as follows: 'ATTENTION PHARMACIST: Dispense the enclosed Medication Guide to each patient.'

3. Reduce the prominence of the orange graphic with white lines that appears across the principal display panel of the carton labeling to provide more white space for inclusion of the product strength and the Medication Guide statement.

Reference ID: 3124344

4. Revise steps 2 and 4 of the Preparation Instructions (b) (4) The revised statements should appear as follows: 'three 8-ounce' or 'five 8-ounce'. (b) (4)

If you have further questions or need clarifications, please contact Nitin Patel, project manager, at 301-796-5412.

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

Reference ID: 3124344

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/s/

ZACHARY A OLESZCZUK on behalf of MANIZHEH SIAHPOUSHAN
05/01/2012

ZACHARY A OLESZCZUK
05/01/2012

CAROL A HOLQUIST
05/01/2012

REGULATORY PROJECT MANAGER
PLR FORMAT LABELING REVIEW

Application: NDA 202535

Name of Drug: PICOPREP (sodium picosulfate, magnesium oxide, citric acid) Powder for oral solution, 10mg/3.5g/12g

Applicant: Ferring Pharmaceuticals, Inc.

Labeling Reviewed

Submission Date: 9-16-11

Receipt Date: 9-16-11

Background and Summary Description

Ferring submitted an NDA on September 16, 2011 requesting approval of PICOPREP for the cleansing of the colon as a preparation for colonoscopy in adults. This drug has been marketed under various trade names outside of the US since 1980, primarily in Europe. A pre-NDA meeting was held on March 21, 2011.

This NDA includes the results of 2 studies comparing PicoPrep to Halflytely (with 10 mg bisacodyl). PicoPrep includes both a stimulant laxative (sodium picosulfate) and osmotic laxative (magnesium oxide and citric acid combining to form magnesium citrate). Sodium picosulfate is a new molecular entity.

Review

The submitted labeling was reviewed in accordance with the labeling requirements listed in the "Selected Requirements for Prescribing Information (SRPI)" section of this review, attached below. Labeling deficiencies are identified with an "X" in the checkbox next to the labeling requirement.

In addition, the proposed label does not include a Medication Guide. To be consistent with the labeling for other bowel preps, a Medication Guide informing patients of the risks associated with fluid and electrolyte disturbances will be required.

Reference ID: 3050686

Conclusions/Recommendations

All labeling deficiencies identified in the SRPI section of this review and identified above will be conveyed to the applicant in the 74-day letter. The applicant will be asked to resubmit labeling that addresses all identified labeling deficiencies by December 16, 2011. The resubmitted labeling will be used for further labeling discussions.

Matthew Scherer	11-23-11
Regulatory Project Manager	Date
Wes Ishihara	
Chief, Project Management Staff	Date

Reference ID: 3050686

Selected Requirements for Prescribing Information (SRPI)

This document is meant to be used as a checklist in order to identify critical issues during labeling development and review. For additional information concerning the content and format of the prescribing information, see regulatory requirements (21 CFR 201.56 and 201.57) and labeling guidances. When used in reviewing the PI, only identified deficiencies should be checked.

Highlights (HL)

- **General comments**
  - ☐ HL must be in two-column format, with ½ inch margins on all sides and between columns, and in a minimum of 8-point font.
  - ☐ HL is limited in length to one-half page. If it is longer than one-half page, a waiver has been granted or requested by the applicant in this submission.
  - ☒ There is no redundancy of information.

The highlights limitation statement and the adverse reaction reporting instructions should be revised to remove repeated information.

[Note, it is possible that these repeated statements are a result of a glitch in desktop SPL rendering software. Nevertheless, the sponsor should double-check that these statements are not repeated.]

- ☐ If a Boxed Warning is present, it must be limited to 20 lines. (Boxed Warning lines do not count against the one-half page requirement.)
- ☐ A horizontal line must separate the HL and Table of Contents (TOC).
- ☐ All headings must be presented in the center of a horizontal line, in UPPER-CASE letters and **bold** type.
- ☐ Each summarized statement must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contains more detailed information.
- ☐ Section headings are presented in the following order:

• **Highlights Limitation Statement** (required statement)
• **Drug names, dosage form, route of administration, and controlled substance symbol, if applicable** (required information)
• **Initial U.S. Approval** (required information)
• **Boxed Warning** (if applicable)
• **Recent Major Changes** (for a supplement)
• **Indications and Usage** (required information)
• **Dosage and Administration** (required information)
• **Dosage Forms and Strengths** (required information)
• **Contraindications** (required heading – if no contraindications are known, it must state "None")
• **Warnings and Precautions** (required information)
• **Adverse Reactions** (required AR contact reporting statement)
• **Drug Interactions** (optional heading)
• **Use in Specific Populations** (optional heading)

Reference ID: 3050686

• **Patient Counseling Information Statement** (required statement)
• **Revision Date** (required information)

Reference ID: 3050686

- **Highlights Limitation Statement**
  - ☐ Must be placed at the beginning of HL, **bolded,** and read as follows: "**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**
  - ☐ Must be **bolded** and note the proprietary and established drug names, followed by the dosage form, route of administration (ROA), and, if applicable, controlled substance symbol.

- **Initial U.S. Approval**
  - ☐ The verbatim statement "Initial U.S. Approval" followed by the 4-digit year in which the FDA initially approved of the new molecular entity (NME), new biological product, or new combination of active ingredients, must be placed immediately beneath the product title line. If this is an NME, the year must correspond to the current approval action.

- **Boxed Warning**
  - ☐ All text in the boxed warning is **bolded**.
  - ☐ Summary of the warning must not exceed a length of 20 lines.
  - ☐ Requires a heading in UPPER-CASE, **bolded** letters containing the word "**WARNING**" and other words to identify the subject of the warning (e.g.,"**WARNING: LIFE-THREATENING ADVERSE REACTIONS**").
  - ☐ Must have the verbatim statement "***See full prescribing information for complete boxed warning.***" If the boxed warning in HL is identical to boxed warning in FPI, this statement is not necessary.

- **Recent Major Changes (RMC)**
  - ☐ Applies only to supplements and is limited to substantive changes in five sections: Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions.
  - ☐ The heading and, if appropriate, subheading of each section affected by the recent change must be listed with the date (MM/YYYY) of supplement approval. For example, "Dosage and Administration, Coronary Stenting (2.2) -- 2/2010."
  - ☐ For each RMC listed, the corresponding new or modified text in the FPI must be marked with a vertical line ("margin mark") on the left edge.
  - ☐ A changed section must be listed for at least one year after the supplement is approved and must be removed at the first printing subsequent to one year.

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- ☐ Removal of a section or subsection should be noted. For example, "Dosage and Administration, Coronary Stenting (2.2) -- removal 2/2010."

- **Indications and Usage**
  - ☒ If a product belongs to an established pharmacologic class, the following statement is required in HL: [Drug/Biologic Product) is a (name of class) indicated for (indication(s)]." Identify the established pharmacologic class for the drug at:

    http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/ucm162549.htm.

The Indication and Usage subsection should be revised to include appropriate pharmacological class(es) (e g., stimulant laxative, osmotic laxative).

- **Contraindications**
  - ☐ This section must be included in HL and cannot be omitted. If there are no contraindications, state "None."
  - ☐ All contraindications listed in the FPI must also be listed in HL.
  - ☐ List known hazards and not theoretical possibilities (i.e., hypersensitivity to the drug or any inactive ingredient). If the contraindication is not theoretical, describe the type and nature of the adverse reaction.
  - ☐ For drugs with a pregnancy Category X, state "Pregnancy" and reference Contraindications section (4) in the FPI.

- **Adverse Reactions**
  - ☐ Only "adverse reactions" as defined in 21 CFR 201.57(a)(11) are included in HL. Other terms, such as "adverse events" or "treatment-emergent adverse events," should be avoided. Note the criteria used to determine their inclusion (e.g., incidence rate greater than X%).
  - ☐ For drug products other than vaccines, the verbatim **bolded** statement, "**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer's phone number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch**" must be present. Only include toll-free numbers.

- **Patient Counseling Information Statement**
  - ☐ Must include the verbatim statement: "**See 17 for Patient Counseling Information**" or if the product has FDA-approved patient labeling: "**See 17 for Patient Counseling Information and (insert either "FDA-approved patient labeling" or "Medication Guide")**.

- **Revision Date**
  - ☐ A placeholder for the revision date, presented as "Revised: MM/YYYY or Month Year,"

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must appear at the end of HL. The revision date is the month/year of application or supplement approval.

Contents: Table of Contents (TOC)

- ☐ The heading **FULL PRESCRIBING INFORMATION: CONTENTS** must appear at the beginning in UPPER CASE and **bold** type.
- ☐ The section headings and subheadings (including the title of boxed warning) in the TOC must match the headings and subheadings in the FPI.
- ☐ All section headings must be in **bold** type, and subsection headings must be indented and not bolded.
- ☐ When a section or subsection is omitted, the numbering does not change. For example, under Use in Specific Populations, if the subsection 8.2 (Labor and Delivery) is omitted, it must read:

  8.1 Pregnancy

  8.3 Nursing Mothers (not 8.2)

  8.4 Pediatric Use (not 8.3)

  8.5 Geriatric Use (not 8.4)
- ☐ If a section or subsection 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**
  - ☐ A horizontal line must separate the TOC and FPI.
  - ☐ The heading – **FULL PRESCRIBING INFORMATION** – must appear at the beginning in UPPER CASE and **bold** type.
  - ☐ The section and subsection headings must be named and numbered in accordance with 21 CFR 201.56(d)(1).

- **Boxed Warning**
  - ☐ Must have a heading, in UPPER CASE, **bold** type, containing the word "**WARNING**" and other words to identify the subject of the warning. Use **bold** type and lower-case letters for

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the text.

- ☐ Must include a brief, concise summary of critical information and cross-reference to detailed discussion in other sections (e.g., Contraindications, Warnings and Precautions).

- **Contraindications**
  - ☐ For Pregnancy Category X drugs, list pregnancy as a contraindication.

- **Adverse Reactions**
  - ☐ Only "adverse reactions" as defined in 21 CFR 201.57(c)(7) should be included in labeling. Other terms, such as "adverse events" or "treatment-emergent adverse events," should be avoided.
  - ☐ For the "Clinical Trials Experience" subsection, 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 clinical practice."
  - ☐ For the "Postmarketing Experience" subsection, the listing of post-approval adverse reactions must be separate from the listing of adverse reactions identified in clinical trials. Include the following verbatim statement or appropriate modification:

    "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."

- **Use in Specific Populations**
  - ☐ Subsections 8.4 Pediatric Use and 8.5 Geriatric Use are required and cannot be omitted.

- **Patient Counseling Information**
  - ☐ This section is required and cannot be omitted.
  - ☒ Must reference any FDA-approved patient labeling, including the type of patient labeling. The statement "See FDA-approved patient labeling (insert type of patient labeling)." should appear at the beginning of Section 17 for prominence. For example:
    - "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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The current statement will need to be revised in the FPI (and Highlights) as this drug will require a Medication Guide to be consistent with other drugs in the class.

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/s/

MATTHEW C SCHERER
11/28/2011

RICHARD W ISHIHARA
11/28/2011