

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

202535Orig1s000

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**

EXCLUSIVITY SUMMARY

NDA # 202535

SUPPL #

HFD # 180

Trade Name Prepopik

Generic Name (sodium picosulfate, magnesium oxide and citric acid) for Oral Solution, 10 mg sodium picosulfate/sachet.

Applicant Name Ferring Pharmaceuticals

Approval Date, If Known July 16, 2012

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES ☒ NO ☐

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3, SE4, SE5, SE6, SE7, SE8

505(b)(2)

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES ☒ NO ☐

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES ☒ NO ☐

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

5 years

e) Has pediatric exclusivity been granted for this Active Moiety?

YES ☐ NO ☒

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES ☐ NO ☒

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES ☐ NO ☐

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES ☒ NO ☐

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# 18519, 18904 magnesium oxide

NDA# 19481, 21314, 18519, Citric acid, magnesium oxide and sodium carbonate irrigation
18904; ANDA-018904
(Withdrawn 2008)

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)
IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical

investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES ☒ NO ☐

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES ☒ NO ☐

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES ☐ NO ☒

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES ☐ NO ☐

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES ☐ NO ☒

If yes, explain:

- (c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Studies FE2009-01 (Split- Dose Dosing) and FE2009-02 (Day- Before Dosing). Both Study FE2009-01 and Study FE2009-02 were Phase 3, randomized, multicenter, assessor-blinded, parallel-group, active-control, non-inferiority studies investigating the efficacy, safety, and tolerability of PICOPREP versus the currently approved HalfLytely for colon cleansing in preparation for colonoscopy in adult subjects.

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1

YES ☐

NO ☒

Investigation #2

YES ☐

NO ☒

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1

YES ☐

NO ☒

Investigation #2

YES ☐

NO ☒

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Studies FE2009-01 (Split- Dose Dosing) and FE2009-02 (Day- Before Dosing). Both Study FE2009-01 and Study FE2009-02 were Phase 3, randomized, multicenter, assessor-blinded, parallel-group, active-control, non-inferiority studies investigating the efficacy, safety, and tolerability of PICOPREP versus the currently approved HalfLytely for colon cleansing in preparation for colonoscopy in adult subjects.

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1

IND # 101738

YES ☒

!
!
! NO ☐
! Explain:

Investigation #2

IND # 101738

YES ☒

!
!
! NO ☐
! Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1

YES ☐

Explain:

!

!

! NO ☐

! Explain:

Investigation #2

YES ☐

Explain:

!

!

! NO ☐

! Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES ☐

NO ☒

If yes, explain:

=====

Name of person completing form: Maureen Dewey

Title: Regulatory Health Project Manager

Date: 7/9/2012

Name of Office/Division Director signing form: Victoria Kusiak, M.D.

Title: Deputy Director, Office of Drug Evaluation III

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05

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

/s/

MAUREEN D DEWEY
07/13/2012

VICTORIA KUSIAK
07/13/2012

NDA 202535
PICOPREP™ (sodium picosulfate, magnesium oxide and citric acid) powder
for oral solution
1.3.3 Debarment Certification

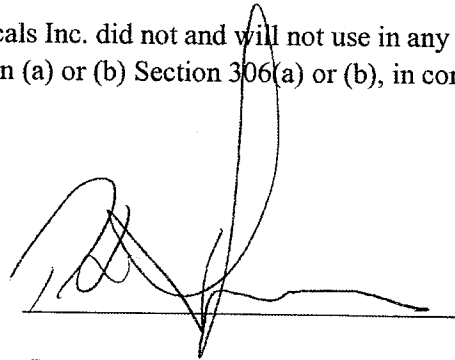
Date: 23 August 2011
; Ver.
Supersedes:
Page 1 of 1

1.3.3 Debarment Certification

Pursuant to FDA's "Guidance for Industry: Submitting Debarment Certification Statement", Section 306(K)(1) of the FDC Act; 21 U.S.C 335a(k)(1), Ferring Pharmaceutical Inc. submits the following Debarment Certification:

The undersigned certifies that Ferring Pharmaceuticals Inc. did not and will not use in any capacity the services of any person debarred under subsection (a) or (b) Section 306(a) or (b), in connection with this application.

Signature:

A handwritten signature in black ink, appearing to read 'Raymond E. Joseph', is written over a horizontal line.

Name of Responsible Person:

Raymond E. Joseph, M.D.

Executive Director, Clinical R&D

Ferring Pharmaceuticals Inc.

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION ¹		
NDA # 202535 BLA #	NDA Supplement # BLA STN #	If NDA, Efficacy Supplement Type:
Proprietary Name: Prepopik Established/Proper Name: (sodium picosulfate, magnesium oxide and citric acid) for Oral Solution Dosage Form: 10 mg sodium picosulfate/sachet		Applicant: Ferring Agent for Applicant (if applicable):
RPM: Maureen Dewey		Division: Gastroenterology and Inborn Errors Products
<div style="display: flex; justify-content: space-between;"> <div style="width: 40%;"> <p><u>NDA:</u> NDA Application Type: <input type="checkbox"/> 505(b)(1) <input checked="" type="checkbox"/> 505(b)(2) Efficacy Supplement: <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)</p> <p>(A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). Consult page 1 of the 505(b)(2) Assessment or the Appendix to this Action Package Checklist.)</p> </div> <div style="width: 55%;"> <p><u>505(b)(2) Original NDAs and 505(b)(2) NDA supplements:</u> Listed drug(s) relied upon for approval (include NDA #(s) and drug name(s)):</p> <p>Provide a brief explanation of how this product is different from the listed drug.</p> <p>If no listed drug, explain.</p> <p><input checked="" type="checkbox"/> This application relies on literature. <input type="checkbox"/> This application relies on a final OTC monograph. <input type="checkbox"/> Other (explain)</p> <p><u>Two months prior to each action, review the information in the 505(b)(2) Assessment and submit the draft to CDER OND IO for clearance. Finalize the 505(b)(2) Assessment at the time of the approval action.</u></p> <p><u>On the day of approval, check the Orange Book again for any new patents or pediatric exclusivity.</u></p> <p><input type="checkbox"/> No changes <input type="checkbox"/> Updated Date of check:</p> <p>If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.</p> </div> </div>		
❖ Actions		
<ul style="list-style-type: none"> Proposed action User Fee Goal Date is <u>July 16, 2012</u> 		<input checked="" type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> CR
<ul style="list-style-type: none"> Previous actions (<i>specify type and date for each action taken</i>) 		<input type="checkbox"/> None

¹ The **Application Information** section is (only) a checklist. The **Contents of Action Package** section (beginning on page 5) lists the documents to be included in the Action Package.

<p>❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain _____</p>	<input type="checkbox"/> Received						
<p>❖ Application Characteristics²</p>							
<p>Review priority: <input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority Chemical classification (new NDAs only):</p> <table border="0"> <tr> <td><input type="checkbox"/> Fast Track</td> <td><input type="checkbox"/> Rx-to-OTC full switch</td> </tr> <tr> <td><input type="checkbox"/> Rolling Review</td> <td><input type="checkbox"/> Rx-to-OTC partial switch</td> </tr> <tr> <td><input type="checkbox"/> Orphan drug designation</td> <td><input type="checkbox"/> Direct-to-OTC</td> </tr> </table> <p>NDAs: Subpart H <input type="checkbox"/> Accelerated approval (21 CFR 314.510) <input type="checkbox"/> Restricted distribution (21 CFR 314.520) Subpart I <input type="checkbox"/> Approval based on animal studies</p> <p><input type="checkbox"/> Submitted in response to a PMR <input type="checkbox"/> Submitted in response to a PMC <input type="checkbox"/> Submitted in response to a Pediatric Written Request</p> <p>Comments:</p> <p>BLAs: Subpart E <input type="checkbox"/> Accelerated approval (21 CFR 601.41) <input type="checkbox"/> Restricted distribution (21 CFR 601.42) Subpart H <input type="checkbox"/> Approval based on animal studies</p> <p>REMS: <input checked="" type="checkbox"/> MedGuide <input type="checkbox"/> Communication Plan <input type="checkbox"/> ETASU <input type="checkbox"/> REMS not required</p>		<input type="checkbox"/> Fast Track	<input type="checkbox"/> Rx-to-OTC full switch	<input type="checkbox"/> Rolling Review	<input type="checkbox"/> Rx-to-OTC partial switch	<input type="checkbox"/> Orphan drug designation	<input type="checkbox"/> Direct-to-OTC
<input type="checkbox"/> Fast Track	<input type="checkbox"/> Rx-to-OTC full switch						
<input type="checkbox"/> Rolling Review	<input type="checkbox"/> Rx-to-OTC partial switch						
<input type="checkbox"/> Orphan drug designation	<input type="checkbox"/> Direct-to-OTC						
<p>❖ BLAs only: Ensure <i>RMS-BLA Product Information Sheet for TBP</i> and <i>RMS-BLA Facility Information Sheet for TBP</i> have been completed and forwarded to OPI/OBI/DRM (Vicky Carter)</p>	<input type="checkbox"/> Yes, dates						
<p>❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 (<i>approvals only</i>)</p>	<input type="checkbox"/> Yes <input type="checkbox"/> No						
<p>❖ Public communications (<i>approvals only</i>)</p>							
<p>• Office of Executive Programs (OEP) liaison has been notified of action</p>	<input type="checkbox"/> Yes <input type="checkbox"/> No						
<p>• Press Office notified of action (by OEP)</p>	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No						
<p>• Indicate what types (if any) of information dissemination are anticipated</p>	<input type="checkbox"/> None <input checked="" type="checkbox"/> HHS Press Release <input type="checkbox"/> FDA Talk Paper <input type="checkbox"/> CDER Q&As <input type="checkbox"/> Other						

² Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA. For example, if the application is a pending BLA supplement, then a new *RMS-BLA Product Information Sheet for TBP* must be completed.

❖ Exclusivity	
<ul style="list-style-type: none"> Is approval of this application blocked by any type of exclusivity? 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes
<ul style="list-style-type: none"> NDA and BLAs: Is there existing orphan drug exclusivity for the “same” drug or biologic for the proposed indication(s)? <i>Refer to 21 CFR 316.3(b)(13) for the definition of “same drug” for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification.</i> 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If, yes, NDA/BLA # _____ and date exclusivity expires: _____
<ul style="list-style-type: none"> (b)(2) NDAs only: Is there remaining 5-year exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i> 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # _____ and date exclusivity expires: _____
<ul style="list-style-type: none"> (b)(2) NDAs only: Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i> 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # _____ and date exclusivity expires: _____
<ul style="list-style-type: none"> (b)(2) NDAs only: Is there remaining 6-month pediatric exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i> 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # _____ and date exclusivity expires: _____
<ul style="list-style-type: none"> NDAs only: Is this a single enantiomer that falls under the 10-year approval limitation of 505(u)? <i>(Note that, even if the 10-year approval limitation period has not expired, the application may be tentatively approved if it is otherwise ready for approval.)</i> 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # _____ and date 10-year limitation expires: _____
❖ Patent Information (NDAs only)	
<ul style="list-style-type: none"> Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought. If the drug is an old antibiotic, skip the Patent Certification questions. 	<input checked="" type="checkbox"/> Verified <input type="checkbox"/> Not applicable because drug is an old antibiotic.
<ul style="list-style-type: none"> Patent Certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent. 	21 CFR 314.50(i)(1)(i)(A) <input type="checkbox"/> Verified 21 CFR 314.50(i)(1) <input type="checkbox"/> (ii) <input type="checkbox"/> (iii)
<ul style="list-style-type: none"> [505(b)(2) applications] If the application includes a paragraph III certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval). 	<input type="checkbox"/> No paragraph III certification Date patent will expire _____
<ul style="list-style-type: none"> [505(b)(2) applications] For each paragraph IV certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). <i>(If the application does not include any paragraph IV certifications, mark “N/A” and skip to the next section below (Summary Reviews)).</i> 	<input checked="" type="checkbox"/> N/A (no paragraph IV certification) <input type="checkbox"/> Verified

- [505(b)(2) applications] For **each paragraph IV** certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation.

Answer the following questions for **each** paragraph IV certification:

- (1) Have 45 days passed since the patent owner's receipt of the applicant's notice of certification?

☐ Yes ☐ No

(Note: The date that the patent owner received the applicant's notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e)).

If "Yes," skip to question (4) below. If "No," continue with question (2).

- (2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)?

☐ Yes ☐ No

If "Yes," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip the rest of the patent questions.

If "No," continue with question (3).

- (3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant?

☐ Yes ☐ No

(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)).

If "No," the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.

- (4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)?

☐ Yes ☐ No

If "Yes," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).

If "No," continue with question (5).

<p>(5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the (b)(2) applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification?</p> <p>(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period).</p> <p><i>If "No," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).</i></p> <p><i>If "Yes," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the OND ADRA and attach a summary of the response.</i></p>	<input type="checkbox"/> Yes <input type="checkbox"/> No
CONTENTS OF ACTION PACKAGE	
❖ Copy of this Action Package Checklist ³	7/17/2012
Officer/Employee List	
❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list (<i>approvals only</i>)	<input checked="" type="checkbox"/> Included
Documentation of consent/non-consent by officers/employees	<input checked="" type="checkbox"/> Included
Action Letters	
❖ Copies of all action letters (<i>including approval letter with final labeling</i>)	Action(s) and date(s) AP 7/16/2012
Labeling	
❖ Package Insert (<i>write submission/communication date at upper right of first page of PI</i>)	
<ul style="list-style-type: none"> • Most recent draft labeling. If it is division-proposed labeling, it should be in track-changes format. 	7/16/2012
<ul style="list-style-type: none"> • Original applicant-proposed labeling 	9/16/2011
<ul style="list-style-type: none"> • Example of class labeling, if applicable 	

³ Fill in blanks with dates of reviews, letters, etc.

❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling (<i>write submission/communication date at upper right of first page of each piece</i>)	<input checked="" type="checkbox"/> Medication Guide <input type="checkbox"/> Patient Package Insert <input type="checkbox"/> Instructions for Use <input type="checkbox"/> Device Labeling <input type="checkbox"/> None
• Most-recent draft labeling. If it is division-proposed labeling, it should be in track-changes format.	7/16/2012
• Original applicant-proposed labeling	12/15/2012
• Example of class labeling, if applicable	
❖ Labels (full color carton and immediate-container labels) (<i>write submission/communication date on upper right of first page of each submission</i>)	
• Most-recent draft labeling	7/10/2012
❖ Proprietary Name <ul style="list-style-type: none"> • Acceptability/non-acceptability letter(s) (<i>indicate date(s)</i>) • Review(s) (<i>indicate date(s)</i>) • Ensure that both the proprietary name(s), if any, and the generic name(s) are listed in the Application Product Names section of DARRTS, and that the proprietary/trade name is checked as the 'preferred' name. 	PicoPrep not acceptable 4/26/2012; Prepopik Acceptable 6/26/2012
❖ Labeling reviews (<i>indicate dates of reviews and meetings</i>)	<input checked="" type="checkbox"/> RPM 11/28/2011 <input checked="" type="checkbox"/> DMEPA 5/1/2012 <input checked="" type="checkbox"/> DRISK 7/3/2012 <input checked="" type="checkbox"/> DDMAC 7/5/2012 <input checked="" type="checkbox"/> SEALD 6/29/2012 <input type="checkbox"/> CSS <input checked="" type="checkbox"/> Other reviews DMPP 7/3/2012
Administrative / Regulatory Documents	
❖ Administrative Reviews (<i>e.g., RPM Filing Review⁴/Memo of Filing Meeting</i>) (<i>indicate date of each review</i>)	505(b)(2) Assessment 7/9/2012 505(b)(2) Clearance 7/2/2012
❖ All NDA (b)(2) Actions: Date each action cleared by (b)(2) Clearance Cmte	<input type="checkbox"/> Not a (b)(2)
❖ NDA (b)(2) Approvals Only: 505(b)(2) Assessment (<i>indicate date</i>)	<input type="checkbox"/> Not a (b)(2)
❖ NDAs only: Exclusivity Summary (<i>signed by Division Director</i>)	<input checked="" type="checkbox"/> Included
❖ Application Integrity Policy (AIP) Status and Related Documents http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	
• Applicant is on the AIP	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
• This application is on the AIP <ul style="list-style-type: none"> ○ If yes, Center Director's Exception for Review memo (<i>indicate date</i>) ○ If yes, OC clearance for approval (<i>indicate date of clearance communication</i>) 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> Not an AP action
❖ Pediatrics (<i>approvals only</i>) <ul style="list-style-type: none"> • Date reviewed by PeRC <u>5/30/2012; 7/11/2012</u> If PeRC review not necessary, explain: _____ • Pediatric Page/Record (<i>approvals only, must be reviewed by PERC before finalized</i>) 	<input checked="" type="checkbox"/> Included

⁴ Filing reviews for scientific disciplines should be filed behind the respective discipline tab.

❖ Debarment certification (original applications only): verified that qualifying language was not used in certification and that certifications from foreign applicants are cosigned by U.S. agent <i>(include certification)</i>	<input checked="" type="checkbox"/> Verified, statement is acceptable
❖ Outgoing communications <i>(letters (except action letters), emails, faxes, telecons)</i>	
❖ Internal memoranda, telecons, etc.	
❖ Minutes of Meetings	
• Regulatory Briefing <i>(indicate date of mtg)</i>	<input checked="" type="checkbox"/> No mtg
• If not the first review cycle, any end-of-review meeting <i>(indicate date of mtg)</i>	<input checked="" type="checkbox"/> N/A or no mtg
• Pre-NDA/BLA meeting <i>(indicate date of mtg)</i>	<input type="checkbox"/> No mtg 4/19/2011
• EOP2 meeting <i>(indicate date of mtg)</i>	<input type="checkbox"/> No mtg 5/13/2009
• Other milestone meetings (e.g., EOP2a, CMC pilots) <i>(indicate dates of mtgs)</i>	
❖ Advisory Committee Meeting(s)	<input checked="" type="checkbox"/> No AC meeting
• Date(s) of Meeting(s)	
• 48-hour alert or minutes, if available <i>(do not include transcript)</i>	
Decisional and Summary Memos	
❖ Office Director Decisional Memo <i>(indicate date for each review)</i>	<input type="checkbox"/> None 7/16/2012
Division Director Summary Review <i>(indicate date for each review)</i>	<input type="checkbox"/> None 7/16/2012
Cross-Discipline Team Leader Review <i>(indicate date for each review)</i>	<input type="checkbox"/> None 7/14/2012
PMR/PMC Development Templates <i>(indicate total number)</i>	<input type="checkbox"/> None (4) 7/16/2012
Clinical Information⁵	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) <i>(indicate date for each review)</i>	7/14/2012
• Clinical review(s) <i>(indicate date for each review)</i>	6/19/2012
• Social scientist review(s) (if OTC drug) <i>(indicate date for each review)</i>	<input type="checkbox"/> None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here <input type="checkbox"/> and include a review/memo explaining why not <i>(indicate date of review/memo)</i>	See Clinical Review, page 21
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers <i>(indicate date of each review)</i>	<input type="checkbox"/> None
❖ Controlled Substance Staff review(s) and Scheduling Recommendation <i>(indicate date of each review)</i>	<input checked="" type="checkbox"/> Not applicable
❖ Risk Management • REMS Documents and Supporting Statement <i>(indicate date(s) of submission(s))</i> • REMS Memo(s) and letter(s) <i>(indicate date(s))</i> • Risk management review(s) and recommendations (including those by OSE and CSS) <i>(indicate date of each review and indicate location/date if incorporated into another review)</i>	<input checked="" type="checkbox"/> None

⁵ Filing reviews should be filed with the discipline reviews.

❖ DSI Clinical Inspection Review Summary(ies) (include copies of DSI letters to investigators)	<input type="checkbox"/> None requested 5/29/2012; 6/20/2012; 6/29/2012
Clinical Microbiology <input checked="" type="checkbox"/> None	
❖ Clinical Microbiology Team Leader Review(s) (indicate date for each review)	<input type="checkbox"/> None
Clinical Microbiology Review(s) (indicate date for each review)	<input type="checkbox"/> None
Biostatistics <input type="checkbox"/> None	
❖ Statistical Division Director Review(s) (indicate date for each review)	<input checked="" type="checkbox"/> None
Statistical Team Leader Review(s) (indicate date for each review)	<input checked="" type="checkbox"/> None
Statistical Review(s) (indicate date for each review)	<input type="checkbox"/> None 6/27/2012 (Efficacy) 5/14/2012 (Safety)
Clinical Pharmacology <input type="checkbox"/> None	
❖ Clinical Pharmacology Division Director Review(s) (indicate date for each review)	<input checked="" type="checkbox"/> None
Clinical Pharmacology Team Leader Review(s) (indicate date for each review)	<input checked="" type="checkbox"/> None
Clinical Pharmacology review(s) (indicate date for each review)	<input type="checkbox"/> None 5/22/2012
❖ DSI Clinical Pharmacology Inspection Review Summary (include copies of DSI letters)	<input checked="" type="checkbox"/> None
Nonclinical <input type="checkbox"/> None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) (indicate date for each review)	<input type="checkbox"/> None 7/16/2012
• Supervisory Review(s) (indicate date for each review)	<input checked="" type="checkbox"/> None
• Pharm/tox review(s), including referenced IND reviews (indicate date for each review)	<input type="checkbox"/> None 5/14/2012
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer (indicate date for each review)	<input checked="" type="checkbox"/> None
❖ Statistical review(s) of carcinogenicity studies (indicate date for each review)	<input type="checkbox"/> No carc
❖ ECAC/CAC report/memo of meeting	<input type="checkbox"/> None Included in P/T review, page
❖ DSI Nonclinical Inspection Review Summary (include copies of DSI letters)	<input checked="" type="checkbox"/> None requested
Product Quality <input type="checkbox"/> None	
❖ Product Quality Discipline Reviews	
• ONDQA/OBP Division Director Review(s) (indicate date for each review)	<input type="checkbox"/> None 7/16/2012
• Branch Chief/Team Leader Review(s) (indicate date for each review)	<input checked="" type="checkbox"/> None
• Product quality review(s) including ONDQA biopharmaceutics reviews (indicate date for each review)	<input type="checkbox"/> None 5/16/2012
❖ Microbiology Reviews <input type="checkbox"/> NDAs: Microbiology reviews (sterility & pyrogenicity) (OPS/NDMS) (indicate date of each review) <input type="checkbox"/> BLAs: Sterility assurance, microbiology, facilities reviews (OMPQ/MAPCB/BMT) (indicate date of each review)	<input checked="" type="checkbox"/> Not needed
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer (indicate date of each review)	<input checked="" type="checkbox"/> None

❖ Environmental Assessment (check one) (original and supplemental applications)	
<input checked="" type="checkbox"/> Categorical Exclusion (<i>indicate review date</i>)(<i>all original applications and all efficacy supplements that could increase the patient population</i>)	See CMC Review 5/16/2012 (page 6) Categorical Exclusion
<input type="checkbox"/> Review & FONSI (<i>indicate date of review</i>)	
<input type="checkbox"/> Review & Environmental Impact Statement (<i>indicate date of each review</i>)	
❖ Facilities Review/Inspection	
<input checked="" type="checkbox"/> NDAs: Facilities inspections (include EER printout) (<i>date completed must be within 2 years of action date</i>) (<i>only original NDAs and supplements that include a new facility or a change that affects the manufacturing sites⁶</i>)	Date completed: 7/9/2012 <input checked="" type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation <input type="checkbox"/> Not applicable
<input type="checkbox"/> BLAs: TB-EER (<i>date of most recent TB-EER must be within 30 days of action date</i>) (<i>original and supplemental BLAs</i>)	Date completed: <input type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation
❖ NDAs: Methods Validation (<i>check box only, do not include documents</i>)	<input checked="" type="checkbox"/> Completed <input type="checkbox"/> Requested <input type="checkbox"/> Not yet requested <input type="checkbox"/> Not needed (per review)

⁶ I.e., a new facility or a change in the facility, or a change in the manufacturing process in a way that impacts the Quality Management Systems of the facility.

Appendix to Action Package Checklist

An NDA or NDA supplemental application is likely to be a 505(b)(2) application if:

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

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

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

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

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

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

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

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

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/s/

MAUREEN D DEWEY
07/17/2012



NDA 202535

PMR/PMC DISCUSSION COMMENTS

Ferring Pharmaceuticals, Inc.
Attention: Brenda Marczi
Vice President, Regulatory Affairs US
4 Gatehall Drive, 3rd Floor
Parsippany, NJ 07054

Dear Ms. Marczi:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for PICOPREP (sodium picosulfate, magnesium oxide and citric acid) for Oral Solution, 10 mg sodium picosulfate/sachet.

We are providing the following postmarketing requirements for your consideration:

Before initiating pediatric studies you will need to justify your proposed dosing regimen across all age groups: <2 years; 2-9 years; >9 years. This justification should be included in your protocol submissions for items 1, 2, and 3 below and should include an analysis of available data originating from controlled clinical studies of PICOPREP (or identical formulations) in pediatric patients, as well as post marketing safety data from countries where PICOPREP (or identical formulations) is approved for pediatric use.

We have determined that you will need to conduct the following studies:

1. PREA Study 1: Conduct a randomized, single-blind, multicenter dose ranging study with PK assessment comparing the safety and efficacy of PICOPREP to NuLytely in children (ages 9 years to 16 years).
 - Protocol submission: February 2013
 - Study completion: July 2015
 - Submission of study report: January 2016
2. PREA Study 2: Conduct a randomized, single-blind, multicenter dose ranging PK study with PK assessment comparing the safety and efficacy of PICOPREP to NuLytely in children (ages 2 years to <9 years).
 - Protocol submission: February 2016
 - Study completion: July 2018
 - Submission of study report: January 2019

3. PREA Study 3: Conduct a randomized, single-blind, multicenter dose ranging study with PK assessment comparing the safety and efficacy of PICOPREP to NuLyteLy in infants (ages 6 months to <2 years).

- Protocol Submission: February 2019
- Study Completion: July 2021
- Study Submission: January 2022

4. PMR Trial 4: [REDACTED] (b) (4)

- Protocol Submission: April 2013
- Study completion: April 2015
- Study Submission: October 2015

If you have any questions, call Maureen Dewey, Senior Regulatory Project Manager, at (301) 796-0845.

Sincerely,

{See appended electronic signature page}

R. Wesley Ishihara
Chief, Project Management Staff
Division of Gastroenterology and Inborn Errors
Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research



NDA 202535

**PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE**

Ferring Pharmaceuticals Inc.
4 Gatehall Drive, 3rd Floor
Parsippany, NJ 07054

ATTENTION: Brenda Marczi, Pharm.D,
Vice President, U.S. Regulatory Affairs

Dear Dr. Marczi:

Please refer to your New Drug Application (NDA) dated and received September 16, 2011, submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act for Sodium Picosulfate, Magnesium Oxide and Citric Acid for Oral Solution

We also refer to your May 23, 2012, correspondence, received May 23, 2012, requesting review of your proposed proprietary name, Prepopik. We have completed our review of the proposed proprietary name, Prepopik and have concluded that it is acceptable.

If **any** of the proposed product characteristics as stated in your May 23, 2012 submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, call Nitin M. Patel, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-5412. For any other information regarding this application, contact the Office of New Drugs (OND) Regulatory Project Manager, Maureen Dewey at (301) 796-0845

Sincerely,
{See appended electronic signature page}
Carol Holquist, RPh
Director
Division of Medication Error Prevention and Analysis
Office of Medication Error Prevention and Risk Management
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

CAROL A HOLQUIST
06/28/2012

Ferring Pharmaceuticals, Inc.
Attention: Brenda Marczi
Vice President, Regulatory Affairs US
4 Gatehall Drive, 3rd Floor
Parsippany, NJ 07054

Dear Ms. Marczi:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for PICOPREP (sodium picosulfate, magnesium oxide and citric acid) for Oral Solution, 10 mg sodium picosulfate/sachet.

We are providing the following postmarketing requirements (PMR) for your consideration:

Before initiating pediatric studies you will need to justify your proposed dosing regimen across all age groups: <2 years; 2-9 years; >9 years. This justification should be included in your protocol submissions for items 1, 2, and 3 below and should include an analysis of available data originating from controlled clinical studies of PICOPREP (or identical formulations) in pediatric patients, as well as post marketing safety data from countries where PICOPREP (or identical formulations) is approved for pediatric use.

We have determined that you will need to conduct the following studies:

1. PREA Study 1: Conduct a randomized, single-blind, multicenter dose ranging study with PK assessment comparing the safety and efficacy of PICOPREP to NuLytely in children (ages 9 years to 16 years).
 - Protocol submission: February 2013
 - Study completion: July 2015
 - Submission of study report: January 2016
2. PREA Study 2: Conduct a randomized, single-blind, multicenter dose ranging PK study with PK assessment comparing the safety and efficacy of PICOPREP to NuLytely in children (ages 2 years to <9 years).
 - Protocol submission: February 2016
 - Study completion: July 2018
 - Submission of study report: January 2019
3. PREA Study 3: Conduct a randomized, single-blind, multicenter dose ranging study with PK assessment comparing the safety and efficacy of PICOPREP to NuLytely in infants (ages 6 months to <2 years).
 - Protocol submission: February 2019
 - Study completion: July 2021
 - Study submission: January 2022
4. PMR Trial 4: A randomized, active control trial in adults to evaluate the effect of Picoprep on renal function long term.
 - Protocol submission: April 2013
 - Study completion: April 2015
 - Study submission: October 2015

If you have any questions, please feel free to contact me.

Maureen Dewey, M.P.H.
Senior Regulatory Project Manager

Division of Gastroenterology and Inborn Errors Products
CDER/FDA

(301) 796-0845 (office)
(301) 796-9905 (fax)

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/s/

MAUREEN D DEWEY
06/21/2012



NDA 202535

LABELING COMMENTS

Ferring Pharmaceuticals, Inc.
Attention: Brenda Marczi
Vice President, Regulatory Affairs US
4 Gatehall Drive, 3rd Floor
Parsippany, NJ 07054

Dear Ms. Marczi:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for PICOPREP (sodium picosulfate, magnesium oxide and citric acid) for Oral Solution, 10 mg sodium picosulfate/sachet.

We also refer to your amendments dated November 7, December 15, 2011, January 20, January 31, February 17, February 21, March 12, March 29, April 13, May 5, May 9, May 21, and May 23, 2012.

We also refer to our November 29, 2011, letter in which we notified you of our target date of May 28, 2012 for communicating labeling changes and/or postmarketing requirements/commitments in accordance with the "PDUFA Reauthorization Performance Goals and Procedures – Fiscal Years 2008 Through 2012."

On December 15, 2011, we received your December 15, 2011 proposed labeling submission to this application, and have proposed revisions that are included as an enclosure.

If you have any questions, call Maureen Dewey, Senior Regulatory Project Manager, at (301) 796-0845.

Sincerely,

{See appended electronic signature page}

R. Wesley Ishihara
Chief, Project Management Staff
Division of Gastroenterology and Inborn Errors
Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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

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/s/

MAUREEN D DEWEY
06/12/2012

RICHARD W ISHIHARA
06/12/2012



NDA 202535

INFORMATION REQUEST

Ferring Pharmaceuticals
Attention: John Berryman
Senior Director Regulatory Affairs
4 Gatehall Drive
3rd Floor
Parsippany, NJ 07054

Dear Mr. Berryman:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for PICOPREP (sodium picosulfate, magnesium oxide, and citric acid) for Oral Solution, 10 mg sodium picosulfate/sachet.

We also refer to your amendments dated November 7, December 15, 2011, January 20, January 31, February 17, February 21, March 12, March 29, April 13, May 5, May 9, May 21, and May 23, 2012.

We are reviewing your submission and have the following information requests. We request a prompt written response by June 18, 2012, in order to continue our evaluation of your NDA.

Labeling

1. We request that you make the following changes to all occurrences of the established name:

- a. The established name must be in parentheses and have a comma before "and anhydrous citric acid" as provided below.

(sodium picosulfate, magnesium oxide, and anhydrous citric acid)

- b. Display product strengths on all labels on the line directly below "(sodium picosulfate, magnesium oxide, and anhydrous citric acid) powder for oral solution" as shown below.

(sodium picosulfate, magnesium oxide, and anhydrous citric acid) powder for oral solution
10 mg/ 3.5 g/ 12 g

Carton Labels and Container Labeling

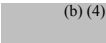
2. Remove the proprietary name, Picoprep from all container labels and carton labeling.
3. To increase readability, revise the presentation of your future proprietary name so that it is presented in title case (Picoprep) and not in all upper case letters. Additionally, part of the name is presented in bold letters (i.e. **PICOPREP**), 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**).
4. The established name is at least half as large as the proprietary name. However, in accordance with 21 CFR 201.10(g)(2), "the established name shall 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, the prominence of the established name must be revised accordingly (i.e. using a darker color font).
5. 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.

Carton Labeling

6. 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 and above the following statement: "Proprietary Name solution is indicated for cleansing of the colon as a preparation for colonoscopy in adults." 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):

Proprietary Name

(sodium picosulfate, magnesium oxide, and anhydrous citric acid)
powder for oral solution

This carton contains:
2  ^{(b) (4)} each containing 16.1 g powder

- 10 mg sodium picosulfate
- 3.5 g magnesium oxide, USP
- 12 g anhydrous citric acid, USP

Proprietary Name solution is indicated for cleansing of the colon as a preparation for colonoscopy in adults.

7. As currently presented, the Medication Guide statement appears on the top panel of the carton labeling and lacks prominence. 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. The revised Medication Guide statement may appear as follows:

(b) (4)

8. 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.
9. 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 any questions, call Maureen Dewey, Senior Regulatory Project Manager, at (301) 796-0845.

Sincerely,

{See appended electronic signature page}

R. Wesley Ishihara
Chief, Project Management Staff
Division of Gastroenterology and Inborn Errors
Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

MAUREEN D DEWEY
06/07/2012

RICHARD W ISHIHARA
06/07/2012

Dewey, Maureen

From: Dewey, Maureen
Sent: Thursday, May 17, 2012 4:07 PM
To: 'Brenda.Marczi@ferring.com'
Cc: 'John.Berryman@ferring.com'; Dewey, Maureen
Subject: NDA 202535 Request for Information

Dear Ms. Marczi:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for PICOPREP (sodium picosulfate, magnesium oxide and citric acid) for Oral Solution, 10 mg sodium picosulfate/sachet.

We also refer to your amendments dated November 7, December 15, 2011, January 20, January 31, February 17, February 21, March 12, March 29, April 13, and May 5, 2012.

We are reviewing your submission dated January 20, 2012 and have the following information requests. We request a prompt written response by May 18, 2012, in order to continue our evaluation of your NDA.

Clinical

We require additional information on patient (CA-005236 CA/SP MALE) identified on page 8/12 under GI disorders. The adverse reaction in question is ischemic colitis.

Please provide the following additional information:

1. The date this adverse event was reported
2. How was this adverse event reported?
 - a. If from a clinical trial, please provide trial name and number, site location, and year
 - b. Was this event spontaneously reported?
 - c. If from regulatory reports, please provide name of report, i.e. PSUR
3. Provide patient's age, co-morbid disease status, and concomitant medications if known.
4. Has this patient been reported in any other documents submitted previously to the Agency describing the adverse event of ischemic colitis?
5. Since the 120 Day Safety update submitted on January 20, 2012, have there been any more cases of ischemic colitis reported?

Please feel free to contact me if you have any questions.

Regards,

Maureen Dewey, M.P.H.
Senior Regulatory Project Manager
Division of Gastroenterology and Inborn Errors Products
CDER/FDA

(301) 796-0845 (office)
(301) 796-9905 (fax)

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/s/

MAUREEN D DEWEY
05/17/2012



NDA 202535

INFORMATION REQUEST

Ferring Pharmaceuticals, Inc.
Attention: Brenda Marcz
Vice President, Regulatory Affairs US
4 Gatehall Drive, 3rd Floor
Parsippany, NJ 07054

Dear Ms. Marcz:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for PICOPREP (sodium picosulfate, magnesium oxide and citric acid) for Oral Solution, 10 mg sodium picosulfate/sachet.

We also refer to your amendments dated November 7, December 15, 2011, January 20, January 31, February 17, February 21, March 12, March 29, April 13, and May 5, 2012.

We are reviewing your submission and have the following information requests. We request a prompt written response by May 18, 2012, in order to continue our evaluation of your NDA.

Clinical

For adverse events (AEs) that occurred in subjects who had electrolyte shifts outside of the normal range:

- 1) For Study 2009-01, provide a tabulation of the frequency [n(%)] of all AEs (including serious adverse events [SAEs]), by treatment arm, that occurred on or past the first day of study drug administration through Visit 6, using Preferred Terms, for the following subjects:
 - a) Subjects who had normal potassium levels at baseline and below the normal range on the day of colonoscopy (Visit 3)
 - b) Subjects who had normal sodium levels at baseline and below the normal range on the day of colonoscopy (Visit 3)
 - c) Subjects who had normal chloride levels at baseline and below the normal range on the day of colonoscopy (Visit 3)

- d) Subjects who had normal calcium levels at baseline and below the normal range on the day of colonoscopy (Visit 3)
 - e) Subjects who had normal magnesium levels at baseline and above the normal range on the day of colonoscopy (Visit 3)
 - f) Subjects who had normal creatinine levels at baseline and above the normal range on the day of colonoscopy (Visit 3)
- 2) Combine populations 1a through 1f to present a cumulative analysis performed in a similar manner.
 - 3) Perform the same analysis as in item 1 and 2 for SAEs only.
 - 4) For each of the 6 analyses in item 1 and 2 above (i.e., for both AEs and SAEs), provide a tabulation of the subjects that contributed to the analysis by presenting a list of the actual subject ID and AE (verbatim term), grouped by treatment arm.

If you have any questions, call Maureen Dewey, Senior Regulatory Project Manager, at (301) 796-0845.

Sincerely,

{See appended electronic signature page}

R. Wesley Ishihara
Chief, Project Management Staff
Division of Gastroenterology and Inborn Errors
Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

MAUREEN D DEWEY
05/11/2012

RICHARD W ISHIHARA
05/11/2012



NDA 202535

INFORMATION REQUEST

Ferring Pharmaceuticals
Attention: John Berryman
Senior Director Regulatory Affairs
4 Gatehall Drive
3rd Floor
Parsippany, NJ 07054

Dear Mr. Berryman:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for PICOPREP (sodium picosulfate, magnesium oxide and citric acid) for Oral Solution, 10 mg sodium picosulfate/sachet.

We also refer to your amendments dated November 7, December 15, 2011, January 20, January 31, February 17, February 21, March 12, March 29, and April 13, 2012.

We are reviewing your submission and have the following information requests. We request a prompt written response by May 7, 2012, in order to continue our evaluation of your NDA.

Carton and Blister Labeling

We request that you make the following changes to all occurrences in the inner carton, outer carton and blister label submitted on April 13, 2012.

1. The established name and dosage form should be stated as shown below:

(sodium picosulfate, magnesium oxide and anhydrous citric acid) powder for oral solution
2. Include the identical "Manufactured by:" and "Manufactured for:" information on all labeling just as it is presented on the blister label.
3. The following comment applies to the blister label:
The proprietary name (PicoprepTM) should be placed above the established name and dosage form.

Submit all three revised labels to the NDA for review.

Clinical Pharmacology

1. On page 25 of the bioanalytical validation report in human plasma ((b) (4) Project Code UA041), Section 3.3.2 “Stability in Plasma at $-20^{\circ}\text{C} \pm 5^{\circ}\text{C}$ and at $-75^{\circ}\text{C} \pm 15^{\circ}\text{C}$ ”, you state “[t]he results of these experiments will be reported later in an amendment to the validation report”. Clarify whether the amendment has been submitted and if so, the exact date of and location within the submission.
2. Provide stability data for the urine samples at $-20^{\circ}\text{C} \pm 5^{\circ}\text{C}$ and at $-75^{\circ}\text{C} \pm 15^{\circ}\text{C}$.
3. On page 31-38 of the bioanalytical validation report in human plasma ((b) (4) Project Code UA041), Table 39 and Table 46, you indicate that the stock and working solution stability, including internal standards stock solution stability, were established for at least 61-62 days. However, according to pages 3 and 8 of the bioanalytical report in human urine (Part B: Human Urine, (b) (4) Project Code N-U-BIO-11-083B), the stock solution was prepared on February 9, 2011, and the urine sample analysis was completed by June 1, 2011, respectively. This time period exceeds the established stock solution stability period. Provide data that support the stability of the stock solution from initial preparation until actual use.

Clinical

1. Your response to our Question #5 in the Information Request dated March 27, 2012, referred to pediatric dosing in the products approved in Canada and the United Kingdom as a justification for the doses proposed in studies under PREA. Explain how the pediatric doses of the products approved in Canada and the United Kingdom were established. Inadequate justification may necessitate dose ranging studies.

If you have any questions, call Maureen Dewey, Senior Regulatory Project Manager, at (301) 796-0845.

Sincerely,

{See appended electronic signature page}

R. Wesley Ishihara
Chief, Project Management Staff
Division of Gastroenterology and Inborn Errors
Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

RICHARD W ISHIHARA
05/01/2012



NDA 202535

**PROPRIETARY NAME REQUEST
UNACCEPTABLE**

Ferring Pharmaceuticals Inc.
4 Gatehall Drive, 3rd Floor
Parsippany, NJ 07054

ATTENTION John B. Berryman, M.S.
Senior Director Regulatory Affairs

Dear Mr. Berryman:

Please refer to your New Drug Application (NDA) dated and received September 16, 2011, submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act for Sodium Picosulfate, Magnesium Oxide and Citric Acid for Oral Solution.

We also refer to your correspondence, dated and received January 31, 2012, requesting review of your proposed proprietary name, Picoprep. We have completed our review of the proposed proprietary name, Picoprep and have concluded that this name is unacceptable for the following reasons:

1. The proposed proprietary name, Picoprep, is orthographically similar to the proprietary names: Loso prep, Pen prep, and Duraprep. We acknowledge that the proposed Picoprep is a prescription drug product, while LoSo prep, Pen prep, and Duraprep are over-the-counter drug products. However, we have determined that this difference in marketing will not prevent errors between these products because postmarketing experience with other drug products demonstrates that name confusion can occur between similarly named over-the-counter drug products and prescription drug products^{1,2,3,4,5,6,7}. The similarity of the names is described further.

-
1. Sudafed-Sotalol mix-ups." ISMP Medication Safety Alert! Community/Ambulatory Care Edition. Volume 5, Issue 5. May 2006.
 2. "Benazepril confused with Benadryl." ISMP Medication Safety Alert! Community/Ambulatory Care Edition. Volume 7, Issue 12. December 2008.
 3. "Sound-alike names." ISMP Medication Safety Alert! Community/Ambulatory Care Edition. Volume 8, Issue 9. September 2008. Regarding cetirizine and sertraline confusion.
 4. "Mucinex-Mucomyst: Too close for comfort." ISMP Medication Safety Alert! Community/Ambulatory Care Edition. Volume 4, Issue 1. January 2005.
 5. "From the database." ISMP Medication Safety Alert! Community/Ambulatory Care Edition. Volume 8, Issue 2. February 2009. Regarding Motrin and Neurontin confusion.
 6. "More on confirmation bias." ISMP Medication Safety Alert! Volume 1, Issue 23. November 20, 1996. Regarding Cozaar and Colace confusion

- A. The proposed proprietary name, Picoprep is orthographically similar to and shares overlapping product characteristics with the over-the-counter product, LoSo prep, a low sodium bowel cleansing system containing one 1.3 ounce packet of Magnesium Carbonate, Citric Acid, and Potassium Citrate effervescent powder for oral solution, four Bisacodyl tablets, 5 mg each, and one Bisacodyl suppository, 10 mg, available at some pharmacies and Gastroenterologists' offices. The orthographic similarity stems from the same shape and length of the names, same letter string 'oprep', similar letters in the second position ('I' vs. 'o'), and beginning letters that may appear similar when scripted ('P' vs. 'L'). Although LoSo prep appears as two words in the list of references, prescribers may script the name as one word (i.e. Losoprep) or with minimum space between 'Loso' and 'prep'. Similarly, the name Picoprep may be inadvertently scripted with a gap between 'Pico' and 'prep'.



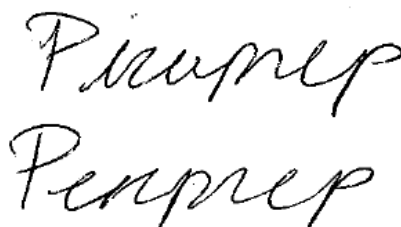
The image displays four handwritten examples of the names 'Picoprep' and 'Losoprep' arranged in a 2x2 grid. The top row shows 'Picoprep' written in a cursive script, with the 'P' and 'L' appearing similar. The bottom row shows 'Losoprep' written in a cursive script, also with the 'P' and 'L' appearing similar. The 'o' in 'oprep' is written in a way that could be mistaken for an 'I' or 'L'.

In addition to the orthographic similarity of this name pair, Picoprep and LoSo prep share product characteristics which include the following: both products are single strength, therefore the strength may be omitted on prescription orders, dose and instructions for use (both may be written as 'Use as directed'), frequency of administration (once before the procedure), overlapping dosage form (solution), overlapping route of administration (oral), and similar patient and prescriber population (patients preparing for colonoscopy and Gastroenterologists). Although LoSo prep is an over-the-counter product, over-the-counter products can be written on a prescription. Therefore, we are concerned that a written order for "LoSo prep as directed before colonoscopy" could be misinterpreted as "Picoprep as directed before colonoscopy". Therefore, the orthographic similarities and overlapping product characteristics increase the likelihood of a medication error to occur in the usual practice setting.

We note that the name LoSo prep was also identified as a potential look and sound-alike name to Picoprep by (b) (4) EPD in the external study. However, (b) (4) did not consider this name further after it was reviewed by the FMEA panel because it was determined that the name, LoSo prep, has enough sound-alike and/or look-alike difference, and/or product profile characteristic differences with Picoprep, and therefore (b) (4) determined the risk for confusion between the names at any point under the proposed prescribing conditions was considered to be minimal. We disagree with (b) (4) orthographic assessment as outlined above.

7. "Safety briefs: Mirapex and Miralax confusion." ISMP Medication Safety Alert! Volume 7, Issue 20. October 3, 2002."

- B. The proposed proprietary name, Picoprep is orthographically similar to and shares overlapping product characteristics with the over-the-counter product, Pen Prep. Pen prep is available as both Magnesium Citrate (17 grams in 10 fluid ounces), a monograph product indicated for relief of occasional constipation (product available on the Daily Med database), and as a colon lavage kit consisting of four 10 fluid ounce bottles of Polyethylene Glycol and two 10 fluid ounce bottles of Magnesium Citrate. This product is available directly from the manufacturer. The orthographic similarity stems from the same shape and similar length of the names, same suffix 'prep', same beginning letter 'P', and similar letters in the second ('i' vs. 'e') and third positions ('c' vs. 'n'). Although Pen prep appears as two words in the list of references, prescribers may script the name as one word (i.e. Penprep) or with minimum space between 'Pen' and 'prep'. Similarly, the name Picoprep may be inadvertently scripted with a gap between 'Pico' and 'prep'.

The image shows two handwritten examples of the names 'Picoprep' and 'Penprep' in a cursive script. The top word is 'Picoprep' and the bottom word is 'Penprep'. Both words are written in a fluid, cursive style with a gap between the first part and the 'prep' suffix.

- In addition to the orthographic similarity of this name pair, Picoprep and Pen prep share product characteristics which include the following: both products are single strength, therefore the strength may be omitted on prescription orders, dose and instructions for use (both may be written as 'Use as directed'), overlapping frequency of administration (once before the procedure), overlapping dosage form (solution), route of administration (oral), and similar patient and prescriber population (patients preparing for colonoscopy and Gastroenterologists). Although Pen prep is only available directly from the manufacturer, a pharmacist may have Pen prep (Magnesium Citrate) readily available in the pharmacy, for use as a laxative due to patient (or healthcare provider) demand. Additionally, a patient may take a prescription to a pharmacy to have the pharmacy order the product. Therefore, we are concerned that a written order for "Picoprep use as directed" could be misinterpreted as "Pen prep use as directed" or vice versa. Thus, the orthographic similarities and overlapping product characteristics increase the likelihood of a medication error to occur in the usual practice setting.
- C. The proposed proprietary name, Picoprep is orthographically similar to and shares overlapping product characteristics with the over-the-counter product, Duraprep, a surgical solution containing Iodine and Isopropyl Alcohol, used as a preoperative skin preparation. The orthographic similarity stems from the same shape and length of the names, same suffix 'prep', similar letters in the second ('i' vs. 'u'), third ('c' vs. 'r'), and fourth ('o' vs. 'a') positions, and similar beginning letters ('P' vs. 'D') when scripted. Additionally, the letter 'P' was misinterpreted as the letter 'D' in our prescription analysis studies.

Picoprep Picoprep
Duraprep Duraprep

In addition to orthographic similarity of this name pair, Picoprep and Duraprep share product characteristics which include the following: both products are single strength, therefore, the strength may be omitted on prescription orders, dose and instructions for use (both may be prescribed as ‘use as directed prior to procedure’, overlap in the frequency of administration (once before procedure), and despite differing dosage forms, both products can be given by a single route of administration, thus the dosage form and the route of administration may be omitted by the prescriber. Although Duraprep is an over-the-counter skin preparation, it could be used in inpatient settings, and inpatient orders could be written for Duraprep, particularly if the patient was undergoing a procedure at the bedside. Additionally, bowel preparations can also be used in inpatient settings and can also be sent to a patient’s bedside. Therefore, an order written for ‘Picoprep use as directed prior to procedure’ for a patient who requires colon lavage prior to an operation, may be misinterpreted as ‘Duraprep use as directed prior to procedure’ by an inpatient pharmacy. Thus, the orthographic similarities and overlapping product characteristics increase the likelihood of a medication error to occur in the usual practice setting.

We note that the name Duraprep was also identified as a potential sound-alike name to Picoprep by (b) (4) EPD in the external study. However, (b) (4) did not consider this name further after it was reviewed by the FMEA panel because it was determined that the name, Duraprep, has enough sound-alike and/or look-alike difference, and/or product profile characteristic differences with Picoprep, and therefore the risk for confusion between the names at any point under the proposed prescribing conditions was considered to be minimal. We disagree with (b) (4) assessment as outlined above. We further acknowledge that Picoprep and Duraprep have different dosage forms and route of administrations, however, we have learned from post-marketing experience that differentiating product characteristics such as dosage form and route of administration may not help prevent medication errors between names with strong orthographic similarities particularly because these elements may not always be specified on prescriptions.

2. We find the inclusion of the “Pico-“ prefix in your Picoprep name concerning because it
 - a) suggests the name of one, but not all of your active ingredients, and b) it defines a very small quantity.
 - A. The prefix ‘pico’ in the proposed proprietary name, Picoprep is part of the name of one of the ingredients in this product (i.e. Sodium Picosulfate), however, the proposed proprietary name does not contain part of the name of the other two ingredients in this product (i.e. Magnesium Oxide and Citric Acid). As such, we find the name misleading in accordance with 21 CFR 201.6(b) which states:

The labeling of a drug which contains two or more ingredients may be misleading by reason, among other reasons, of the designation of such drug in such labeling by a name which includes or suggests the name of one or more but not all such ingredients, even though the names of all such ingredients are stated elsewhere in the labeling.

- B. The prefix ‘Pico’ in the proposed proprietary name, Picoprep is a known designated metric prefix which defines a very small quantity (i.e. $p = 10^{-12}$). We are concerned that the use of this prefix may suggest a much smaller quantity of the product (i.e. smaller than the proposed total of 10 ounces for this product) or smaller amount of clear liquids required to be consumed prior to colonoscopy (smaller than the recommended total of 64 ounces for this product), to patients or healthcare providers. Therefore, we find the prefix ‘Pico’ misleading for this product.

We note that you have not proposed an alternate proprietary name in your submission dated January 31, 2012. If you intend to have a proprietary name for this product, we recommend that you submit a new request for a proposed proprietary name review. (See the Guidance for Industry, *Contents of a Complete Submission for the Evaluation of Proprietary Names*, <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075068.pdf> and “PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2008 through 2012”.)

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, call Nitin M. Patel, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-5412. For any other information regarding this application, contact the Office of New Drugs (OND) Regulatory Project Manager, Maureen Dewey at (301) 796-0845

Sincerely,

{See appended electronic signature page}

Carol Holquist, RPh
Director
Division of Medication Error Prevention and Analysis
Office of Medication Error Prevention and Risk Management
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

CAROL A HOLQUIST
04/27/2012



American Medical Association
515 North State Street, 8th Floor
Chicago, Illinois 60654

Phone: 312-464-4045
Telefax: 312-464-4028
stephanie.shubat@ama-assn.org
www.unitedstatesadoptednames.com

Stephanie C. Shubat, MS
Director USAN
USAN Council Secretary

April 25, 2012

ZZ-144

Re: sodium picosulfate

John B. Berryman
Senior Director, Regulatory Affairs
Ferring Pharmaceuticals Inc.
4 Gatehall Drive, 3rd Floor
Parsippany, NJ 07054

Dear Mr. Berryman,

I am pleased to inform you that the USAN Council has adopted the name, **sodium picosulfate** as a USAN for PICOLAXTM.

Please review the USAN information on the enclosed adoption statement for accuracy, initial, and return the statement and the review confirmation form to me within 60 days of the date listed above. After July 1, 2012, the USAN information on **sodium picosulfate** will be scheduled for posting on the USAN Web site (www.ama-assn.org/go/usan). At the same time, the USAN information on **sodium picosulfate** will be submitted to the United States Pharmacopeial Convention, Inc., for publication in the *USP Dictionary of USAN and International Drug Names*.

You may mail, fax, or e-mail any changes regarding the publication of **sodium picosulfate** to me any time before July 1, 2012.

Sincerely,

Stephanie C. Shubat, M.S.
Director, USAN Program
Secretary, USAN Council

enclosure: N12/49

April 25, 2012

STATEMENT ON A NONPROPRIETARY NAME ADOPTED BY THE USAN COUNCIL:

USAN (ZZ-144)

SODIUM PICOSULFATE

PRONUNCIATION

soe' di um pee" coe sul" fate

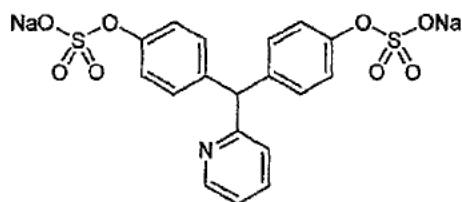
THERAPEUTIC CLAIM

Colon cleansing agent

CHEMICAL NAMES

1. Phenol, 4,4'-(2-pyridinylmethylene)bis-, 1,1'-bis(hydrogen sulfate), sodium salt (1:2)
2. (pyridin-2-ylmethylene)bis(4,1-phenylene) disodium bis(sulfate)

STRUCTURAL FORMULA



MOLECULAR FORMULA

$C_{18}H_{13}NNa_2O_8S_2$

MOLECULAR WEIGHT

481.4

TRADEMARK

PICOLAX™

SPONSOR

Ferring Pharmaceuticals

CODE DESIGNATION

CAS REGISTRY NUMBER

10040-45-6

WHO NUMBER

2265

SCS



NDA 202535

INFORMATION REQUEST

Ferring Pharmaceuticals
Attention: John Berryman
Senior Director Regulatory Affairs
4 Gatehall Drive
3rd Floor
Parsippany, NJ 07054

Dear Mr. Berryman:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for PICOPREP (sodium picosulfate, magnesium oxide and citric acid) for Oral Solution, 10 mg sodium picosulfate/sachet.

We also refer to your amendments dated November 7 and December 15, 2011, January 20, January 31, February 17, February 21 and March 29, 2012.

We are reviewing your submission and have the following information requests. We request a prompt written response by April 16, 2012, in order to continue our evaluation of your NDA.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We acknowledge that you have requested a deferral of pediatric studies in patients (b) (4) because the product will be ready for approval in adults prior to the completion of pediatric studies and because additional safety and effectiveness data is needed, and that you have provided a "Proposed Pediatric Plan Summary". However, your submission is unsatisfactory. Re-submit your deferral request and pediatric plan that fulfills the requirements as per section 505B of the FDCA, including your timeline for completion of pediatric studies as described below.

As stated in section 505B of the FDCA, a deferral request must include a pediatric plan. A pediatric plan is a statement of intent that outlines the studies sufficient to demonstrate an appropriate dose, safety, and efficacy in the specified pediatric population. The pediatric plan

must contain a timeline for the completion of pediatric studies (*i.e.* the dates of (1) protocol submission, (2) study completion and (3) submission of study reports). In addition, you must submit certification of the grounds for deferral and evidence that the studies are being conducted or will be conducted with due diligence and at the earliest possible time. See Draft Guidance for Industry, How to Comply with Pediatric Research Equity Act, <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm079756.pdf>.

When developing your pediatric plan consider the following:

1. Note that if your pediatric development program will rely on extrapolation of efficacy from adequate and well controlled studies in adults, you must include data to support the extrapolation, as well as the plans for the studies to support dosing and safety in the pediatric population.
2. FDA would consider granting a partial waiver for patients less than 6 months of age for your product and proposed indication. Submit a partial waiver request for patients less than 6 months of age with justification and supporting data.

Under PREA, a waiver may be granted for one of the following reasons:

- A. Necessary studies are impossible or highly impracticable (because, for example, the number of patients is so small or the patients are geographically dispersed).
- B. The product would be ineffective or unsafe in one or more of the pediatric age group(s) for which a waiver is being requested. Note: If this is the reason the studies are being waived, this information MUST be included labeling.
- C. The product fails to represent a meaningful therapeutic benefit over existing therapies for pediatric patients **and** is unlikely to be used in a substantial number of pediatric patients in the pediatric age group(s) for which a waiver is being requested.

In addition, a partial waiver can be granted if the applicant can demonstrate that reasonable attempts to produce a pediatric formulation necessary for that age group have failed.

3. You stated that your third pediatric trial (a randomized, single-blind, multicenter dose ranging study comparing the non-inferiority of PICOPREP to a comparator (b) (4) (b) (4) would be initiated “only if PICOPREP represents a meaningful therapeutic benefit over existing treatments for neonate and young children and is likely to be used in a substantial number of neonate and young children.” If you believe a partial waiver is appropriate for patients (b) (4) you must provide supporting data.
4. You stated in your “Proposed Pediatric Plan Summary” that the pediatric trials would not begin until “sufficient additional safety or effectiveness data for PICOPREP has been collected to allow dosing in adolescent children.” Explain what “additional safety or

effectiveness data” you are referring to and why it is necessary before the adolescent trial begins.

5. Provide a rationale for the doses you have suggested for your pediatric trials. If necessary, your pediatric plan should include a dose-finding component.
6. In your “Proposed Pediatric Plan Summary” you referenced two articles that you stated you sponsored, and would like FDA to review. You should plan on providing the full study data and reports so that we may evaluate whether the data collected in those trials can be used to fulfill your PREA requirements. Please provide your timeline for submitting this data to the FDA.
7. Provide an explanation for your proposed patient numbers in the pediatric trials.

Pediatric studies conducted under the terms of section 505B of the Federal Food, Drug, and Cosmetic Act (the Act) may also qualify for pediatric exclusivity under the terms of section 505A of the Act. If you wish to qualify for pediatric exclusivity please consult Division of Gastroenterology and Inborn Errors Products. Please note that satisfaction of the requirements in section 505B of the Act alone may not qualify you for pediatric exclusivity under 505A of the Act.

If you have any questions, call Maureen Dewey, Senior Regulatory Project Manager, at (301) 796-0845.

Sincerely,

{See appended electronic signature page}

R. Wesley Ishihara
Chief, Project Management Staff
Division of Gastroenterology and Inborn Errors
Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

RICHARD W ISHIHARA
04/11/2012



NDA 202-535

INFORMATION REQUEST

Ferring Pharmaceuticals Inc.
Attention: John B. Berryman
Senior Director, Regulatory Affairs
4 Gatehall Drive, 3rd Floor
Parsippany, NJ 07054

Dear Mr. Berryman:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for PICOPREP (sodium picosulfate, magnesium oxide and citric acid) for Oral Solution.

We are reviewing the Chemistry, Manufacturing and Control section of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

- The proposed first fixed (b) (4) for magnesium oxide, is not acceptable unless it is justified by supporting data from your manufacturing experience.
- A lot to lot variable (b) (4) for magnesium oxide is not acceptable. However, a fixed (b) (4) magnesium oxide is recommended to compensate for expected manufacturing loss. Submit the updated master batch record reflecting a (b) (4) of magnesium oxide.
- Content uniformity tests (with acceptance limits) should be included (b) (4)
- Submit CoAs for 3 production scale batches (010901T-2, 010902T-2, 010903T-2).
- Provide a USAN name for sodium picosulfate.

If you have any questions, call Cathy Tran-Zwanetz, Regulatory Project Manager, at (301) 796-3877.

Sincerely,

{See appended electronic signature page}

Moo-Jhong Rhee, Ph.D.
Branch Chief, Branch IV
Division of New Drug Quality Assessment II
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

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/s/

MOO JHONG RHEE

03/19/2012

Chief, Branch IV

Dewey, Maureen

From: Dewey, Maureen
Sent: Monday, March 19, 2012 5:58 PM
To: 'Brenda.Marczi@ferring.com'
Cc: Dewey, Maureen
Subject: NDA 202535 PICOPREP - Clarification of Information Request
Signed By: Maureen.Dewey@fda.hhs.gov

Dear Brenda,

Thank you for your email dated March 16, 2012. We appreciate the clarification on the adverse event collection strategy for those that are frequently occurring.

We are requesting further clarification regarding the patient listing provided in the response letter. In particular, the query for all adverse events of abdominal bloating, distension, pain/cramping, and watery diarrhea identified 19 reported events from 16 patients. However, review of the data submitted to FDA identified at least one patient that experienced one of the frequently occurring adverse events that was not included in the listing. The patient in question (patient id# 2009-01-104029) reportedly had diarrhea; his information is displayed below.

Because of this discrepancy, please clarify whether the patients listed in the response letter are intended to represent a *subset* of all patients that experienced one of the frequently occurring adverse events. If so, please describe how this subset is defined. If the listing is intended to include *all* patients with one of the frequently occurring adverse events, please provide an updated listing that includes all patients.

usubjid	trtsdt	aeterm	aedecod	aestdtc	aesdt	aeacn	aerel
2009-01-104029	(b) (4)	DIARRHEA	Diarrhoea	(b) (4)	(b) (4)	DOSE NOT CHANGED	UNRELATED

Regards,

Maureen Dewey, M.P.H.

Senior Regulatory Project Manager

Division of Gastroenterology and Inborn Errors Products

CDER/FDA

(301) 796-0845 (office)

(301) 796-9905 (fax)

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/s/

MAUREEN D DEWEY
03/19/2012



NDA 202535

INFORMATION REQUEST

Ferring Pharmaceuticals
Attention: John Berryman
Senior Director Regulatory Affairs
4 Gatehall Drive
3rd Floor
Parsippany, NJ 07054

Dear Mr. Berryman:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for PICOPREP (sodium picosulfate, magnesium oxide and citric acid) for Oral Solution, 10 mg sodium picosulfate/sachet.

We also refer to your amendments dated November 7 and December 15, 2011, January 20, January 31, February 17 and February 21, 2012.

We are reviewing your submission and have the following information requests. We request a prompt written response by March 26, 2012, in order to continue our evaluation of your NDA.

Clinical Pharmacology

1. Submit an electronic pharmacokinetic (PK) data set, which should include patient ID numbers, dose, demographics, plasma concentration at each time point, time at which plasma PK samples were collected, plasma PK parameters (e.g., AUC, C_{max} , $t_{1/2}$), urine concentration, and urine PK parameters for each patient for picosulfate, bis-(p-hydroxyphenyl)-pyridyl-2-methane (BHPM), and magnesium.
2. You have stated that picosulfate is metabolized by bacteria in the colon to its active metabolite BHPM. However, we have noted that there is some quantifiable level of BHPM in plasma around 2 hours. Provide your explanation for this observation.

Clinical

3. Provide evidence from available data that each component of PICOPREP bowel prep makes a contribution to the effect of the combined product. Provide evidence that sodium picosulfate alone as a bowel cleansing agent is superior to magnesium citrate alone as a bowel cleansing agent.

In the previous letter dated January 20, 2012, we requested an analysis showing the estimated effectiveness of sodium picosulfate and magnesium citrate individually as bowel prep agents, compared against each other as well as the combination product

PICOPREP using the primary endpoint for analysis (success vs. failure using the Aronchick scale) and the secondary endpoint (using the Ottawa scale). You provided information in the form of studies that looked at a combination product "Picolax" that is identical to Picoprep compared to "Citramag" (magnesium citrate) for colon cleansing prior to radiographic studies. However, you did not provide data supporting each component of the combination product. Again, we are interested in the extent to which each component of the combination product contributes to the overall effect of the product.

Prescribing Information

4. The prescribing information you submitted contained a Medication Guide. Clarify whether you plan to submit other patient labeling (i.e., "Instructions for Use").

Container Label

5. Remove or decrease the prominence of the round shaped graphic (appears as an intestine) directly above the established name. As currently presented, the graphic distracts from the established name.
6. 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 form. The revised presentation of the established name, dosage form, and strength statement may appear as follows:



Note that the dosage form and established name are presented in the same prominence and the removal of the proposed proprietary name "Picoprep" in the statement (b) (4)



7. Delete or decrease the manufacturers name on the principal display panel of the container label. The manufacturer's name is duplicative, competes for prominence with other

important information such as the established name and strength, and will crowd the label when the principal display panel is revised to include the above information.

If you have any questions, call Maureen Dewey, Senior Regulatory Project Manager, at (301) 796-0845.

Sincerely,

{See appended electronic signature page}

R. Wesley Ishihara
Chief, Project Management Staff
Division of Gastroenterology and Inborn Errors
Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

MAUREEN D DEWEY
03/19/2012

RICHARD W ISHIHARA
03/19/2012



NDA 202535

INFORMATION REQUEST

Ferring Pharmaceuticals
Attention: John Berryman
Senior Director Regulatory Affairs
4 Gatehall Drive
3rd Floor
Parsippany, NJ 07054

Dear Mr. John Berryman:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for PICOPREP (sodium picosulfate, magnesium oxide and citric acid) for Oral Solution, 10 mg sodium picosulfate/sachet.

We also refer to your amendments dated November 7 and December 16, 2011.

We are reviewing your submission and have the following information requests. We request a prompt written response by February 3, 2012, in order to continue our evaluation of your NDA.

For studies FE2009-01 and FE2009-02:

1. Provide the statistical program to replicate findings for the tables entitled "Shifts from Normal Baseline to Outside the Normal Range at Visit 3, 4, and 5 in Chemistry Values (Safety Analysis Set)" (FE2009-01: CSR, Table 10-9, page 68; FE2009-02: CSR, Table 10-10, page 69).
2. Submit a revised adverse event analysis data set that includes information for the occurrence of all adverse events reported associated with abdominal bloating, distension, pain/cramping, and watery diarrhea. The current data set documents only episodes that "induced actions" listed in the study protocol (FE2009-01: Study Protocol, page 41; FE2009-02: Study Protocol, page 41).

If you have any questions, call Maureen Dewey, Senior Regulatory Project Manager, at (301) 796-0845.

Sincerely,

{See appended electronic signature page}

R. Wesley Ishihara
Chief, Project Management Staff
Division of Gastroenterology and Inborn Errors
Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

MAUREEN D DEWEY
01/25/2012

RICHARD W ISHIHARA
01/25/2012



NDA 202535

INFORMATION REQUEST

Ferring Pharmaceuticals
Attention: John Berryman
Senior Director Regulatory Affairs
4 Gatehall Drive
3rd Floor
Parsippany, NJ 07054

Dear Mr. John Berryman:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for PICOPREP (sodium picosulfate, magnesium oxide and citric acid) for Oral Solution, 10 mg sodium picosulfate/sachet.

We also refer to your amendments dated November 7 and December 16, 2011.

We are reviewing the clinical section of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

- 1) Provide evidence from available data (e.g., the scientific literature) that each component of PICOPREP bowel prep, i.e., sodium picosulfate 10 mg and magnesium oxide 3.5 mg plus citric acid 12 g (combined to form magnesium citrate in solution) makes a contribution to the effect of the product and the dosage of each component.

For this analysis, provide data in tabular form presenting the estimated effectiveness of sodium picosulfate and magnesium citrate (individually) as bowel prep agents, compared against each other as well as the combination product PICOPREP, using the primary endpoint for analysis (success vs. failure using the Aronchick scale) and the secondary endpoint (using the Ottawa scale).

- 2) Discuss the potential for bisacodyl and sodium picosulfate (individually) to result in colonic mucosal aberrations (e.g., aphthous ulcers) or precipitate ischemic colitis. Provide an overview of pre- and post-market data regarding the frequency of ischemic colitis, rectal bleeding, intestinal bleeding, or gastrointestinal bleeding with the use of the PICOPREP product. A response referring us to the already submitted datasets or postmarketing safety update reports (PSURs) would be unacceptable.

- 3) Provide a tabulation of known cases of electrolyte imbalances or derangements that occurred in patients who have used PICOPREP and were associated with any of the following: dehydration, syncope, loss of consciousness, seizures, and cardiac arrhythmias.
- 4) Provide any case reports of flares of inflammatory bowel disease (IBD), specifically ulcerative colitis and Crohn's disease, associated with the use of PICOPREP.
- 5) As noted in the pre-NDA meeting minutes (meeting date March 21, 2011), if you do not perform a TQT study, you will need to submit a request for a waiver of the requirement for a TQT study with adequate justification (based in part on human PK data) for FDA to review. Submit your request for a waiver as soon as possible

If you have any questions, call Maureen Dewey, Senior Regulatory Project Manager, at (301) 796-0845.

Sincerely,

{See appended electronic signature page}

Richard W. Ishihara
Chief, Project Management Staff
Division of Gastroenterology and Inborn Errors
Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

MAUREEN D DEWEY
01/19/2012

RICHARD W ISHIHARA
01/19/2012



NDA 202535

**REQUEST FOR METHODS
VALIDATION MATERIALS**

Ferring Pharmaceuticals
Attention: John Berryman
Senior Director Regulatory Affairs
4 Gatehall Drive
Third Floor
Parsippany, NJ 07054

Dear Mr. John Berryman:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for PICOPREP (sodium picosulfate, magnesium oxide and citric acid) for Oral Solution, 10 mg sodium picosulfate /sachet.

We will be performing methods validation studies on PICOPREP (sodium picosulfate, magnesium oxide and citric acid) for Oral Solution, 10 mg sodium picosulfate /sachet, as described in NDA 202535

In order to perform the necessary testing, we request the following sample materials and equipments:

30 Sachets PICOPREP for Oral Solution

(b) (4)

Please send the MSDSs and the Certificates of Analysis for the sample and reference material.

Forward these materials via express or overnight mail to:

Food and Drug Administration
Division of Pharmaceutical Analysis
Attn: James F. Allgire
1114 Market Street, Room 1002
St. Louis, MO 63101

Please notify me upon receipt of this letter. If you have questions, you may contact me by telephone (314-539-3813), FAX (314-539-2113), or email (James.Allgire@fda.hhs.gov).

Sincerely,

{See appended electronic signature page}

James F. Allgire
Team Leader
Division of Pharmaceutical Analysis, HFD-920
Office of Testing and Research
Office of Pharmaceutical Science
Center for Drug Evaluation and Research

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/s/

JAMES F ALLGIRE
12/01/2011



NDA 202535

FILING COMMUNICATION

Ferring Pharmaceuticals Inc.
Attention: John Berryman, MS
Senior Director, Regulatory Affairs
4 Gatehall Drive, 3rd Floor
Parsippany, NJ 07054

Dear Mr. Berryman:

Please refer to your New Drug Application (NDA) dated September 16, 2011, received September 16, 2011, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act, for PICOPREP, (sodium picosulfate, magnesium oxide, citric acid) Powder for oral solution, 10mg/3.5g/12g.

We also refer to your amendment dated November 7, 2011.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is **Standard**. Therefore, the user fee goal date is July 16, 2012.

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, midcycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing commitment requests by May 28, 2012.

During our filing review of your application, we identified the following potential review issues:

1. There is no USAN name for sodium picosulfate. Your application cannot be approved without a USAN name for all active ingredients. You should apply for a USAN name as soon as possible.
2. You have defined the Intent-to-Treat (ITT) analysis set as the following: "All randomized subjects who received any study treatment and produced efficacy assessment data." We

previously advised that this is a modified ITT data set and recommended that you use the ITT, defined as all randomized subjects, for the primary analysis. We ask that you re-analyze the primary efficacy data using all randomized subjects. Subjects without an efficacy assessment should be classified as treatment failures. Please include with the analysis results: (1) a listing of subjects with their treatment assignments and their efficacy outcomes and (2) the statistical program used to perform the analysis.

3. In both Studies 2009-01 and 2009-02, there are discrepancies in the number of subject-discontinuations between Table 7-1 in the study report and Table 14.1.1 under Subject Disposition of the “demographic” file.

Please clarify the following discrepancies:

Study 2009-01

	Table 7-1 Study Report			Table 14.1.1 Subject Disposition		
	PicoPrep	HalfLyte	Total	PicoPrep	HalfLyte	Total
Discontinuation from the Study	1	3	4	3	6	9
Subject Withdrawal	1	0	1	3	2	5

Study 2009-02

	Table 7-1 Study Report			Table 14.1.1 Subject Disposition		
	PicoPrep	HalfLyte	Total	PicoPrep	HalfLyte	Total
Discontinuation from the Study	9	7	16	13	8	21
Subject Withdrawal	5	1	6	8	2	10

4. We note that proposed labeling 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.
5. We note that you have not submitted a request for proprietary name review. For more information, please see *Guidance for Industry: Contents of a Complete Submission for the Evaluation of Proprietary Names (February 2010)* available at the following link:
<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075068.pdf>

We are providing the above comments to give you preliminary notice of potential review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review. Issues may be added, deleted, expanded upon, or modified as we review the application. If you respond to these issues late in the review cycle, we may not consider your response before we take an action on your application.

During our preliminary review of your submitted labeling, we have identified the following labeling format issues:

6. In the Highlights, the highlights limitation statement and the adverse reaction reporting instructions appear to be repeated in the SPL rendering of your proposed label. You should revise this section to remove any redundancy.

7. In the Highlights, the Indications and Usage should be revised to include appropriate pharmacological class(es) (e.g., stimulant laxative, osmotic laxative).
8. To address comment 4, above, the Full Prescribing Information (FPI) section 17 Patient Counseling Information should be revised to reference a Medication Guide. You should replace “See FDA-approved patient labeling (Patient Information)” with “See FDA-approved patient labeling (Medication Guide).” Similarly, the Highlights should be revised to state, “See 17 for Patient Counseling Information and Medication Guide.”

We request that you resubmit labeling that addresses these issues by December 16, 2011. The resubmitted labeling will be used for further labeling discussions.

Please respond only to the above requests for information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We acknowledge receipt of your request for a full deferral of pediatric studies for this application. Once we have reviewed your request, we will notify you if the full deferral request is denied.

If you have any questions, call Matthew Scherer, Regulatory Project Manager, at (301) 796-2307.

Sincerely,

{See appended electronic signature page}

Donna Griebel, MD
Director
Division of Gastroenterology and Inborn Errors
Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

DONNA J GRIEBEL
11/29/2011



NDA 202535

NDA ACKNOWLEDGMENT

Ferring Pharmaceuticals Inc.
Attention: John Berryman, MS
Senior Director, Regulatory Affairs
4 Gatehall Drive, 3rd Floor
Parsippany, NJ 07054

Dear Mr. Berryman:

We have received your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for the following:

Name of Drug Product: PICOPREP (sodium picosulfate, magnesium oxide, citric acid)
Powder for solution

Date of Application: September 16, 2011

Date of Receipt: September 16, 2011

Our Reference Number: NDA 202535

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on November 15, 2011, in accordance with 21 CFR 314.101(a).

If you have not already done so, promptly submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action under 21 CFR 314.101(d)(3). The content of labeling must conform to the content and format requirements of revised 21 CFR 201.56-57.

You are also responsible for complying with the applicable provisions of sections 402(i) and 402(j) of the Public Health Service Act (PHS Act) [42 USC §§ 282 (i) and (j)], which was amended by Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law No, 110-85, 121 Stat. 904).

The NDA number provided above should be cited at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Gastroenterology and Inborn Errors Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size. Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, please see <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/DrugMasterFilesDMFs/ucm073080.htm>.

If you have any questions, call me at (301) 796-2307.

Sincerely,

{See appended electronic signature page}

Matthew Scherer, MBA
Senior Regulatory Project Manager
Division of Gastroenterology and Inborn Errors
Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

MATTHEW C SCHERER
10/04/2011

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration

Form Approved: OMB No. 0910-0396
Expiration Date: August 31, 2012

CERTIFICATION: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

TO BE COMPLETED BY APPLICANT

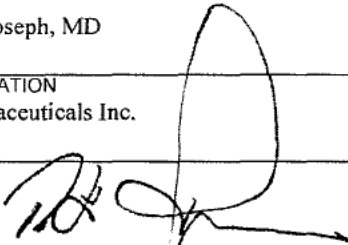
With respect to all covered clinical studies (or specific clinical studies listed below (if appropriate)) submitted in support of this application, I certify to one of the statements below as appropriate. I understand that this certification is made in compliance with 21 CFR part 54 and that for the purposes of this statement, a clinical investigator includes the spouse and each dependent child of the investigator as defined in 21 CFR 54.2(d).

Please mark the applicable checkbox.

- ☒ (1) As the sponsor of the submitted studies, I certify that I have not entered into any financial arrangement with the listed clinical investigators (enter names of clinical investigators below or attach list of names to this form) whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). I also certify that each listed clinical investigator required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b) did not disclose any such interests. I further certify that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).

Clinical Investigators	See attached list	

- ☐ (2) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that based on information obtained from the sponsor or from participating clinical investigators, the listed clinical investigators (attach list of names to this form) did not participate in any financial arrangement with the sponsor of a covered study whereby the value of compensation to the investigator for conducting the study could be affected by the outcome of the study (as defined in 21 CFR 54.2(a)); had no proprietary interest in this product or significant equity interest in the sponsor of the covered study (as defined in 21 CFR 54.2(b)); and was not the recipient of significant payments of other sorts (as defined in 21 CFR 54.2(f)).
- ☐ (3) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that I have acted with due diligence to obtain from the listed clinical investigators (attach list of names) or from the sponsor the information required under 54.4 and it was not possible to do so. The reason why this information could not be obtained is attached.

NAME Raymond E. Joseph, MD	TITLE Executive Director, Clinical R & D
FIRM/ORGANIZATION Ferring Pharmaceuticals Inc.	
SIGNATURE 	DATE (mm/dd/yyyy) 08/22/2011

Paperwork Reduction Act Statement

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number. Public reporting burden for this collection of information is estimated to average 1 hour per response, including time for reviewing instructions, searching existing data sources, gathering and maintaining the necessary data, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information to the address to the right:

Department of Health and Human Services
Food and Drug Administration
Office of Chief Information Officer
1350 Piccard Drive, 420A
Rockville, MD 20850



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 101738

MEETING MINUTES

Ferring Pharmaceuticals Inc.
Attention: John Berryman, MS
Senior Director, Regulatory Affairs
4 Gatehall Drive, Third Floor
Parsippany, NJ 07054

Dear Mr. Berryman:

Please refer to your Investigational New Drug Application (PIND) file for PICOPREP (sodium picosulfate, magnesium oxide and citric acid) for Oral administration.

We also refer to the meeting between representatives of Ferring Pharmaceuticals and the FDA on March 21, 2011. The purpose of the meeting was to discuss a planned New Drug Application (NDA) submission.

A copy of the official minutes of the meeting is attached for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 796-2307.

Sincerely,

{See appended electronic signature page}

Matthew Scherer
Regulatory Project Manager
Division of Gastroenterology
Office of Drug Evaluation III
Center for Drug Evaluation and Research

ENCLOSURE:
Meeting Minutes



**FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

MEMORANDUM OF MEETING MINUTES

Meeting Type: Type B
Meeting Category: Pre-NDA
Meeting Date and Time: March 21, 2011, 1:00 to 2:00 p.m.
Meeting Location: White Oak, Building 22, Room 1311

Application Number: IND 101738
Product Name: PicoPrep
Indication: Bowel cleansing prior to colonoscopy
Sponsor/Applicant Name: Ferring Pharmaceutical, Inc.

Meeting Chair: Robert Fiorentino
Meeting Recorder: Matthew Scherer

FDA ATTENDEES

Donna Griebel, MD, Director, Division of Gastroenterology Products (DGP)
Rob Fiorentino, MD, Acting Medical Team Leader, DGP
Aisha Peterson-Johnson, MD, MBA, Medical Officer, DGP
Milton Fan, PhD, Statistician, Division of Biostatistics 3
Sue-Chih Lee, PhD, Clinical Pharmacology Team Leader, Division of Clinical Pharmacology 3
Dilara Jappar, PhD, Clinical Pharmacologist, Division of Clinical Pharmacology 3
Sushanta Chakder, PhD, Supervisory Pharmacologist, DGP
Tamal Chakraborti, PhD, Pharmacologist, DGP
Matthew Scherer, MBA, Senior Regulatory Project Manager, DGP

SPONSOR ATTENDEES

Paul Korner, MD, President of US Development
Ray Joseph, MD, Executive Director of Clinical Research and Development
Arthur Czech, Research Manager
Mike Cimino, Senior Manager of Manufacturing
Anthony Acs, Project Manager
Ronald Hargreaves, Vice President of Regulatory Affairs
John Berryman, Senior Director of Regulatory Affairs

(b) (4)



1. BACKGROUND

Ferring is developing PicoPrep (sodium picosulfate, magnesium oxide and citric acid) Oral Solution for the cleansing of the colon prior to colonoscopy. The same formulation has been marketed in various countries beginning in 1980. Ferring has completed 2 Phase 3 clinical trials in the US and has requested a pre-NDA meeting to discuss the content of an expected NDA submission.

2. DISCUSSION

Question 1: Based upon the preliminary data provided, does the Agency agree that the clinical data package for PICOPREP comprising these two completed studies is sufficient for filing the NDA?

FDA Response:

No, please see Additional Clinical Pharmacology Comments regarding the need for additional studies.

However, the two clinical studies conducted (as represented by the preliminary data provided) appear reasonable for evaluating the clinical efficacy of PicoPrep. The adequacy of the trial results to support the proposed indication ultimately will be a review issue. Furthermore, the specific wording of the indication statement will be a review issue.

Discussion

Ferring noted that picosulfate is not a pharmacologically active entity. See discussion under Additional Clinical Pharmacology Comments, below.

Question 2: Based upon the superiority of results over the comparator preparation, does the Agency agree that the NDA for PICOPREP qualifies for priority review?

FDA Response:

Review priority will be determined at the time of NDA filing.

If you desire to pursue priority designation, your formal request should include a detailed rationale for why you believe PicoPrep offers a *significant* improvement compared to products currently marketed. For additional information, please see the Office of New Drugs MAPP 6020.3: Review Classification Policy: Priority (P) and Standard (S) (July 2007), available at the following link:

<http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/StaffPoliciesandProcedures/ucm082000.pdf>

Discussion

Ferring presented rationale to justify a Priority NDA review designation. See attachment.

Question 3: Because of the two different dosing regimens in the two Phase 3 studies, Ferring intends to provide separate efficacy analyses within the ISE for each regimen, while we plan to combine the safety assessment in the ISS into one analysis. Does the Agency agree with this plan?

FDA Response:

Please note that separate Clinical Study Reports and efficacy analyses should be performed for each of the two Phase 3 studies irrespective of the ISE. Your ISE should provide comparative analyses across these studies that support the dosing regimen(s) that you intend to pursue in labeling. Results or findings that did not favor the study treatment should also be addressed, including identification of specific patient or demographic subgroups that had treatment benefits inconsistent with the main effect.

**Please refer to the draft Guidance for Industry: Integrated Summary of Effectiveness, available at:
<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm079803.pdf>**

We agree that the ISS should include safety assessments across all studies. However, we would like to see safety information from each regimen described in the individual Clinical Study Reports.

Discussion
Ferring agreed.

Question 4: If superiority to the comparator is confirmed by FDA review, does the Agency agree that PICOPREP can be claimed as superior to the comparator in product labeling?

FDA Response:

It is premature for the Agency to provide agreement regarding product labeling. The wording for labeling will be determined at the time of the review.

Discussion
Ferring acknowledged.

Question 5: Given the favorable ECG findings from the Phase 3 studies, does the Agency agree that these result support the safety of PICOPREP with respect to cardiac proarrhythmic potential?

FDA Response:

No, we do not agree. While the Phase 3 studies did not appear to show evidence of cardiac arrhythmias associated with the use of PicoPrep, these studies were neither powered nor designed to rule out a specific cardiac safety signal. In order to conclusively demonstrate that PicoPrep (unlike other drugs in this class) does not have the risk of rare, but serious arrhythmias associated with the use of other osmotic laxatives, an adequately designed clinical program would be required.

In addition, you do not appear to have performed the appropriate bioavailability or PK studies to evaluate whether a TQT study is warranted. See Additional Clinical Pharmacology Comment #1.

Discussion

Ferring clarified that it expects that class-labeling related to the cardiac risk secondary to electrolyte imbalances would be included in the PicoPrep labeling.

Question 6: Ferring plans to request deferral from pediatric evaluation of PICOPREP until after approval of the product for use in the adult population. Does the Agency agree with this plan?

FDA Response:

Please submit a pediatric plan at the time of your NDA submission. Include in the plan any planned or ongoing pediatric studies, the specific age groups that will be studied, and any age groups to be deferred or waived. Also include associated timelines. All age groups (ages 0 months through 17 years) must be addressed in the pediatric plan and certification of the grounds for deferral or waiver of any assessments should be included. The proposed pediatric plan should be appropriately supported by epidemiological data. Furthermore, evidence that the studies are being conducted or will be conducted with due diligence and at the earliest possible time should be provided in the plan.

Discussion

Ferring agreed.

Question 7: Based upon the data and information presented in the briefing book as well as previous filings and communications, are there any other issues or further considerations arising from the Division's review that Ferring needs to address to support a successful NDA submission?

Additional Clinical Pharmacology Comments:

- 1. Since picosulfate is an NME, the ADME characteristics of this active ingredient in humans will need to be characterized. In addition, you will need to evaluate the human pharmacokinetic profile of active components, sodium picosulfate and magnesium citrate in PicoPrep. This data does not appear to have been presented within the meeting package. However, this information will be required for filing your NDA submission.**

In addition, we note that you have been previously advised by FDA (FDA/sponsor meeting dated April 16, 2009), to determine the pharmacokinetics (PK) of this product in healthy subjects and in elderly patients, and to conduct and compare the PK parameter between hepatic impairment and healthy subjects, and between renal impairment and healthy subjects. Please indicate if these studies have not been performed and provide your rationale.

Note that if there is substantial systemic exposure of sodium picosulfate, you should conduct *in vitro* studies, including transporters and CYP 450 enzymes, to determine whether drug-drug interaction studies are needed. Since this product has not been approved before in the U.S., a thorough QTc study may be required if sodium picosulfate is bioavailable. You should plan to submit a protocol for a thorough QT study to the Agency for review and comment prior to initiating the QT study.

Discussion

Ferring presented summaries of 2 additional phase 1 trials that have been completed, in both healthy humans and elderly populations assessing electrolyte hemodynamic changes and QTc (C01 and C02), as well as data supporting the claim that picosulfate is minimally absorbed and rapidly cleared in animals (see attached slides). Ferring further asserts that picosulfate is inactive and that the major metabolite, BHPM, is pharmacologically active.

FDA strongly recommended that Ferring include the requested PK characterization and noted that these data are required per 21 CFR 320.21(a). Both picosulfate and BHPM should be assessed in the human PK study.

Ferring explained that it is currently working with a lab to develop a human assay.

FDA requested that Ferring submit a rationale to not include elderly, renal impairment, and hepatic impairment patients in a PK study. Ferring agreed to submit this justification with its PK protocol.

FDA recommended that Ferring submit a TQT protocol and/or request for a waiver of the requirement for a TQT study with justification for FDA review.

- 2. Within the NDA, please evaluate the effect of magnesium citrate on serum magnesium level.**

Discussion

Ferring presented information on human serum Mg²⁺ levels (see attached slide). FDA noted that this information appears reasonable and that Ferring should include an analysis of the magnesium data in its NDA submission.

- 3. In the meeting package, it was stated that [REDACTED] (b) (4) This mechanism appears to be contradictory to the desired effect. Please explain.**

Other comments from the FDA:

- For the safety data, please include analyses of metabolic acidosis (gap and non-gap), bilirubin, calcium, osmolality, and uric acid (in addition to standard chemistry panels and other labs planned). Additionally, please provide an analysis of how any abnormal values recover over time.**

- **At the appropriate time, we recommend you schedule a pre-submission meeting with DGP to orient the review team to your NDA. We also recommend that you schedule a post-submission meeting with DGP to present your data and conclusions.**
- **Request for CDISC/data format:**

Please provide the following full case report tabulation (CRT) for each adequate and well-controlled clinical study (per 21 CFR 314.126) you plan to include in your NDA/BLA submission:

1. All clean/locked clinical data presented in electronic datasets, submitted utilizing SAS Version 5 Transport, along with the annotated case report form (aCRF) and a thorough data definition file. We recommend that the electronic datasets, aCRF, and data definition file fully comply with the latest CDISC/SDTM, CDISC/CDASH, and CDISC/Define.XML standards respectively.

2. All corresponding analysis data presented in electronic datasets, submitted utilizing SAS Version 5 Transport, along with a thorough data definition file. We recommend that these electronic datasets fully incorporate the modeling approaches described by both the latest CDISC/ADaM standard and the FDA Study Data Specifications document

(<http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionsRequirements/ElectronicSubmissions/UCM199759.pdf>). We recommend that the data definition file fully comply with the latest CDISC/Define.XML standard.

3. A well commented and organized software program written for each analysis dataset and efficacy table created.

3. OTHER: PRESCRIBING INFORMATION

Proposed prescribing information (PI) submitted with your application must conform to the content and format regulations found at 21 CFR 201.56 and 201.57.

Summary of the Final Rule on the Requirements for Prescribing Information for Drug and Biological Products, labeling guidances, sample tool illustrating Highlights and Table of Contents, an educational module concerning prescription drug labeling, and fictitious prototypes of prescribing information are available at:
<http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/ucm084159.htm>. We encourage you to review the information at this website and use it as you draft prescribing information for your application.

4. ISSUES REQUIRING FURTHER DISCUSSION

None.

5. ACTION ITEMS

None.

6. ATTACHMENTS AND HANDOUTS

The sponsor's slide presentation is attached.

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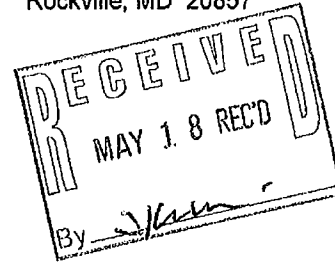
/s/

MATTHEW C SCHERER
04/19/2011



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857



PIND 101,738

Ferring Pharmaceuticals, Inc.
Attention: Ronald T. Hargreaves, Ph.D.
Vice President, Regulatory Affairs
4 Gatehall Drive, Third Floor
Parsippany, NJ 07054

Dear Dr. Hargreaves:

Please refer to your Pre-Investigational New Drug Application (PIND) file for PICOLAX (sodium picosulfate, magnesium oxide, and citric acid) for bowel cleansing prior to colonoscopy.

We also refer to the meeting between representatives of your firm and the FDA on April 16, 2009. The purpose of the meeting was to obtain comments from the FDA on the adequacy of the existing preclinical and chemistry and manufacturing controls (CMC) data for PICOLAX.

A copy of the official minutes of the meeting is attached for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 796-2137.

Sincerely,

{See appended electronic signature page}

Stacy Barley, R.N., M.S.N., M.H.A.
LCDR/USPHS
Regulatory Health Project Manager
Division of Gastroenterology Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure -- Meeting Minutes

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MEMORANDUM OF MEETING MINUTES

MEETING DATE: April 16, 2009
TIME: 2:00 p.m. – 3:00 p.m. EDT
LOCATION: White Oak Bldg 22 Room 1313
APPLICATION: PIND 101,738
DRUG NAME: PICOLAX
TYPE OF MEETING: Type B

MEETING CHAIR: John Hyde, Ph.D., M.D., Medical Team Leader

MEETING RECORDER: Stacy Barley, R.N., M.S.N., M.H.A., Regulatory Project Manager

FDA ATTENDEES:

Anne Pariser, M.D., Acting Deputy Director, Division of Gastroenterology Products (DGP)
John Hyde, Ph.D., M.D., Medical Team Leader, DGP
Marie Kowblansky, Ph.D., Pharmaceutical Assessment Leader, ONDQA
Sushanta Chakder, Ph.D., Supervisory Pharmacologist, DGP
Dinesh Gautam, Pharm.D., Ph.D., Pharmacology Reviewer, DGP
Christopher Leptak, M.D., Medical Reviewer, DGP
Stacy Barley, R.N., M.S.N., M.H.A., Regulatory Project Manager, DGP
Richard Ishihara, Regulatory Project Manager, DGP
Mike Welch, Ph.D., Statistical Team Leader, Division of Biometrics III
Jane Bai, Pharm.D., Ph.D., Clinical Pharmacology Reviewer, Office of Clinical Pharmacology

EXTERNAL CONSTITUENT ATTENDEES:

Ron Hargreaves, Ph.D., Vice President, Regulatory Affairs, Ferring Pharmaceuticals, Inc.
John Kim, RPh, J.D., Director, Regulatory Affairs, Ferring Pharmaceuticals, Inc.
Raymond Joseph, M.D., Director, Clinical Development for Gastroenterology, Ferring
Pharmaceuticals, Inc.
Arthur Czech, Senior Clinical Research Associate, Ferring Pharmaceuticals, Inc.

(b) (4)

(b) (4)

BACKGROUND:

Ferring Pharmaceuticals, Inc., requests assistance from the FDA with the development program for PICOLAX.

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MEETING OBJECTIVES:

- To obtain comments from the FDA that will assist Ferring Pharmaceuticals, Inc. with the submission of an IND in order to initiate the clinical development of PICOLAX in the United States.
- To obtain comments from the FDA that will assist Ferring with the later submission of an NDA.

DISCUSSION POINTS:

Questions from Ferring Pharmaceuticals, Inc. are in plain text. The preliminary FDA responses sent to Ferring on April 15, 2009, are in **bold text**. The meeting discussion from April 16, 2009, is in ***bold italics***.

Questions and Answers**Preclinical (toxicology)**

1. Does the Division agree that the preclinical studies summarized above and in Attachments 1-7 are sufficient to support the proposed Phase 3 clinical study and complete the preclinical data necessary for submission of an NDA?

FDA Response:

No, we do not agree. In your 14-day toxicity studies in rats and dogs, microscopic examinations of only a limited number of tissues were conducted, and your studies used only sodium picosulfate, not the combination you intend to market. Thus, these studies are not adequate to assess the safety of the proposed clinical trial. In addition, you need to conduct the complete battery of reproductive toxicity studies with your product. For the marketing application, toxicology studies in a rodent and a nonrodent species for a minimum of 4 weeks duration with the combination you intend to market will be required (please refer to ICH Guidance M3, *Nonclinical Safety Studies for the Conduct of Human Clinical Trials for Pharmaceuticals*, July 1997).

Meeting Discussion:

Ferring will submit full study reports in the IND. In response to Ferring's question regarding whether examination of all tissues from the 14-day toxicity study in rats will fulfill the requirements, the FDA stated that examinations of other fixed tissues in the rat study would not be useful. The FDA stated that 14-day toxicity studies are acceptable for the IND application; however, one-month rodent and non-rodent toxicology studies will be needed for the NDA submission.

Ferring proposed to conduct the required Segment II and Segment III reproductive toxicology studies in parallel with Phase 3 clinical studies. The FDA stated that Ferring can do that; however, adequate pregnancy precautions must be undertaken in the clinical trials.

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Clinical

2. Does the Division agree that the proposed clinical studies will be adequate to demonstrate the safety and efficacy of PICOLAX for the indication stated above?

FDA Response:

As discussed in our response to Question 1, your preclinical studies appear to be inadequate to support human studies with PICOLAX at this time. If you believe that there may be human exposure data from the published literature and clinical trials conducted outside the U.S. that you want us to consider in support of your proposed U.S. studies, you will need to submit a complete description and analysis of those studies to provide such support. Studies with different active ingredients or composition would be limited in their ability to provide support.

In the absence of a complete IND submission and in the absence of specific results of any Phase 2 studies or comparable information, it is premature for us to provide agreement on what would be acceptable studies for a Phase 3 program. We strongly encourage you to obtain and provide the kinds of information that would be generated in Phase 2 development before embarking on Phase 3 studies (see also comment e, below). The following comments on your study proposals should be considered advisory only.

Regarding your two proposed Phase 3 clinical trials (#2009-01 and #2009-02), the overall designs appear generally similar to those of studies done for bowel preparation products, and they would be reasonable to include in the submission of your IND, although some elements of the study designs may be a review issue. Given the analogous study designs, please consider the following points of advice as they pertain to both of your proposed Phase 3 trials:

- a) Study design. If you decide to conduct a non-inferiority clinical trial, we highly recommend that you consult the guidance document ICH E10 to determine which reference studies with the comparator product are appropriate in calculating the non-inferiority (NI) margin. You will need to submit discussion describing how the NI margin was determined and its clinical relevance. We suggest that you request feedback from us regarding the choice of an appropriate NI margin prior to the initiation of your clinical trial.

Meeting Discussion:

Ferring indicated that the 15% NI margin was based on applications approved in the past. The FDA stated that a 15% NI margin is not recommended. Recent advice to sponsors for this indication has encouraged the use of a 9% margin.

- b) Safety evaluation. Your studies complete the final safety monitoring on Visit 4 (the day following the colonoscopy and two to three days following treatment). We encourage you to add an additional safety assessment including full physical, laboratory testing,

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and adverse event determination at around Week 1 and at Week 4 post-exposure. We cannot comment more completely on what would constitute adequate and acceptable safety monitoring until we have reviewed your IND submission.

Meeting Discussion:

Ferring will add additional safety assessments, telephone interviews, and lab testing.

- c) **Blinding.** We understand that the two active treatments have differing dosing schedules and volumes of consumption, preventing full blinding. However, please consider additional measures that would help ensure that the examiner is truly blinded to the subject's treatment. Have you considered a control that would allow both split and same-day dosing as you are proposing for your product?

Meeting Discussion:

To assist with blinding, Ferring indicated that the study coordinators would sign affidavits, the colonoscopist would be instructed not to ask the patients how their bowel preparation was performed, and all colonoscopies will be scheduled for the morning.

- d) **Disposition of subjects.** Although you are screening and randomizing 500 subjects (250 subjects per treatment arm), you state that you will stop recruitment when 122 evaluable subjects per arm are completed. This is a rather large discrepancy between the numbers you will potentially randomize and the number you intend to analyze. Any subject that is screened, enrolled, randomized, and receives treatment (even partial) should be evaluated in some way and the data included in both the safety and efficacy analyses. Additionally, any subjects that withdraw from the study or are lost to follow-up, regardless of reason, should be determined to be treatment failures. We recommend that you specify a fixed number you intend to enroll based on reasonable estimates of patient loss and not plan to stop enrollment early based on accruing outcome information.

Meeting Discussion:

The FDA asked that Ferring maintain appropriate firewalls and blinding to protect the integrity of the trial results. This is especially important since the trial is single blind and the endpoints are subjective. Additionally, changes to the protocol analytical plan or SAP made after study initiation would be a serious review concern.

In addition, please consider the following recommendations as part of your drug development plan:

- e) **Phase 2 development.** You have not presented specific data to support your choices regarding size of doses needed, amount of fluids needed, necessary amount of each active component in your formulation (see also comment i, below), split vs. same-day dosing, timing of administration, timing between doses for same-day dosing, or time needed from completion of preparation before undergoing colonoscopy. We strongly encourage you to provide such information, or to conduct smaller Phase 2

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investigations to explore these issues if reliable data are not available to address them, before designing your Phase 3 studies.

Meeting Discussion:

Ferring presented additional data (see ATTACHMENTS for slides presented by Ferring at the meeting). Ferring said they had the kind of Phase 2 information the FDA was requesting, and they would provide it in the IND submission. The FDA asked that the submission include complete copies of any articles Ferring planned to refer to in support of their IND protocol.

- f) You should determine the pharmacokinetics (PK) of this product in healthy subjects and in elderly patients, and conduct and compare the PK parameters between hepatic impairment and healthy subjects, and between renal impairment and healthy subjects.
- g) If there is substantial systemic exposure of sodium picosulfate, you should conduct in-vitro studies including transporters and CYP 450 enzymes to determine whether drug-drug interaction studies are needed. Since this product has not been approved before in the U.S., a thorough QTc study is strongly recommended if sodium picosulfate is bioavailable. We strongly recommend you submit the protocol for a thorough QT study to the Agency for review and comment prior to initiating the QT study.
- h) A population pharmacokinetic analysis of exposure/response relationship related to adverse events is encouraged if sodium picosulfate is bioavailable.

Meeting Discussion (f, g, and h):

Ferring stated they did not think there would be more than trace absorption. Ferring also made reference to 20 patients in an investigation unit over a weekend that were serially monitored with an electrocardiogram and had no significant findings. The FDA stated that, according to the guidances, to support the NDA for a new molecular entity, the FDA requires studies in humans to identify if there is absorption. Serum measurements should be obtained at baseline and continuing 24 hours after the second dose. The FDA suggested Ferring refer to the guidances as to how much absorption of a drug would trigger the need for additional studies.

- i) For a product containing two or more drugs, evidence will be needed that each component makes a contribution to the claimed effects (cf. 21 CFR 300.50). In your development program, you will need to give consideration to how you will generate such evidence. Typically, this would involve conducting studies using a factorial design, in which the combination is compared not only to placebo, but to each drug individually as well.

Meeting Discussion:

Ferring felt that a factorial study would not be ethical because using only one component would not work. The FDA responded that a factorial design was not a requirement, but that some sort of evidence must be provided to support the need for the combination. If Ferring claims neither component alone would work, convincing evidence for that claim needs to be provided in the NDA.

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It is recommended that you refer to the following Guidances for Industry on the Agency's web page (<http://www.fda.gov/cder/guidance/index.htm>)

- *Guidance for Industry Drug Interaction Studies – Study Design, Data Analysis, and Implications for Dosing and Labeling (September 2006)*
- *Guidance for Industry E14 Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs (Oct 2005)*

Chemistry, Manufacturing and Controls

3. Can Ferring provide 6 months accelerated and 6 months long term stability data for the new registration batches (new sources of magnesium oxide and citric acid) along with 6 months accelerated and 3 years long term stability as supportive data for the NDA submission to support 3 year expiration dating?

FDA Response:

Your proposal for submission of stability data is reasonable. However, the assignment of a three year expiration date based on supporting stability data will be a review issue and will depend on the comparative trends that are observed in the data. To support your case, you should also provide a comparison of the critical quality attributes such as particle size, crystalline form, impurities, etc., for each of the materials from the two suppliers.

Meeting Discussion:

No additional discussion.

4. After the Phase 3 study, if it becomes necessary to change again the manufacturing source of magnesium oxide USP or citric acid USP, or both, what bridging study will be required to justify clinical equivalence, since we cannot conduct a bioequivalence study based on pharmacokinetic parameters?

FDA Response:

It will not be necessary to do a bioequivalence study. It will be sufficient to provide the route of synthesis, a comparison of the critical quality attributes such as particle size, crystalline form, impurities, etc., for each of the materials from the two suppliers, and provide at least three months of stability data for product manufactured with drug substance from the new source.

Meeting Discussion:

No additional discussion.

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ATTACHMENTS/HANDOUTS:

Slide presentation by Ferring Pharmaceutical, Inc.

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Linked Applications	Sponsor Name	Drug Name / Subject
IND 101738	FERRING PHARMACEUTICALS INC	sodium picosulfate, magnesium oxide, citric acid

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/s/

STACY R BARLEY
05/13/2009