CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-881

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

NDA 21-881

March 24, 2006

Brian E. Harvey, M.D., Ph.D.,
Director, Division of Gastroenterology Products
Office of New Drugs, Office of Drug Evaluation III
Center for Drug Evaluation and Research
Food and Drug Administration
5901-B Ammendale Road
Beltsville, MD 20705

RE: NDA 21-881 for MOVIPREP® (PEG 3350, sodium sulfate, sodium chloride, potassium chloride, sodium ascorbate and ascorbic acid) for oral solution Administrative Amendment: Correction to Patent Information

Dear Dr. Harvey,

This amendment corrects unsuitable information submitted in Sections 1.4.1 Patent Information and 1.4.2 Patent Certification of MOVIPREP® NDA 21-881.

Unfortunately, patent information for a related product was inadvertently submitted in Section 1.4.1 on FDA From 3542a. Specifically we referenced the following patent which does not apply to MOVIPREP®:
US Patent No 5274,001
Issue Date: 12-28-1993
Expiration Date: 12-28-2013
Title: Orthostatic Lavage Solutions

Furthermore, Section 1.4.2 Patent Certification is not appropriate for a 505(b)(1) in accord with 21CFR 314.50(i)

Therefore, we formally withdraw the Patent Information submitted in Section 1.4.1 and 1.4.2, without replacement.

This administrative amendment is submitted in Archival Copy only, with two additional desk copies being provided for Tanya D Clayton, BS, Regulatory Project Manager.

Registered Office: New Road, Hengoed, Mid Glamorgan CF82 8SJ – Tel: 44 (0)1443 812183 – Fax: 44 (0)1443 816648
Registered in England No 3527131

For all communications related to this application, please contact Ramona Krailler, Ph.D., Regulatory Affairs Manager, Norgine Limited, at +44 7795 005 484.

Sincerely,

Ramona Krailler

Ramona E Krailler, Ph.D.
Regulatory Affairs Manager
Norgine Limited
Chaplin House
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1.4.1 Patent Information

For each patent that claims a drug substance (active ingredient), drug product (formulation and composition), or method of use, Norgine B.V. is providing a FDA Form 3542a under this section. MOVIPREP is covered by the following US Patents:

US Patent No 5274,001
Issue Date: 12-28-1993
Expiration Date: 12-28-2013
Title: Orthostatic Lavage Solutions

Norgine B.V. believes these patents would be infringed if a person not licensed by the owner engaged in the manufacture, use or sale of the drug product formulation described in this application.

Department of Health and Human Services
Food and Drug Administration

PATENT INFORMATION SUBMITTED WITH THE FILING OF AN NDA, AMENDMENT, OR SUPPLEMENT

For Each Patent That Claims a Drug Substance (Active Ingredient), Drug Product (Formulation and Composition) and/or Method of Use

Form Approved: OMB No. 0910-0513
Expiration Date: 07/31/06
See OMB Statement on Page 3.

NDA NUMBER
21-881

NAME OF APPLICANT / NDA HOLDER
NORGINE BV

The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act.

TRADE NAME (OR PROPOSED TRADE NAME)
MOVIPREP®

ACTIVE INGREDIENT(S)
PEG 3350, sodium sulfate, sodium chloride, potassium chloride, ascorbic acid, sodium ascorbate

STRENGTH(S)
Not applicable

DOSAGE FORM
Powder for reconstitution

This patent declaration form is required to be submitted to the Food and Drug Administration (FDA) with an NDA application, amendment, or supplement as required by 21 CFR 314.53 at the address provided in 21 CFR 314.53(d)(4).
Within thirty (30) days after approval of an NDA or supplement, or within thirty (30) days of issuance of a new patent, a new patent declaration must be submitted pursuant to 21 CFR 314.53(c)(2)(ii) with all of the required information based on the approved NDA or supplement. The information submitted in the declaration form submitted upon or after approval will be the only information relied upon by FDA for listing a patent in the Orange Book.

For hand-written or typewriter versions (only) of this report: If additional space is required for any narrative answer (i.e., one that does not require a "Yes" or "No" response), please attach an additional page referencing the question number.

FDA will not list patent information if you file an incomplete patent declaration or the patent declaration indicates the patent is not eligible for listing.

For each patent submitted for the pending NDA, amendment, or supplement referenced above, you must submit all the information described below. If you are not submitting any patents for this pending NDA, amendment, or supplement, complete above section and sections 5 and 6.

1. GENERAL

a. United States Patent Number
5274,001

b. Issue Date of Patent
12.28.1993

c. Expiration Date of Patent
12.28.2013

d. Name of Patent Owner
Professor Thomas Borody

Address *(of Patent Owner)*
Centre for Digestive Diseases, 144 Great North Road

City/State
Five Dock, New South Wales, Australia

ZIP Code
2046

FAX Number *(if available)*
+61 29712 1675

Telephone Number
+61 29713 4011

E-Mail Address *(if available)*

e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States)

Jones Tullar and Cooper PC

Address *(of agent or representative named in 1.e.)*
PO Box 2266 Eads Station

City/State
Arlington

ZIP Code
VA2202

FAX Number *(if available)*
(703) 415 1508

Telephone Number
(703) 415 1500

E-Mail Address *(if available)*

f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above? ☐ Yes ☒ No

g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date? ☐ Yes ☒ No

For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use that is the subject of the pending NDA, amendment, or supplement.

2. Drug Substance (Active Ingredient)

2.1	Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement?	☒ Yes	☐ No
2.2	Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement?	☐ Yes	☒ No
2.3	If the answer to question **2.2** is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b).	☐ Yes	☐ No
2.4	Specify the polymorphic form(s) claimed by the patent for which you have the test results described in **2.3**.		
2.5	Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section **4** below if the patent claims a pending method of using the pending drug product to administer the metabolite.)	☐ Yes	☒ No
2.6	Does the patent claim only an intermediate?	☐ Yes	☒ No
2.7	If the patent referenced in **2.1** is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	☐ Yes	☒ No

3. Drug Product (Composition/Formulation)

3.1	Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement?	☒ Yes	☐ No
3.2	Does the patent claim only an intermediate?	☐ Yes	☒ No
3.3	If the patent referenced in **3.1** is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	☐ Yes	☐ No

4. Method of Use

Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:

4.1	Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?	☐ Yes	☒ No
4.2	Patent Claim Number *(as listed in the patent)* 1.	Does the patent claim referenced in **4.2** claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement?	☒ Yes ☐ No
4.2a	If the answer to **4.2** is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	Use: *(Submit indication or method of use information as identified specifically in the approved labeling.)* MOVIPREP® is indicated for bowel cleansing prior to colonoscopy,	

5. No Relevant Patents

For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product.	☒ Yes	

6. Declaration Certification

6.1 ***The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment, or supplement pending under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.***

Warning: A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.

6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner *(Attorney, Agent, Representative or other Authorized Official) (Provide Information below)*	Date Signed
PETER STEIN, MANAGING DIRECTOR	JUNE 1, 2005

NOTE: Only an NDA applicant/holder may submit this declaration directly to the FDA. A patent owner who is not the NDA applicant/holder is authorized to sign the declaration but may not submit it directly to FDA. 21 CFR 314.53(c)(4) and (d)(4).

Check applicable box and provide information below.

☒ NDA Applicant/Holder	☐ NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official
☐ Patent Owner	☐ Patent Owner's Attorney, Agent (Representative) or Other Authorized Official

Name NORGINE BV	
Address Hogehilweg 7	City/State Amsterdam Zuid-Oost
ZIP Code 1101CA	Telephone Number +31 20 56 70 900
FAX Number *(if available)* +31 20 56 70 999	E-Mail Address *(if available)*

1.4.2 Patent Certification

In the opinion and to the best knowledge of Norgine B.V., there are no patents that claim the drug substances or product formulation referred to in this application.

EXCLUSIVITY SUMMARY FOR NDA # 21-881 SUPPL # N/A

Trade Name: Moviprep®
Generic Name: PEG 3350, sodium sulfate, sodium chloride, potassium chloride, sodium ascorbate and ascorbic acid

Applicant Name: Norgine, B.V. (Marilyn Carlson, US Agent) HFD # HFD-180

Approval Date If Known: August 2, 2006

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

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

a) Is it an original NDA?
YES / X / NO /___/

b) Is it an effectiveness supplement?

YES /___/ NO /X/

If yes, what type? (SE1, SE2, etc.) _____

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 /_X__/ 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:

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d) Did the applicant request exclusivity?

YES /___/ NO /X/

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

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

No

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule, previously been approved by FDA for the same use? (Rx to OTC switches should be answered NO-please indicate as such)

YES /___/ NO /_X__/

If yes, NDA #_____. Drug Name _____.

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

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

YES /___/ NO /X/

IF THE ANSWER TO QUESTION 3 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 /__X__/

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

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 / X/ NO /___/

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

The active moiety is PEG 3350.

- **NDA 19-011 (GoLytely)**
- **NDA 18-983 (Colyte)**
- **NDA 19-284 (OCL solution)**
- **NDA 19-797 (NuLytely)**
- **NDA 21-551 (HalfLytely Bisacodyl Kit)**

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. IF "YES" GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDA'S 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 / X / 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 / X / 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 /__X_/ 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 / X /

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 / X /

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:

1. **Study 011 2001 (German Study)**
2. **Study 021 2001 (French Study)**

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 / X/
Investigation #2	YES /___/	NO / X/

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 / X /
Investigation #2	YES /___/	NO /X /

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"):

1. **Study 011 2001 (German Study)**
2. **Study 021 2001 (French Study)**

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?

IND 63,268

YES /X / NO /___/ Explain: _____
German Study

YES /X / NO /___/ Explain: _____
French Study

(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? **N/A**

YES /___/ Explain _____ NO /___/ Explain _____

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 /X /

If yes, explain: _____

{See appended electronic signature page}

Tanya Clayton
Regulatory Health Project Manager

Brian E. Harvey, M.D., Ph.D.
Division Director
Division of Gastroenterology Products
Office of New Drug Evaluation III
Center for Drug Evaluation and Research

cc: Original NDA-DFS
HFD-93 Mary Ann Holovac

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

/s/

Tanya Clayton
8/30/2006 03:18:45 PM

Brian Harvey
8/30/2006 03:51:56 PM

1.4.9 Statement of Claimed Exclusivity and Certifications

Norgine B.V. is claiming a three-year exclusivity under the provisions of Sec. 314.108(b)(4). NDA 21-881 contains new clinical investigations that are essential to approval of the application or supplement and were conducted or sponsored by the applicant.

Norigine B.V. certifies that to the best of its knowledge each of the clinical investigations included in the application meets the definition of ``new clinical investigation'' set forth in Sec. 314.108(a)

A list of all published studies or publicly available reports of clinical investigations known to Norgine B.V. through a literature search that are relevant to the conditions for which Norgine is seeking approval of NDA 21-881 is included on the following pages.

PubMed (bibliographic information that includes MEDLINE and OLDMEDLINE) was searched using the following search string: (PEG OR polyethylene) AND (vitamin c OR ascorbic) AND (bowel OR gastrointestinal OR GI). Three citations were returned: none were clinical trials.

Norigine B.V. certifies that it has thoroughly searched the scientific literature and, to the best of its knowledge, the list is complete and accurate. In the opinion of Norgine B.V. this published information does not provide sufficient basis for approval of the conditions described in NDA 21-881 without reference to the new clinical investigation(s) in the application.

Norgine B.V. certifies that the clinical trials were conducted or sponsored by Norgine B.V. under European Clinical Trail Applications of which the applicant (or its subsidiary Norgine International Limited) was the sponsor.

1: Courtois F, Seidman EG, Delvin E, Asselin C, Bernotti S, Ledoux M, Levy E. Related Articles, Links

Membrane peroxidation by lipopolysaccharide and iron-ascorbate adversely affects Caco-2 cell function: beneficial role of butyric acid.
Am J Clin Nutr. 2003 Mar;77(3):744-50.
PMID: 12600871 [PubMed - indexed for MEDLINE]

2: Itoh K, Matsui S, Tozuka Y, Oguchi T, Yamamoto K. Related Articles, Links

Improvement of physicochemical properties of N-4472. Part II: characterization of N-4472 microemulsion and the enhanced oral absorption.
Int J Pharm. 2002 Oct 10;246(1-2):75-83.
PMID: 12270610 [PubMed - indexed for MEDLINE]

3: Maragos CM, Hotchkiss JH, Fubini SL. Related Articles, Links

Quantitative estimates of N-nitrosotrimethylurea formation in the porcine stomach.
Carcinogenesis. 1990 Sep;11(9):1587-91.
PMID: 2401048 [PubMed - indexed for MEDLINE]

PubMed

National Library of Medicine

[Sign In] [R

All Databases PubMed Nucleotide Protein Genome Structure OMIM PMC Journals

Search PubMed for (PEG OR polyethylene) AND (vitamin c OR asc Preview Go

Limits **Preview/Index** History Clipboard Details

About Entrez

Text Version

Entrez PubMed
Overview
Help | FAQ
Tutorial
New/Noteworthy
E-Utilities

PubMed Services
Journals Database
MeSH Database
Single Citation Matcher
Batch Citation Matcher
Clinical Queries
Special Queries
LinkOut
My NCBI (Cubby)

Related Resources
Order Documents
NLM Catalog
NLM Gateway
TOXNET
Consumer Health
Clinical Alerts
ClinicalTrials.gov
PubMed Central

- Enter terms and click Preview to see only the number of search results.
- To combine searches use # before search number, e.g., (#2 OR #3) AND asthma.
- Click on query # to add to strategy

Search	Most Recent Queries	Time	Result
#1	Search **(PEG OR polyethylene) AND (vitamin c OR ascorbic) AND (bowel OR gastrointestinal OR GI)**	05:13:00	3

Add Term(s) to Query or View Index:

- Enter a term in the text box; use the pull-down menu to specify a search field.
- Click Preview to add terms to the query box and see the number of search results, or click Index to view terms within a field.

All Fields Preview Index

Click AND OR NOT to add a term to the query box.

Query Translation:

```
(PEG[All Fields] OR (polyethylene[Text Word] OR polyethene
[Text Word] OR ("polyethylenes"[TIAB] NOT Medline[SB])
OR "polyethylenes"[MeSH Terms] OR "polyethylene"[MeSH
Terms])) AND ((("ascorbic acid"[TIAB] NOT Medline[SB])
OR "ascorbic acid"[MeSH Terms] OR vitamin c[Text Word]) OR
ascorbic[All Fields]) AND ((("intestines"[TIAB] NOT Medline
[SB]) OR "intestines"[MeSH Terms] OR bowel[Text Word]) OR
gastrointestinal[All Fields] OR GI[All Fields])
```

Search URL

Result:

3

Translations:

polyethylene	polyethylene[Text Word] OR polyethene[Text Word] OR ("polyethylenes"[TIAB] NOT Medline[SB]) OR "polyethylenes"[MeSH Terms] OR "polyethylene"[MeSH Terms]
vitamin c	("ascorbic acid"[TIAB] NOT Medline[SB]) OR "ascorbic acid"[MeSH Terms] OR vitamin c[Text Word]
bowel	("intestines"[TIAB] NOT Medline[SB]) OR "intestines"[MeSH Terms] OR bowel[Text Word]

Database:

PubMed

User query:

(PEG OR polyethylene) AND (vitamin c OR ascorbic) AND (bowel OR gastrointestinal OR GI)

PEDIATRIC PAGE

(Complete for all APPROVED original applications and efficacy supplements)

NDA # : 21-881 **Supplement Type (e.g. SE5):** N/A **Supplement Number:** N/A

Stamp Date: June 2, 2006 **Action Date:** August 2, 2006

Trade and generic names/dosage form: Moviprep® (PEG 3350, sodium sulfate, sodium chloride, potassium chloride, ascorbic acid, sodium ascorbate)

Applicant: Norgine B.V. (Marilyn Carlson, US Agent) **Therapeutic Class:** 3S

Indication(s) previously approved: N/A

Each approved indication must have pediatric studies: Completed, Deferred, and/or Waived.

Number of indications for this application(s): 1

Indication #1: for cleansing of the colon as preparation for colonoscopy in adults 18 years of age or older.

Is there a full waiver for this indication (check one)?

☒ **Yes: Please proceed to Section A. Yes, there is a full waiver for this indication.**
No: Please check all that apply: ____Partial Waiver ____Deferred ____Completed
NOTE: More than one may apply
Please proceed to Section B, Section C, and/or Section D and complete as necessary.

ection A: Fully Waived Studies

Reason(s) for full waiver:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population Yes**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☒ **Other:** The drug product does not represent a meaningful therapeutic benefit over existing treatments for pediatric patients and is not likely to be used in a substantial number of pediatric patients.

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived:

Min____	**kg**____	**mo.**____	**yr.**____	**Tanner Stage**____
Max____	**kg**____	**mo.**____	**yr.**____	**Tanner Stage**____

Reason(s) for partial waiver:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Adult studies ready for approval**

- ☐ **Formulation needed**
- ☐ **Other:**_____

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred:

Min _____ **kg**_____ **mo.**_____ **yr.**_____ **Tanner Stage**_____
Max_____ **kg**_____ **mo.**_____ **yr.**_____ **Tanner Stage**_____

Reason(s) for deferral:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**

Adult studies ready for approval

- ☐ **Formulation needed**

Other:_____

Date studies are due (mm/dd/yy): __

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies:

Min _____ **kg**_____ **mo.**_____ **yr.**_____ **Tanner Stage**_____
Max_____ **kg**_____ **mo.**_____ **yr.**_____ **Tanner Stage**_____

Comments:

If there are additional indications, please proceed to Attachment A Otherwise, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

{See appended electronic signature page}

_____
Regulatory Project Manager

cc: NDA
HFD-950/Grace Carmouze
(revised 9-24-02) FOR QUESTIONS ON COMPLETING THIS FORM CONTACT, PEDIATRIC TEAM, HFD-950
301-796-7654

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/s/

Tanya Clayton
8/29/2006 05:56:13 PM

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1.4.3 Debarment Certification

Norgine B.V. hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research

DATE: April 10, 2006

FROM: Brian E. Harvey, M.D., Ph.D.
Division Director, DGP/ODE III/OND

SUBJECT: Division Director Concurrence Memo
NDA 21-881

APPLICANT: Norgine B.V.

DRUG: MOVIPREP® (PEG 3350, sodium sulfate, sodium chloride, potassium chloride, sodium ascorbate, and ascorbic acid) for oral solution

DATE SUBMITTED: June 10, 2005

DIVISION RECOMMENDATION:

Both the primary Medical Officer and Medical Team Leader have recommended that NDA 21-881, MOVIPREP® (PEG 3350, sodium sulfate, sodium chloride, potassium chloride, sodium ascorbate, and ascorbic acid) oral solution, be approved for cleansing of the large bowel as a preparation for colonoscopy in the adult population.

In addition, the primary Medical Officer and Medical Team have recommended that the indications of [redacted] be denied, since the sponsor did not evaluate MOVIPREP in these indications.

In discussions with the primary Medical Officer and Medical Team, it appears that the proposed DSI inspection was not for cause and therefore is not required for this action.

Finally, the Medical Team has recommended a full waiver of pediatric studies be granted, because this drug product does not represent a meaningful therapeutic benefit over the

currently available liquid purgative products and is not likely to be used in a substantial number of pediatric patients.

However, based upon the work of the Chemistry and Inspection Teams, the following recommendation was provided: "From a Chemistry, Manufacturing, and Controls perspective, this NDA application is approvable pending satisfactory CGMP inspections on the manufacturing facilities". Therefore, I support an approvable action for this NDA at this time. I concur with the Medical Team to waive the DSI inspection of the investigational sites. Since there are no unresolved clinical issues, the ultimate approval of this product will be based upon the sponsor's correction of the CGMP inspection deficiencies and agreement on a finalized product label in the next cycle.

RECOMMENDATIONS FOR REGULATORY ACTIONS

I concur with the recommendations of the review team as outlined in the Approvable action letter dated April 10, 2006:

"We completed our review of this application, as amended, and it is approvable. Before the application may be approved, however, it will be necessary for you to address the following deficiency:

> During a recent inspections of the manufacturing facilities for this application, our field investigator conveyed deficiencies to the facilities' representatives. Satisfactory resolution to these deficiencies is required before this application may be approved.

When you respond to the above deficiency, include a safety update as described at 21 CFR 314.50(d)(5)(vi)(b). The safety update should include data from all non-clinical and clinical studies of the drug under consideration regardless of indication, dosage form, or dose level.

1. Describe in detail any significant changes or findings in the safety profile.

2. When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:

   - Present new safety data from the studies for the proposed indication using the same format as the original NDA submission.
   - Present tabulations of the new safety data combined with the original NDA data.
   - Include tables that compare frequencies of adverse events in the original NDA with the retabulated frequencies described in the bullet above.
   - For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.

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/s/

Brian Harvey
4/10/2006 01:02:09 PM
MEDICAL OFFICER

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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

FILING COMMUNICATION

NDA 21-881

Norgine International Limited
Attention: Marilyn R. Carlson, D.M.D., M.D., RAC
US Agent
1229 Caminito Graciela
Encinitas, California 92024

Dear Dr. Carlson:

Please refer to your June 7, 2005 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Moviprep® (PEG 3350, sodium sulfate, sodium chloride, potassium chloride, sodium ascorbate and ascorbic acid) for oral solution.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, this application has been filed under section 505(b) of the Act on August 9, 2005 in accordance with 21 CFR 314.101(a).

At this time, we have not identified any potential filing 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.

If you have any questions, call Tanya Clayton, B.S., Regulatory Health Project Manager, at (301) 827-4005.

Sincerely,

{See appended electronic signature page}

Brian Strongin, R.Ph., M.B.A.
Chief, Project Management Staff
Division of Gastrointestinal and Coagulation
Drug Products, HFD-180
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

Julieann DuBeau
8/22/2005 02:59:44 PM
Signing for Brian Strongin.

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NDA SUPPLEMENT ACTION PACKAGE CHECKLIST SIGN-OFF SHEET

Application Information			
NDA 21-881	Efficacy Supplement Type SE- N/A	Supplement Number N/A	
Drug: Moviprep, (PEG 3350, sodium sulfate, sodium chloride, potassium chloride, ascorbic acid, sodium ascorbate)		Applicant: Norgine B.V. (Marilyn Carlson, US Agent)	
RPM: Tanya Clayton		HFD-180	Phone # 796-0871
Application Type: (X) 505(b)(1) ( ) 505(b)(2)		Reference Listed Drug (NDA #, Drug name):	
❖ Application Classifications:			
• Review priority		(X) Standard ( ) Priority	
• Chem class (NDAs only)		3	
• Other (e.g., orphan, OTC)			
❖ User Fee Goal Dates		**August 2, 2006**	

Reviewers Sign Off List

Moo Jhong Rhee, Ph.D., Chemistry ~~Team Leader~~ Branch Chief 8/1/06

Ruyi He, M.D., Medical Team Leader 8/1/06

Brian Strongin, R.Ph., M.B.A, Chief, Project Management Staff 8-1-06

Brian E. Harvey, M.D., Ph.D., Division Director 8/1/06

NDA SUPPLEMENT ACTION PACKAGE CHECKLIST SIGN-OFF SHEET

Application Information		
NDA 21-881	Efficacy Supplement Type SE- N/A	Supplement Number N/A
Drug: Moviprep, (PEG 3350, sodium sulfate, sodium chloride, potassium chloride, ascorbic acid, sodium ascorbate	Applicant: Norgine B.V. (Marilyn Carlson, US Agent)	
RPM: Tanya Clayton	HFD-180	Phone # 796-0871
Application Type: (X) 505(b)(1) ( ) 505(b)(2)	Reference Listed Drug (NDA #, Drug name):	
❖ Application Classifications:		
• Review priority	(X) Standard ( ) Priority	
• Chem class (NDAs only)	3	
• Other (e.g., orphan, OTC)		
❖ User Fee Goal Dates	**April 10, 2006**	

Reviewers Sign Off List

Stella Grosser PhD Statistics T.L. 4/6/06

Moo Jhong Rhee, Ph.D., Chemistry Team Leader 4/7/06

Ruyi He, M.D., Medical Team Leader Ruyi He M.D 4/6/06

Dennis Bashaw, ~~Ph.D.~~ Pharm D., Biopharmaceutics Team Leader

Jasti Choudary, B.V.Sc., Ph.D., Supervisory Pharmacologist 4/10/06

Brian Strongin, R.Ph., M.B.A, Chief, Project Management Staff 4-4-06

Brian E. Harvey, M.D., Ph.D., Division Director 4/10/06

NDA ACTION PACKAGE CHECKLIST

Application Information

NDA 21-881		
Drug: **Moviprep®** (PEG 3350, sodium sulfate, sodium chloride, potassium chloride, ascorbic acid, sodium ascorbate)	Applicant: Norgine, B.V. (Marilyn Carlson, US Agent)	
RPM: Tanya Clayton	HFD-180	Phone 301-796-0871
Application Type: (X) 505(b)(1) () 505(b)(2)	Reference Listed Drug (NDA #, Drug name):	

❖ Application Classifications:	
• Review priority	(X) Standard ( ) Priority
• Chem class (NDAs only)	3
• Other (e.g., orphan, OTC)	N/A
❖ User Fee Goal Date	August 2, 2006
❖ Special programs (indicate all that apply)	(X) None Subpart H ( ) 21 CFR 314.510 (accelerated approval) ( ) 21 CFR 314.520 (restricted distribution) ( ) Fast Track ( ) Rolling Review
❖ User Fee Information	
• User Fee	(X) Paid -
• User Fee waiver	() Small business ( ) Public health ( ) Barrier-to-Innovation ( ) Other
• User Fee exception	( ) Orphan designation ( ) No-fee 505(b)(2) ( ) Other
❖ Application Integrity Policy (AIP)	
• Applicant is on the AIP	( ) Yes (X) No
• This application is on the AIP	( ) Yes (X) No
• Exception for review (Center Director's memo)	N/A
• OC clearance for approval	N/A
❖ Debarment certification: verified that qualifying language (e.g., willingly, knowingly) was not used in certification and certifications from foreign applicants are co-signed by U.S. agent.	(X) Verified
❖ Patent	
• Information: Verify that patent information was submitted	(X) Verified
• Patent certification [505(b)(2) applications]: Verify type of certifications submitted	21 CFR 314.50(i)(1)(*i*)(A) () I ( ) II ( ) III ( ) IV 21 CFR 314.50(i)(1) () (ii) ( ) (iii)
• For paragraph IV certification, verify that the applicant notified the patent holder(s) of their certification that the patent(s) is invalid, unenforceable, or will not be infringed (certification of notification and documentation of receipt of notice).	( ) Verified

❖ Exclusivity (approvals only)	
• Exclusivity summary	Pending-will be completed post approval
• Is there an existing orphan drug exclusivity protection for the active moiety for the proposed indication(s)? *Refer to 21 CFR 316.3(b)(13) for the definition of sameness for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification!*	( ) Yes, Application #_____ **(X)** No
❖ Administrative Reviews (Project Manager, September 28, 2005)	X
General Information	
❖ Actions	
• Proposed action	**(X** AP ( ) TA ( ) AE ( ) NA
• Previous actions (specify type and date for each action taken)	N/A
• Status of advertising (approvals only)	**(X)** Materials requested in AP letter ( ) Reviewed for Subpart H
❖ Public communications	
• Press Office notified of action (approval only)	**(X**)Yes ( ) No ( ) Not applicable
• Indicate what types (if any) of information dissemination are anticipated	**(X)** None ( ) Press Release ( ) Talk Paper ( ) Dear Health Care Professional Letter
❖ Labeling (package insert, patient package insert (if applicable), MedGuide (if applicable)	
• Division's proposed labeling (only if generated after latest applicant submission of labeling)	X
• Most recent applicant-proposed labeling (1st and 2nd cycles)	X
• Original applicant-proposed labeling	X
• Labeling reviews (Office of Drug Safety trade name review) • *ODS DMETS*- February 16, 2006 (1st cycle) and July 14, 2006 (2nd cycle) • *ODS DDMAC* – February 9, 2006 (1st cycle) and July 26, 2006 (2nd cycle)	X
• Other relevant labeling (e.g., most recent 3 in class)	N/A
❖ Labels (immediate container & carton labels)	
• Division proposed (only if generated after latest applicant submission)	X
• Applicant proposed	X
• Reviews DMETS); DDMAC	X
❖ Post-marketing commitments	
• Agency request for post-marketing commitments	N/A
• Documentation of discussions and/or agreements relating to post-marketing commitments	N/A
❖ Outgoing correspondence (i.e., letters, E-mails, faxes)	X
❖ Memoranda and Telecons	X
❖ Minutes of Meetings	
• Pre-NDA meeting (August 25, 2004) •	X
• Filing meeting (August 1, 2005)	X
• Post Action Industry Meeting (June 29, 2006)	X

• Pre-Approval Safety Conference	N/A
❖ Advisory Committee Meeting	N/A
• Date of Meeting	N/A
• 48-hour alert	N/A
❖ Federal Register Notices, DESI documents, NAS, NRC (if any are applicable)-Tentative Final Monograph	N/A
Summary Application Review	
Summary Review (e.g., Office Director, Division Director, Medical Team Leader) ❖ 2006/July 28, 2006 (2nd cycle)	Division Director- April 10, 2006 Medical Team Leader- April 3,
Clinical Information	
❖ Clinical review March 31, 2006 (1st cycle and July 28, 2006)	X
❖ Microbiology (efficacy) review	N/A
❖ Safety Update review	X (MO's review)
❖ Pediatric Page (separate page for each indication addressing status of all age groups)	X -Draft
❖ Demographic Worksheet *(NME approvals only)*	N/A
❖ Statistical review	X-March 29, 2006
❖ Biopharmaceutical	X-November 21, 2005, April 3, 2006
❖ Controlled Substance Staff review and recommendation for scheduling	N/A
❖ Clinical Inspection Review Summary (DSI)	X-April 3, 2006-email
• Clinical studies	X
• Bioequivalence studies	N/A
CMC Information	
❖ CMC review	X-April 6, 2006 ;July 25, 2006
❖ Environmental Assessment	
• Categorical Exclusion	X-refer to CMC Review
• Review & FONSI	N/A
• Review & Environmental Impact Statement	N/A
❖ Micro (validation of sterilization & product sterility	N/A
❖ Facilities inspection (provide EER report)	X
❖ Methods validation	X
Nonclinical Pharm/Tox Information	
❖ Pharm/tox review, including referenced IND reviews (February 24, 2006)	X-February 24, 2006
❖ Nonclinical inspection review summary	N/A
❖ Statistical review of carcinogenicity studies	N/A
❖ CAC/ECAC report	N/A

Salix Pharmaceuticals, Inc.
1700 Perimeter Park Drive, Morrisville, North Carolina 27560 • USA
Phone (919) 862-1000 • Fax (919) 862-1095 (Main)
Fax (919) 862-1087 (R&D)

TELECOPY

PLEASE DELIVER IMMEDIATELY!

TO	Tanya Clayton	**FAX#**	301-796-9894
FROM	Ramona Krailler	**DATE**	August 2, 2006
# OF PAGES	3, including cover page	**RE**	Formal Submission of Labeling Responsive to August 1, 2006 Comments from DMETS.

Message:

As requested, fax copy of the cover letter for the submission.

Ramona Krailler

Please call 919-862-1057 if you have any problems receiving this telecopy. Thank you.

NDA 21-881

August 2, 2006

Brian E. Harvey, M.D., Ph.D.,
Director, Division of Gastroenterology Products
Office of New Drugs, Office of Drug Evaluation III
Center for Drug Evaluation and Research
Food and Drug Administration
5901-B Ammendale Road
Beltsville, MD 20705-1266

Attention: Tanya Clayton

RE: **NDA 21-881 for MoviPrep® (PEG 3350, sodium sulfate, sodium chloride, potassium chloride, sodium ascorbate and ascorbic acid for oral solution) Amended Labeling**

Dear Dr. Harvey,

Enclosed please find revised component artwork (outer carton and container label) responsive to commentary from DMETS as communicated via e-mail on August 1, 2006.

In addition, please find responses to each of the comments from DMETS. The DMETS commentary is provided in bold type followed by Norgine's response.

We reviewed your proposal to delete the container label on the disposable container for reconstitution. We also note that you indicate that the provision of an unlabeled container is consistent with other associated components used to measure and administer drug products (e.g., measuring cups in cold/cough drug products, dosing cups, syringes, etc.) DMETS disagrees with this proposal and your analogy because Moviprep will be reconstituted and stored in the disposable container, thus the product will need to be identified. Your analogy is more related to the 8 ounce glass that will be used to administer Moviprep.

Additionally, DMETS believes that the outer carton could be disposed of leaving an unlabeled disposable container. Without the appropriate labeling on this container it may become lost leading to an inability to reconstitute Moviprep accurately. As noted above, this is even more concerning in an inpatient setting since after reconstitution the container will contain 1 liter of unidentifiable solution.

Norgine acknowledge that measuring cups, dosing cups and syringes are more likely to be quickly emptied of their contents whilst the MOVIPREP disposable container will be used for reconstitution and storage. However, we believe the risk of losing the instructions for reconstitution is largely, if not completely, eliminated by the presence of the instructions on the individual MOVIPREP pouches. Nevertheless, the container label does now contain a

NDA 21-881

"Directions for use" statement. In addition, we provide the reconstituted solution composition information, storage conditions consistent with the package insert and the customary advisory statements. This proposed container label addresses the specific DMETS concerns related to product identity and appropriate reconstitution.

Increase the size of the established name so that is at least ½ the size of the proprietary name. Additionally, where the established name is presented in white font on a blue background; the contrast is difficult to read. Increase the readability of the established name.

The size of the established name is increased so that it is at least ½ the size of the proprietary name. This is done for three uses on the outer carton, including the panel where the established name is presented in white font on a blue background, thereby increasing readability.

It appears the dark blue rectangle in the center of the carton is for a pharmacy label. Please place a clarification statement in the middle of the rectangle that states "Place Pharmacy Label Here." If this is not for the pharmacy label please provide an explanation as to the purpose of this dark blue rectangle.

The dark blue rectangle in the center of the carton (outer carton) is not for the pharmacy label. It is an area on a side corner of the outer carton which is cut at the top and bottom edges (solid line), folded on the sides and (twice) in the center (dashed lines) and pushed towards the interior of the outer carton in order to create a pocket in which the container is placed. (We have provided photographs of a prototype to illustrate and clarify.)

We trust you will find these responses satisfactory

For all communications related to this application, please contact Ramona Krailler, Ph.D., Head, US Regulatory Affairs, Norgine Limited, at +44 7795 005 484.

Sincerely,

Ramona E Krailler

Ramona E Krailler, Ph.D.
Head, US Regulatory Affairs
Norgine Limited
Chaplin House
Widewater Place, Moorhall Road
Harefield, Uxbridge, Middlesex
UB9 6NS
United Kingdom
011 44 7795 005 484 (phone)
011 44 1895 453 729 (fax)

Marilyn R. Carlson, D.M.D., M.D., RAC
US Agent
Norgine Limited
entreMeDica, Inc.
1229 Caminito Graciela
Encinitas, California 92024
USA
(858) 759-8265 (land line phone)
(858) 759-8384 (fax)

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research

DATE: 7/28/2006

FROM: Ruyi He, MD
Medical Team Leader
Division of Gastroenterology Products/ODE III

SUBJECT: GI Team Leader AP Comments
NDA 21-881/BZ

APPLICANT: Norgine B.V.

DRUG: MOVIPREP® (PEG 3350, sodium sulfate, sodium chloride, potassium chloride, sodium ascorbate, and ascorbic acid) for oral solution

I. RECOMMENDATION

I concur with Dr. Eric Brodsky's recommendations that NDA 21-881/BZ, MOVIPREP® (PEG 3350, sodium sulfate, sodium chloride, potassium chloride, sodium ascorbate, and ascorbic acid) oral solution, be approved for cleansing of the large bowel as a preparation for colonoscopy in the adult population. For approval of this application, the sponsor needs to incorporate the Division's recommendations into the MOVIPREP labeling.

The sponsor requested a deferral for pediatric studies until after adequate post-marketing experience in adults. I recommend that the full waiver of pediatric studies be granted, because this drug product does not represent a meaningful therapeutic benefit over the currently available liquid purgative products and is not likely to be used in a substantial number of pediatric patients.

Risk management activities and phase 4 commitments/requests are not recommended.

II. BACKGROUND

Norgine originally submitted the MoviPrep® (PEG 3350, sodium sulfate, sodium chloride, potassium chloride, sodium ascorbate, and ascorbic acid for oral solution)

application (NDA 21-881) on June 10, 2005 for bowel cleansing prior to colonoscopy, [redacted]. On April 10, 2006, the Division of Gastroenterology Products (DGP) took an approvable action on this NDA because:

"During recent inspections of the manufacturing facilities for this application, our filed investigator conveyed deficiencies to the facilities' representatives. Satisfactory resolution to these deficiencies is required before this application may be approved."

During the initial MoviPrep NDA review, the primary medical reviewer (Dr. Eric Brodsky) and myself, from a clinical perspective, recommended approval of the original application for cleansing of the colon as a preparation for colonoscopy in adults if the sponsor agreed to important labeling changes (please see Dr. Brodsky's April 2006 MoviPrep NDA review and my Medical Team Leader's Memo for this original submission).

On June 2, 2006 the sponsor provided a complete response to April 10, 2006 Approvable Letter. The sponsor amended NDA 21-881 to add a new supplier of Sodium Chloride, USP [redacted] and to formally withdraw [redacted] as a supplier of Sodium Chloride, USP which was identified with deficiencies for the manufacturing facilities.

Dr. Sharon Kelly from Division of Post-Marketing Assessment in her review for this 2nd cycle resubmission concluded that "From a Chemistry, Manufacturing, and Controls perspective, this NDA application can be approved. Satisfactory CGMP inspections have been completed for all the manufacturing facilities." Please see her review dated on July 20, 2006 for details. Based on her review, I concluded that the sponsor has provided satisfactory resolution to these deficiencies identified in April 10, 2006 Approvable Letter. Therefore, I concur with Dr. Eric Brodsky's recommendations that NDA 21-881/BZ, MOVIPREP® (PEG 3350, sodium sulfate, sodium chloride, potassium chloride, sodium ascorbate, and ascorbic acid) oral solution, be approved for cleansing of the large bowel as a preparation for colonoscopy in the adult population.

In addition, the sponsor indicated that since the last Safety Update there have not been any new safety findings that may reasonably affect the statement of contraindications, warnings, precautions, and adverse reactions.

III. Labeling Recommendations:

I concur with Dr. Eric Brodsky's labeling recommendations listed in his review. The labeling recommendations are summarized as following:

- Move the sentence regarding glucose-6-phosphodehydrogenase (G-6-PD) deficiency from the CONTRAINDICATIONS section to the General subsection of the PRECAUTIONS section.
- WARNINGS to the MOVIPREP label about the risk of generalized tonic-clonic seizures and electrolyte changes associated with use of polyethylene glycol (PEG) colon preparation products in patients with no prior history of seizures.

- Adding a table in the ADVERSE REACTIONS section of the label detailing the most common drug-related adverse events.

For detailed labeling recommendations, please see Dr. Eric Brodsky's review.

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/s/

Ruyi He
7/28/2006 11:55:23 AM
MEDICAL OFFICER

Brian Harvey
7/28/2006 01:09:25 PM
MEDICAL OFFICER
I concur with the approval of the NDA as outlined in this Medical Team Leader memo.

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications

Predecisional Agency Information

Date: July 26, 2006
From: Michael Brony, DDMAC
To: Tanya Clayton, GI
Re: NDA 21-881 Moviprep (PEG 3350, sodium sulfate, sodium chloride, potassium chloride, sodium ascorbate and ascorbic acid) for oral solution draft labeling review

- In the ADVERSE REACTIONS section of the draft PI states:

[ ]

Because phrases such as, "less frequently" and "transient "isolated cases" minimize the risks associated with Moviprep use, DDMAC recommends that these phrases be deleted. In place of those phrases, DDMAC recommends displaying the incidence of the adverse reactions.

Additionally, lines 207-208 states:

"Published literature contains isolated reports of serious adverse events following the administration of PEG-based products in patients over 60 years of age"

Did the literature give incidences of these serious adverse events? If so, we recommend replacing the phrase, "isolated reports" with the actual incidence rates.

DDMAC has no comments at this time on any of the carton or package labels.

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/s/

Michael Brony
7/26/2006 09:43:22 AM
DDMAC REVIEWER

Appears This Way
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MEMORANDUM OF MEETING MINUTES

Meeting Date: June 2, 2006

Time: 11:00-12:00 p.m.

Location: White Oak, Conference Room 1421

Application: NDA 21-881

Type of Meeting: Type A

Meeting Chair: Ruyi He, M.D.

Meeting Recorder: Tanya Clayton, B.S.

FDA Attendees, Titles, and Office/Division:

Division of Gastroenterology Products	
Brian E. Harvey, M.D., Ph.D.	Division Director
Joyce Korvick, M.D., M.P.H.	Deputy Division Director
Ruyi He, M.D.	Medical Team Leader
Eric Brosky, M.D.	Medical Reviewer
Marie Kowblansky, Ph.D.	Chemistry Team Leader
Tanya Clayton, B.S.	Regulatory Health Project Manager
Office of Compliance	
John Dietrick	Team Leader

External Constituent Attendees and Titles:

Norgine International Limited	
Ramona Krailer, Ph.D.	U.S. Regulatory Affairs Manager
Ian Cox, MSc	Director, Product Development
Russell Thomson, Ph.D.	Site Head of Quality
Salix Pharmaceuticals	
Jill Kompa, M.S., RAC	Director, Regulatory Affairs
Teresa Roberts	Director, Quality
Bill Forbes, Pharm. D.	Vice President, Research and Development
Joy Lockhart	Executive Director, Manufacturing
Shanda Lottes	Interim Head Clinical, Research and Development

Background:

On April 18, 2006, the Sponsors requested a Type A meeting for the purpose of addressing the CMC deficiencies specified in the NDA approvable letter dated April 10, 2006.

An April 20, 2006 background package was submitted which contained 5 questions for discussion.

Following introductions, the Sponsor agreed to proceed directly to the questions for discussion.

List of Specific Questions, Grouped by Discipline

Office of Regulatory Affairs (ORA), Field Operations

1) We request ORA to provide an overview of the manufacturing compliance issues relevant to the MoviPrep NDA.

The April 10, 2006 Approvable letter for MoviPrep cited the need for satisfactory resolution to deficiencies identified by the field investigators during the inspection of the manufacturing facilities. Norgine wish to obtain clarification as to the nature and extent of these deficiencies. In order to facilitate this discussion, we would respectfully ask the ORA, Field Operations, to provide an overview of the issues including all sites specifically identified by FDA as having deficiencies and preventing the approval of MoviPrep.

Response

Compliance has finished the review of the inspection and it is classified as acceptable for the Norgine site.

However, the [redacted] is not acceptable at this time. We have notified this company of the deficiencies by letter on May 19, 2006.

Additional Discussion

We have confirmed that the performance qualification and cleaning validation data are not required for NDA approval. However, these will be completed prior to shipping of the drug product.

The [redacted] was the only supplier site that was deficient at the time of the action letter dated, April 10, 2006 and at the present time.

2) We request ORA to provide confirmation that the proposed replacement supplier of Sodium Chloride, USP, ———————, located in ———————————, has an acceptable cGMP status as an API manufacturing site and has no outstanding compliance issues.

Please see the response to #2 above. We wish to obtain confirmation from ORA, Field Operations, that ——— has an acceptable compliance status.

Response
The ——— facility is acceptable at this time.

3) Does Field Operations find the response to the Form FDA483 issued to Norgine, Hengoed (the drug product manufacturing facility) acceptable and the facility acceptable for the manufacture of MoviPrep®? How quickly can that assessment be formally communicated to the Division of Gastroenterology Drug Products?

Norgine's drug product manufacturing facility was inspected for a preapproval inspection during the dates of March 27-31, 2006. As a result of the inspection, a Form FDA483 was issued containing 6 observations. Norgine submitted a complete 483 response to Field Operations on April 7, 2006. Subsequent to the April 10, 2006 Approvable letter for MoviPrep, Norgine have become aware that the Field may require an Establishment Inspection Report (EIR) to be completed for the facility prior to recommendation of approval.

We request the Field Operations to confirm that the 483 response from Norgine has been found acceptable. In addition, we would ask the Field Operations to also provide a status of the EIR for the Hengoed site including estimated dates of completion in order to facilitate the MoviPrep NDA approval. Finally, we would ask Field Operations to also indicate how the assessments will be communicated to the Division of Gastroenterology Drug Products.

Response
The Norgine, U.K. facility is acceptable at this time.

Office of New Drug Chemistry

4) Does the Division Chemistry review team agree that the proposed information for an amendment to provide for a new, replacement, sodium chloride supplier is adequate?

Norgine have been advised that the currently proposed supplier in the NDA of Sodium Chloride, USP, ——— located at ———, has been issued an FDA Form 483 in response to a pre-approval inspection conducted in March 2006. (Note: Norgine wish to obtain concurrence from the Field Operations that this site indeed is one of the sites identified as having outstanding compliance issues for the MoviPrep NDA). If the ——— site is confirmed to have outstanding compliance issues, Norgine would propose to amend the NDA to replace the ——— site with another supplier that has a satisfactory FDA inspection history in order to resolve the issue. Norgine has identified the following potential new supplier of Sodium Chloride, USP:

[ ]

——— has indicated that they have an acceptable cGMP compliance status with FDA as an active pharmaceutical ingredient manufacturer based on a GMP inspection conducted on April 5-6, 2006 in which no Form FDA 483 was issued.

Norgine would propose to amend the NDA and submit the following information on the new supplier with the following information:

1. Manufacturing flow chart of the same level of detail as previously provided for the original supplier;

2. Confirmation that the material meets the requirements of the USP as demonstrated by supplier's Certificates of Analysis (COA);

3. Commit to validate the results of the supplier's COA from the first batch of material intended to be used for commercial production;

4. Commit to place the first three batches of MoviPrep manufactured using material from ——— on stability in accord with the postapproval stability protocol described in the NDA.

5. Provide the FDA inspection history for ——— regarding their cGMP status.

If the Division is in agreement with the proposed approach to amend the NDA, we would also concurrently withdraw ——— from the NDA.

We ask the Division to confirm that the proposed information is adequate and that the overall approach is acceptable in order to resolve the supplier issue of Sodium Chloride, USP and facilitate the approval of MoviPrep.

Response

We agree with the information you plan to submit for your proposed new supplier: manufacturing flow chart, confirmation that the material meets USP specifications, and a commitment to place the first three batches of MoviPrep manufactured using material from ——— on stability testing in accord with the post approval stability protocol described in the NDA.

Division of Gastroenterology Products

5) If a new sodium chloride, USP supplier is submitted to NDA 21-881 by June 1, 2006, will the Division of Gastroenterology Drug Products waive the request for a Safety Update as described in the April 10, 2006 approvable letter?

The April 10, 2006 Approvable letter has requested that when Norgine amend the NDA to indicate satisfactory resolution of the manufacturing issues, a safety update is also provided. Norgine intends to amend the NDA immediately after the requested Type A meeting once agreements are reached regarding resolution of the manufacturing issues. As we expect the meeting to be held in the near future and there are no ongoing studies regarding MoviPrep to warrant a safety update, we would request that the safety update be waived if the NDA amendment can occur on or before June 1, 2006.

Response

No, the Safety Update is required for your MoviPrep NDA resubmission. However, if there are no new safety findings, then the Safety Update requirement may be satisfied by stating that since the last Safety Update there have not been any new safety findings "that may reasonably affect the statement of contraindications, warnings, precautions, and adverse reactions in the ... labeling." For more information regarding the Safety Update requirement see 21 CFR 314.50(d)(vi)(b).

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/s/

Tanya Clayton
6/29/2006 03:01:33 PM

Eric Brodsky
6/29/2006 03:27:08 PM
I am signing as the acting medical team leader
for Dr. Ruyi He (the medical team leader)

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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-881

Norgine International Limited
Attention: Marilyn R. Carlson, D.M.D., M.D., RAC
US Agent
entreMeDica, Inc.
1229 Caminito Graciela
Encinitas, California 92024

Dear Dr. Carlson:

We acknowledge receipt on June 2, 2006 of your June 2, 2006 resubmission to your new drug application for Moviprep (PEG 3350, sodium sulfate, sodium chloride, potassium chloride, sodium ascorbate and ascorbic acid) for oral solution.

We consider this a complete, class 1 response to our April 10, 2006 action letter. Therefore, the user fee goal date is August 2, 2006.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We note that you have not fulfilled the requirement. We are waiving the requirement for pediatric studies for this application.

If you have any question, call me at (301) 796-0871.

Sincerely,

{See appended electronic signature page}

Tanya Clayton, B.S.
Regulatory Health Project Manager
Division of Gastroenterology Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

Tanya Clayton
6/15/2006 04:41:45 PM

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*** TX REPORT ***
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RECIPIENT ADDRESS	918587598384
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TIME USE	00'21
PAGES SENT	2
RESULT	OK

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation III

FACSIMILE TRANSMITTAL SHEET

DATE: May 22, 2006

To: Marilyn R. Carlson, D.M.D., M.D., RAC	**From:** Tanya D. Clayton, BS Regulatory Project Manager
Company: US Agent for Norgine International Limited	Division of Gastroenterology Products
Fax number: 858-759-8384	**Fax number:** 301-796-9905
Phone number: 858-759-8265	**Phone number:** 301-796-0871

Subject: IND 67,947 (Movicol) Information Request

Total no. of pages including cover: 2

Comments:
Please find attached an Information Request, per our medical reviewer.

Document to be mailed: YES √NO

Please respond to the following:

1) Provide the final safety report including the final autopsy report from case 206-0000515(0.0). We received the initial safety report on May 18, 2006 under IND 67,947/S-051.

2) Provide the final safety reports including the final autopsy reports for all Movicol-associated deaths.

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation III

FACSIMILE TRANSMITTAL SHEET

DATE: May 2, 2006

To: Marilyn Carlson, D.M.D., M.D., RAC	**From:** Tanya D. Clayton, BS Regulatory Project Manager
Company: US Agent for Norgine International Limited	Division of Gastroenterology Products
Fax number: 858-759-8384	**Fax number:** 301-796-9905
Phone number: 858-759-8265	**Phone number:** 301-796-0871

Subject: Meeting Granted for NDA 21-881

Total no. of pages including cover: 1

Comments:

This correspondence is to notify you that your April 18, 2006 Meeting request has been granted. The proposed meeting date is June 2, 2006, 11:00-12:00 pm.

Please let me know if this meeting date is acceptable.
Best regards.

Document to be mailed: YES √NO

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/s/

Tanya Clayton
5/2/2006 11:43:10 AM

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********** -COMM. JOURNAL- ********** DATE APR-10-2006 ***** TIME 14:16 *********

MODE = MEMORY TRANSMISSION START=APR-10 14:14 END=APR-10 14:16

FILE NO.=060

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-FDA/CDER/DDDDP/HFD540 -

********** -301 827 2075 - ***** - 301 827 2075- **********

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation III

FACSIMILE TRANSMITTAL SHEET

DATE: April 10, 2006

To: Ramona Krailler	**From:** Marlene Swider Regulatory Project Manager Division of Gastroenterology Products
Company: Norgine International, Limited	
Fax number: (919) ~~862-1087~~ 228-4247	**Fax number:** 301-796-9905
Phone number: 011 44 7795 005 484	**Phone number:** 301-796-2104

Subject: NDA 21-881 (Moviprep) Action Letter

Total no. of pages including cover: 4

Comments:
Please find attached the action letter for NDA 21-881

Document to be mailed: YES √NO

Swider, Marlene

From: Kompa, Jill [Jill.Kompa@Salix.com]
Sent: Friday, April 07, 2006 3:36 PM
To: Swider, Marlene
Cc: Krailler, Ramona
Subject: MoviPrep Artwork Revised
Attachments: MoviBox.pdf; MoviLabel.pdf; MoviSachetA.PDF; MoviSachetB.PDF

Hi Marlene,

On behalf of Ramona Krailler, please find the revised pdf files of the MoviPrep pouches (A&B), the container label, and the carton. In response to the telecom yesterday (April 6) and your email, we have incorporated all of the Agency's comments and believe these components to be final. These are also being submitted as hard copies via an NDA amendment today.

In addition, the overwrap packaging is child-resistant in accord with CPSC's regulations. Therefore, we have left out the statement regarding the packaging NOT be child resistant.

Please call us if you have any questions.

Kind regards,

Jill

Jill Kompa, M.S., RAC
ector, Regulatory
ix Pharmaceuticals
1700 Perimeter Park Drive
Morrisville, NC 27560
Phone: 919-862-1047
Cell: 919-360-3314
Fax: 919-862-1095
Email: jill.kompa@salix.com

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4 Page(s) Withheld

_____ § 552(b)(4) Trade Secret / Confidential

X § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation ODEIII

FACSIMILE TRANSMITTAL SHEET

DATE: April 4, 2006

To: Ramona Krailler	**From:** Tanya Clayton, B.S.
Company: Norgine International, Limited	Division of Gastroenterology Products
Fax number: (919) 862-1087	**Fax number: (301) 796-9894**
Phone number: 011 44 7795 005 484	**Phone number:** (301) 796-0871

Subject: Second Fax sent to Norgine B.V. with update changes to label and carton

Total no. of pages including cover: 4

Comments: As agreed yesterday, here is a second fax with updated changes to MoviPrep carton and package insert.

Document to be mailed: ☐ YES ☑ NO

General Comments:

1. The kit as a whole should be labeled with the proprietary name MoviPrep, as it is on the mixer label, rather than the individual components. Your proposal to label both mixer label, carton labeling, and pouch labels with the proprietary name MoviPrep, i.e. each separate component, is misleading, as it implies reconstitution is not necessary.

The following comments pertain to the Mixer Label:

2. The statement " [redacted] " is ambiguous and confusing and does not adequately identify the fact that the product is a powder which must be reconstituted prior to administration and should be deleted from the label.

3. We recommend revising the label to include the statement "[redacted] ."

4. The box on the front display panel of the mixer label currently includes the contents of each pouch A and pouch B. Because the pouches are provided separately and are not found directly inside the mixer container, the pouch contents should be relocated to the respective pouch label and removed from the mixer label. However, we recommend that the "On reconstitution in 1 liter..." block be kept on the label. Furthermore, we recommend revising the label to include the statement "Bottle for reconstitution of Moviprep."

5. We recommend revising the font and color, as the current font type and blue print color are difficult to read on the white background. In addition, the information seems crowded as there are no spaces between the numbered steps of the patient instructions.

6. The pouch contents are expressed using multiple terminal zeros following the decimal point. The use of terminal zeroes may result in error as decimals are often overlooked. As evidenced by our post-marketing surveillance, the use of terminal zeroes could potentially result in a ten-fold medication dose error. The use of terminal zeroes in the expression of strength or volume is not in accordance with the General Notices (page 10) of 2004 USP, which states, "...to help minimize the possibility of error in the dispensing and administration of the drugs....the quantity of active ingredient when expressed in whole numbers shall be shown without a decimal point that is followed by a terminal zero." In addition, the use of trailing zeroes is specifically listed as a dangerous abbreviation, acronym, or symbol in the 2006 National Patient Safety Goals of The Joint Commission for the Accreditation of Hospitals (JCAHO). Lastly, safety groups such as ISMP also list terminal zeroes on their dangerous abbreviations and dose designations list. Revise the labels and labeling so that strengths, etc. are expressed without the use of a terminal zero (e.g., 4.7 g rather than 4.700 g).

7. Add a statement "*Keep out of the reach of children.*"

8. We recommend removing the light blue lines located under the light blue font as they are distracting and make the instructions difficult to read.

The following comments pertain to the Pouch Label (A and B)

9. See Container Label Comments 5, 6, and 7.

10. The individual pouch components, PEG-3350, Sodium Sulfate, Sodium Chloride, Potassium Chloride, Sodium Ascorbate, and Ascorbic Acid for Oral Solution should not be referred to as MoviPrep solution. The

individual pouches should be revised to read "Pouch A contains... (name and amount of ingredients)... for reconstitution of MoviPrep". Furthermore, relocate the "Each Pouch A contains..." information box to the front display panel so the information is clear and easily located to someone reading the pouch for the first time. In addition, "Pouch A" should be relocated from the bottom left hand corner of the label to the center and made more prominent.

11. The **Directions for Use** section should be revised to include the number of pouches to be used when preparing the product. In addition, exact directions for how the patient is to drink the solution should also be included. For example, "Dissolve the contents of one Pouch A and one Pouch B in one liter of water and drink one 8 oz glass of the solution (approximately 240 mL) every 15 - 30 minutes until gone."

12. We recommend revising the pouch label to include a highlighted statement "This one Pouch A must be reconstituted with one Pouch B."

The following comments pertain to the Carton Labeling

13. See Comments 1

14. See Mixer Label Comments 2, 5, and 6.

15. We recommend revising the carton labeling to read "MoviPrep Kit" as MoviPrep is the final product once the powder has been reconstituted into an oral solution.

16. Similarly, the carton labeling should be revised to include a statement such as "This kit contains:
2 x Pouch A each containing 100 g PEG-3350,....
2 x Pouch B each containing..."

The kit contents should also include the mixer.

The following comments pertain to the **How Supplied** section

17. Please indicate the size of the mixer container, informing patients and practitioners as to the volume that the mixer container can be filled (i.e., 1 liter or 2 liters).

18. The term "Packet" does not adequately identify how the product is supplied. In order to be consistent throughout the labels and labeling, use the term pouch instead of packet and revise the **HOW SUPPLIED** section to read the "Moviprep Kit contains four pouches..."

19. In addition, we recommend revising the statement "When made up to 1 liter volume with water..." to read " Once reconstituted with one Pouch A, one Pouch B and one liter of water, the one liter solution will contain...".

The following comments pertain to the Package Insert

20. Please substitute the current paragraph in the ***Carcinogenesis, Mutagenesis, Impairment of Fertility*** (section) with the following: "Long-term studies in animals to evaluate carcinogenic potential have not been performed with MoviPrep. Studies to evaluate potential for impairment of fertility or mutagenic potential have not been performed with MoviPrep."

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/s/

Marlene Swider
4/4/2006 02:05:48 PM
CSO

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Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation ODEIII

FACSIMILE TRANSMITTAL SHEET

DATE: April 3, 2006

To: Ramona Krailler	**From:** Tanya Clayton, B.S.
Company: Norgine International, Limited	Division of Gastroenterology Products
Fax number: (919) 862-1087	**Fax number:** (301) 796-9950
Phone number: 011 44 7795 005 484	**Phone number:** (301) 796-0871

Subject: MoviPrep Label Changes by FDA

Total no. of pages including cover: 4

Comments: Per our earlier conversation, please find FDA recommendations for the carton and other labels.

Also, as requested, the names of the participants for today's labeling meeting are:
Brian Strongin, R. Ph., MBA, Chief Regulatory Project Manager Staff
Sharon Kelly, Ph.D., Chemist
Eric Brodsky, M.D., Clinical Reviewer
Wen-Jen Chen, Ph.D., Statistician
Tien-Mien Chen, Ph.D., Biopharmaceutic Staff
Alina Mahmud, R Ph, Team Leader DMETS
Joyce Korvick, M.D,, Deputy Director DGP
Stella Grosser, Ph.D., Team Leader Statistics
Ruyi He, M.D., Clinical Team Leader
Marlene Swider, MHSA, Regultory Project Manager

Document to be mailed: ☐ YES ☑ NO

General Comments:

1. The kit as a whole should be labeled with the proprietary name MoviPrep, as it is on the mixer label, rather than the individual components. Your proposal to label both mixer label, carton labeling, and pouch labels with the proprietary name MoviPrep, i.e. each separate component, is misleading, as it implies reconstitution is not necessary.

The following comments pertain to the Mixer Label:

2. The statement " [redacted] ;" is ambiguous and confusing and does not adequately identify the fact that the product is a powder which must be reconstituted prior to administration and should be deleted from the label.

3. We recommend revising the label to include the statement " [redacted] ;"

4. We recommend revising the font and color, as the current font type and blue print color are difficult to read on the white background. In addition, the information seems crowded as there are no spaces between the numbered steps of the patient instructions.

5. The pouch contents are expressed using multiple terminal zeros following the decimal point. The use of terminal zeroes may result in error as decimals are often overlooked. As evidenced by our post-marketing surveillance, the use of terminal zeroes could potentially result in a ten-fold medication dose error. The use of terminal zeroes in the expression of strength or volume is not in accordance with the General Notices (page 10) of 2004 USP, which states, "...to help minimize the possibility of error in the dispensing and administration of the drugs....the quantity of active ingredient when expressed in whole numbers shall be shown without a decimal point that is followed by a terminal zero." In addition, the use of trailing zeroes is specifically listed as a dangerous abbreviation, acronym, or symbol in the 2006 National Patient Safety Goals of The Joint Commission for the Accreditation of Hospitals (JCAHO). Lastly, safety groups such as ISMP also list terminal zeroes on their dangerous abbreviations and dose designations list. Revise the labels and labeling so that strengths, etc. are expressed without the use of a terminal zero (e.g., 4.7 g rather than 4.700 g).

6. Add a statement "*Keep out of the reach of children.*"

7. We recommend removing the light blue lines located under the light blue font as they are distracting and make the instructions difficult to read.

The following comments pertain to the Pouch Label (A and B)

8. See Container Label Comments 7, 14, and 15.

9. The individual pouch components, PEG-3350, Sodium Sulfate, Sodium Chloride, Potassium Chloride, Sodium Ascorbate, and Ascorbic Acid for Oral Solution should not be referred to as MoviPrep solution. The individual pouches should be revised to read "Pouch A contains... (name and amount of ingredients)... for reconstitution of MoviPrep". Furthermore, relocate the "Each Pouch A contains..." information box to the front display panel so the information is clear and easily located to someone reading the pouch for the first time. In addition, "Pouch A" should be relocated from the bottom left hand corner of the label to the center and made more prominent.

10. The **Directions for Use** section should be revised to include the number of pouches to be used when preparing the product. In addition, exact directions for how the patient is to drink the solution should also be

included. For example, "Dissolve the contents of one Pouch A and one Pouch B in one liter of water and drink one 8 oz. glass of the solution (approximately 240 mL) every 15 - 30 minutes until gone."

11. We recommend revising the pouch label to include a highlighted statement "This one Pouch A must be reconstituted with one Pouch B."

The following comments pertain to the Carton Labeling

12. See Comments 1

13. See Mixer Label Comments 2, 4, and 5.

14. We recommend revising the carton labeling to read "MoviPrep Kit" as MoviPrep is the final product once the powder has been reconstituted into an oral solution.

15. Similarly, the carton labeling should be revised to include a statement such as "This kit contains:
2 x Pouch A each containing 100 g PEG-3350, ...
2 x Pouch B each containing..."

The kit contents should also include the mixer.

The following comments pertain to the **How Supplied** section

16. Please indicate the size of the mixer container, informing patients and practitioners as to the volume that the mixer container can be filled (i.e., 1 liter or 2 liters).

17. The term "Packet" does not adequately identify how the product is supplied. In order to be consistent throughout the labels and labeling, use the term pouch instead of packet and revise the **HOW SUPPLIED** section to read the "MoviPrep Kit contains four pouches..."

18. In addition, we recommend revising the statement "When made up to 1 liter volume with water..." to read" Once reconstituted with one Pouch A, one Pouch B and one liter of water, the one liter solution will contain...."

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/s/

Marlene Swider
4/3/2006 03:05:37 PM
CSO

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MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research

DATE: 4/3/2006

FROM: Ruyi He, MD
Medical Team Leader
Division of Gastroenterology Products/ODE III

SUBJECT: GI Team Leader AP Comments
NDA 21-881

APPLICANT: Norgine B.V.

DRUG: MOVIPREP® (PEG 3350, sodium sulfate, sodium chloride, potassium chloride, sodium ascorbate, and ascorbic acid) for oral solution

I. RECOMMENDATION

I concur with Dr. Eric Brodsky's recommendations that NDA 21-881, MOVIPREP® (PEG 3350, sodium sulfate, sodium chloride, potassium chloride, sodium ascorbate, and ascorbic acid) oral solution, be approved for cleansing of the large bowel as a preparation for colonoscopy in the adult population. For approval of this application, the sponsor needs to incorporate the Division's recommendations into the MOVIPREP labeling.

I recommend that MOVIPREP® (PEG 3350, sodium sulfate, sodium chloride, potassium chloride, sodium ascorbate, and ascorbic acid) oral solution, be denied for the indications of [redacted]. The sponsor did not evaluate MOVIPREP for use in [redacted].

The sponsor requested a deferral for pediatric studies until after adequate post-marketing experience in adults. I recommend that the full waiver of pediatric studies be granted, because this drug product does not represent a meaningful therapeutic benefit over the currently available liquid purgative products and is not likely to be used in a substantial number of pediatric patients.

Risk management activities and phase 4 commitments/requests are not recommended.

II. BACKGROUND

There are two classes of colon preparation products approved in the United States: sodium phosphate-based products and polyethylene glycol (PEG)-based products.

Approved PEG-based products include GoLYTELY®, Colyte®, OCL Solution®, NuLYTELY®, and Tri Lyte™. HalfLytely® is a combination product containing two liters of a PEG-based oral solution and 20 mg of oral bisacodyl tablets (a stimulant laxative).

Norgine B.V. (Norgine) submitted this new drug application on June 10, 2005 to support the approval of MOVIPREP® (PEG 3350, sodium sulfate, sodium chloride, potassium chloride, sodium ascorbate, and ascorbic acid) oral solution, a purgative, "for bowel cleansing prior to colonoscopy [redacted]." The proposed MOVIPREP dosage regimen consists of two liters of MOVIPREP, containing 200 grams of polyethylene glycol (PEG) 3350 and Vitamin C (sodium ascorbate and ascorbic acid), with one additional liter of clear fluid. For comparison, the approved GoLYTELY® oral solution (NDA 19-011), a PEG-based colon preparation product, contains 236 grams of PEG 3350 in four liters of fluid and the approved NuLYTELY® oral solution (NDA 19-797), another PEG-based colon preparation product, contains 420 grams of PEG 3350 in four liters of fluid. All of the approved PEG-based colon preparations including GoLYTELY and NuLYTELY do not contain Vitamin C.

III. DISCIPLINE REVIEW SUMMARY AND COMMENTARY:

A. OPDRA/DDMAC/DMETS:

DMETS has no objections to the use of the proprietary name, MOVIPREP. DDMAC finds the proprietary name, MOVIPREP, acceptable from a promotional perspective.

One site in the [redacted] and one site in the [redacted] were selected for Division of Scientific Investigation (DSI) to conduct audits. Both centers were selected because they contained the [redacted] number of patients per site in the Study. [redacted] and [redacted] included [redacted] and [redacted] patients in the safety population, respectively.

Dr. Leslie Ball, Branch Chief in the Division of Scientific Investigations, informed the Division that somehow the DSI consult got cancelled mistakenly by one of their internal staff members in which she was never notified. In this way, according to Dr. Ball, the DSI inspection will not be complete prior to the action date of April 10, 2006. Because of robust efficacy results provided in this NDA, I believe that the outcome of clinical inspection will not affect the totality of efficacy for this NDA.

B. Chemistry and Manufacturing:

Dr. Sharon Kelly, the CMC reviewer, stated that the following chemistry issue remains: the MOVIPREP sponsor changed their manufacturing plant and the FDA is currently inspected their new manufacturing plant. Dr. Kelly believes if the inspection has no significant deficiencies then she will recommend approval of this application from a CMC standpoint. Dr. Kelly's review is pending at this time.

C. Pre-Clinical Pharmacology/Toxicology:

The Pharmacology Review Team concluded that the NDA may be approved pending labeling changes. Further nonclinical studies are not recommended.

The toxicity profiles of MOVIPREP were characterized in 2-week oral toxicity studies in rats and dogs. The results indicated that the kidney was the target organ of toxicity in rats based on the changes of the clinical chemistry and the kidney weight. In dogs, the major treatment related toxicity was decreased terminal body weight gain, emesis, diarrhea, and salvation. The results suggested that the gastrointestinal tract was the target organ of toxicity in dogs.

There are no nonclinical safety issues remaining at this time. For more information, please see Dr. Ke Zhang's review.

D. Biopharmaceutics:

No human PK data were provided in this NDA. It was concluded within Office of Clinical Pharmacology and Biopharmaceutics that the NDA is acceptable. Further, no additional PK studies were needed to address the combination drug issues since PEG 3350 is known to act locally within the GI lumen and is minimally absorbed into systemic circulation and Vitamin C is not considered as a drug. Please see Dr. Tien-Mien Chen's memo for details.

E. Clinical/Statistical:

Efficacy:

The two efficacy trials (the German and French studies) were randomized, investigator-blinded, active-controlled, parallel-group, multi-center (12 and 17 sites in the German and French studies, respectively), colon preparation trials of MOVIPREP in patients scheduled to have an elective colonoscopy.

In the German study, patients were randomized 1:1 to MOVIPREP solution or GoLYTELY solution. In the French study, patients were randomized 1:1 to MOVIPREP solution or OSPS containing about 60 grams of sodium phosphate. In the German study,

the study treatments were split between the evening prior to the colonoscopy and the morning of the colonoscopy (split-dosing). In contrast, in the French study, the study treatments were given entirely on the day prior to the colonoscopy.

In the German and French studies, the pre-specified primary efficacy endpoint was a responder analysis. Responders were defined as patients who had an overall effective colon preparation, allowing adequate visualization of the entire colonic mucosa — achievement of a grade A or B on a 4-level Overall Colon Cleansing Scale. Non-responders were defined as patients who achieved a grade of C or D on this 4-level scale. The pre-specified statistical analysis in the German and French studies was a non-inferiority analysis with a pre-specified 15% margin between MOVIPREP and the active comparator (GoLYTELY in the German study and Oral Sodium Phosphate Solution (OSPS) in the French study).

Table 1 displays the results of the primary efficacy endpoint — the percentage of patients who had an overall effective colon preparation allowing adequate visualization of the entire colonic mucosa in both studies.

Table 1: The summary of efficacy results in the German and French studies- per protocol population

	Treatment Group	Responder (A or B) n (%= n/N)	Non-Responder (C or D) n (%=n/N)
The German Study	MOVIPREP (split doses) N=153	136 (88.9)	17 (11.1)
	GoLYTELY (split doses) N=155	147 (94.8)	8 (5.1)
	Rate difference, (%)	(-5.9)*	
The French Study	MOVIPREP (evening only) N=137	100 (73.0)	37 (27.0)
	OSPS (day before the colonoscopy) N=143	92 (64.3)	51 (35.7)
	Rate difference, (%)	(8.7)**	

* The lower bound of the 97.5% confidence interval was -12.0%
**The lower bound of the one-sided 97.5% confidence interval was -2.2%

In the German Study, the percentage of patients in the MOVIPREP and GoLYTELY treatment groups who responded to the effective colon cleansing scale (the primary efficacy endpoint) was 88.9% and 94.8%, respectively. The rate difference between the MOVIPREP and GoLYTELY treatment groups was -5.9% and the lower bound of the 97.5% confidence interval was -12.0%. .

In the French Study, the percentage of patients in the MOVIPREP and OSPS treatment groups who responded to the effective colon cleansing scale (the primary efficacy endpoint) was 73% and 64.3%, respectively. The rate difference between the MOVIPREP and OSPS treatment groups was 8.7% and the lower bound of the 97.5% confidence interval was -2.2%

Although from the statistical perspective, the non-inferiority margin of 15% selected by the applicant for the two studies is not acceptable, from the clinical standpoint, the above studies did provide substantial efficacy evidence that MOVIPREP is effective for colon preparation allowing adequate visualization of the colonic mucosa (at least better than placebo).

In summary, the clinical data from the two well-controlled MOVIPREP studies support the efficacy of two MOVIPREP regimens (split-dosing and evening-only dosing) for cleansing of the colon as a preparation for colonoscopy.

Safety:

Of the 800 subjects/patients in the total safety population in this NDA, 413 (51.6%), 179 (22.4%), and 171 (21.4%) patients received MOVIPREP, GoLYTELY, and OSPS, respectively and 37 (4.6%) subjects received a two liter PEG-based investigational product with 200 to 250 grams of PEG 3350. Of the 413 patients who received MOVIPREP, 214 (51.8%) and 199 (48.2%) received the split-dose and evening-only regimens, respectively.

In the four MOVIPREP studies (the German and French studies and two phase 2, uncontrolled MOVIPREP studies), no patient died and three patients experienced drug-related serious adverse events (one patient who received MOVIPREP and two patients who received OSPS). The serious adverse events were vomiting, hypokalemia, ECG changes.

In the four MOVIPREP studies, six patients experienced drug-related study discontinuations (four patients who received MOVIPREP and two patients who received GoLYTELY). Of the four patients who had MOVIPREP-related study discontinuations, two patients experienced nausea, one patient had malaise, and one patient vomited. Of the two patients who had GoLYTELY-related study discontinuations, one patient had nausea and the other patient had nausea and vomiting. Most of these adverse events resolved without sequelae.

In the two controlled MOVIPREP studies, the most common drug related adverse events associated with MOVIPREP administration were abdominal distension, anal discomfort, thirst, nausea, abdominal pain, and malaise. In these two studies there were no appreciable differences in the frequencies of the most common drug-related adverse events in patients who received MOVIPREP compared to the patients who received the active comparator.

In summary, the safety of MOVIPREP for cleansing of the colon as a preparation for colonoscopy is acceptable for approval of this NDA.

F. Pediatric Use:

The sponsor requested a deferral for pediatric studies until after adequate post-marketing experience in adults. I recommend that the full waiver of pediatric studies be granted. Currently, NuLYTELY, a PEG-based colon preparation, is approved for "bowel cleansing prior to colonoscopy" in pediatric patients ≥ six months of age. Furthermore, OSPS is professionally labeled OTC for colon cleansing in pediatric patients ≥ 12 years of age. PEG-related products containing similar amounts of PEG 3350 are likely to be equally efficacious and safe in pediatric patients. Therefore, MOVIPREP is not likely to "represent a meaningful therapeutic benefit over existing treatments for pediatric patients". In addition, colon preparation is not performed in a substantial number of pediatric patients.

IV. Labeling Recommendations:

I concur with Dr. Eric Brodsky's labeling recommendations listed in his review. The labeling recommendations are summarized as following:

- Adding WARNINGS to the MOVIPREP label about the risk of generalized tonic-clonic seizures and electrolyte changes associated with use of polyethylene glycol (PEG) colon preparation products in patients with no prior history of seizures.
- Adding a CLINICAL STUDIES section to the MOVIPREP label.
- Adding a table in the ADVERSE REACTIONS section of the label detailing the most common drug-related adverse events.

For detailed labeling recommendations, please see Dr. Eric Brodsky's review.

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

/s/

Ruyi He
4/3/2006 05:49:50 PM
MEDICAL OFFICER

He, Ruyi

From: Ball, Leslie
Sent: Monday, April 03, 2006 10:19 AM
To: Kadar, Attila T
Cc: Mercado, Tania; Hackett, Rebecca R; Salewski, Joseph; Lewin, Constance; Malek, Khairy W; Tesch, Dianne; He, Ruyi
Subject: NDA 21-881

Importance: High

Dr. Kadar:

I was informed today by Dr. Malek that the inspections for NDA 21-881 was cancelled by you. This was discovered because the PDUFA due date is next week and the review division requested the inspection results. Dr. Malek discovered that the inspections for NDA 21-881 were never done.

Please be aware that as the email below states, the only inspection that DSI requested to be cancelled was for BLA [redacted].

The inspections for NDA 21-881 (Dr. [redacted] were never cancelled by DSI.

Please let me know if, in fact, the inspections for NDA 21-881 were cancelled.

Please let us know how DSI can ensure that this misunderstanding does not happen again.

Leslie

From: Ball, Leslie
Sent: Thursday, January 26, 2006 9:17 PM
To: Kadar, Attila T
Cc: Mercado, Tania; Hackett, Rebecca R; Rhoads, Joanne L; Salewski, Joseph; Young, Robert S K
Subject: FW: Foreign Inspection for BLA [redacted]
Importance: High

Per your voice mail message, I am confirming that the foreign inspection for BLA [redacted]

Thanks for all your hard work. We remain committed, as I know you do, in meeting the Agency's goals and mission.

Leslie

-----Original Message-----
From: Ball, Leslie
Sent: Thursday, January 26, 2006 4:49 PM
To: Keegan, Patricia; Kadar, Attila T; Sickafuse, Sharon; Gootenberg, Joseph; Pai-Scherf, Lee; Ross, David B; Weiss, Karen;

Pazdur, Richard
Cc: Young, Robert S K; Mercado, Tania; Hackett, Rebecca R; Rhoads, Joanne L; Salewski, Joseph; Malek, Khairy W; Kewley, James M
Subject: RE: Foreign Inspection for BLA [redacted]

Thanks for this information. DSI will prepare the clinical inspection summary based on inspection of the two domestic sites.

-----Original Message-----
From: Keegan, Patricia
Sent: Wednesday, January 25, 2006 3:17 PM
To: Kadar, Attila T; Ball, Leslie; Sickafuse, Sharon; Gootenberg, Joseph; Pai-Scherf, Lee; Ross, David B; Weiss, Karen; Pazdur, Richard
Cc: Young, Robert S K; Mercado, Tania; Hackett, Rebecca R; Rhoads, Joanne L; Salewski, Joseph; Malek, Khairy W; Kewley, James M
Subject: RE: Foreign Inspection for BLA [redacted]

In light of our need to take action before the inspection results and given the inspection of the 2 US sites, we withdraw our request for inspection of the EU sites

-----Original Message-----
From: Kadar, Attila T
Sent: Wednesday, January 25, 2006 2:38 PM
To: Ball, Leslie; Sickafuse, Sharon; Gootenberg, Joseph; Pai-Scherf, Lee; Keegan, Patricia; Ross, David B; Weiss, Karen; Pazdur, Richard
Cc: Kadar, Attila T; Young, Robert S K; Mercado, Tania; Hackett, Rebecca R; Rhoads, Joanne L; Salewski, Joseph; Malek, Khairy W; Kewley, James M
Subject: RE: Foreign Inspection for BLA [redacted]

Dear Dr. Ball,

The Investigator is standing by and we need to know if both Assignments are still effective as of today or cancelled
or partially cancelled.

The inspections planned are:

1. NDA-21-881 [redacted]
   Drug: Moviprep Gut cleansing prior to colonoscopy.
2. BLA [redacted]

Please let me know as soon as possible, because Investigator Kewley would need VISAs for two countries in [redacted]

As you know, we must meet the NFT submission date requirements and we are running out of time.

In case of cancellation of the inspections, I could immediately assign Investigator Kewley to one of the many urgent Assignments.

Thank you very much for your cooperation.

Sincerely,

Dr. Kadar

-----Original Message-----
From: Ball, Leslie
Sent: Monday, January 23, 2006 10:51 AM
To: Sickafuse, Sharon; Gootenberg, Joseph; Pai-Scherf, Lee; Keegan, Patricia; Ross, David B; Weiss, Karen; Pazdur, Richard
Cc: Kadar, Attila T; Young, Robert S K; Mercado, Tania; Hackett, Rebecca R; Rhoads, Joanne L; Salewski, Joseph; Malek, Khairy W; Kewley, James M
Subject: RE: Foreign Inspection for BLA [redacted]

Sharon:

Please see email below regarding foreign inspection of BLA [redacted] ; in [redacted]

While the original assignment was issued on November 1, 2005, the International and Technical Operations Branch, ORA, was unable to find a field investigator to conduct this inspection to meet the PDUFA deadline of March 1, 2006, despite aggressive attempts to schedule the inspection.

The two domestic inspections for the BLA have been completed.

Please let us know if you would like to proceed with the foreign inspection on this NDA, given the completion date beyond the PDUFA deadline.

Leslie Ball

Leslie K. Ball, MD
CAPT, USPHS
Branch Chief
Good Clinical Practice Branch 2
Division of Scientific Investigations
CDER, FDA
HFD 47
7520 Standish Place
Rockville, MD 20855

phone: 301-827-5455
fax: 301-827-5290
BallL@cder.fda.gov

-----Original Message-----

From: Kadar, Attila T
Sent: Friday, January 20, 2006 8:51 PM
To: Ball, Leslie
Cc: Young, Robert S K; Mercado, Tania; Hackett, Rebecca R; Rhoads, Joanne L; Salewski, Joseph; Malek, Khairy W; Kewley, James M
Subject: RE: Foreign Inspection for BLA 125084

Dear Dr. Ball,

This is to inform you that we have just received agreement, clearance and final approval for Compliance Officer, James (Jim) Michael Kewley of the New York District, Buffalo Office to conduct the BLA STN # [redacted] and NDA # 21-881 Drug Moviprep in [redacted] The inspections will be done within the time frame from March 3-25, 2006.

As always, I do immediately notify you as I receive such approvals and provide your Office with the pertinent information of the traveling Field Investigator:

James M. Kewley,
Compliance Officer
300 Pearl Street
Suite # 100
Buffalo, NY 14202
HFR-NE340
Telephone: (716)+541-4499

It is my understanding that with these two Assignments we are catching up with our backlogs and I am looking forward to a New Year when my new colleague, Miss Mercado and I will be able to keep up with all the Assignments that are coming to our Office.

Please provide Jim Kewley with the background information on both Assignments.

Thank you very much for your understanding.

I shall remain,

Your Most Humble Public Servant,

Attila T. Kadar

-----Original Message-----

From: Ball, Leslie
Sent: Thursday, January 19, 2006 11:05 AM
To: Kadar, Attila T
Cc: Young, Robert S K; Mercado, Tania; Hackett, Rebecca R; Rhoads, Joanne L; Salewski, Joseph
Subject: RE: Foreign Inspection for BLA

Dr. Kadar:

Thanks for getting back to me on this. Let us know as soon as possible when you have firm plans for the inspection and the dates that the inspection will occur.

Leslie

-----Original Message-----

From: Ball, Leslie
Sent: Thursday, January 19, 2006 10:00 AM
To: Mercado, Tania; Kadar, Attila T
Cc: Young, Robert S K; Hackett, Rebecca R; Rhoads, Joanne L; Salewski, Joseph
Subject: Foreign Inspection for BLA
Importance: High

Leslie K. Ball, MD
CAPT, USPHS
Branch Chief
Good Clinical Practice Branch 2
Division of Scientific Investigations
CDER, FDA
HFD 47
7520 Standish Place
Rockville, MD 20855

phone: 301-827-5455
fax: 301-827-5290
BallL@cder.fda.gov

18 Page(s) Withheld

_____ § 552(b)(4) Trade Secret / Confidential

X § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-881

INFORMATION REQUEST LETTER

Norgine International, Limited
Attention: Ramona Krailler, Ph.D.
Regulatory Affairs Manager
Keaton House, Widewater Place, Moorhall Road
Harefield, Uxbridge, Middlesex
UB9 6NS
United Kingdom

Dear Dr. Krailler:

Please refer to your June 7, 2005 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Moviprep® (PEG 3350, sodium sulfate, sodium chloride, potassium chloride, sodium ascorbate and ascorbic acid) for oral solution.

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 the Safety Update.
2. Provide the synopsis of the German Phase 3 study, if available.
3. Provide the number of and percentage of patients who were Caucasian, Black, Asian and other.
4. Provide the English narratives of discontinuations due to adverse events in all 6 submitted studies.

Please submit the requested information immediately in order to allow us adequate time to review this new information during your current review cycle.

If you have any questions, call Tanya Clayton, B.S., Regulatory Health Project Manager, at (301) 796-0871.

Sincerely,

{See appended electronic signature page}

Brian Strongin, R.Ph., M.B.A
Chief, Project Management Staff
Division of Gastroenterology Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

Brian Strongin
3/13/2006 05:35:04 PM

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*** TX REPORT ***
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TRANSMISSION OK

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TIME USE	00'22
PAGES SENT	2
RESULT	OK

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation III

FACSIMILE TRANSMITTAL SHEET

DATE: February 13, 2006

To: Marilyn R. Carlson, D.M.D., M.D., RAC	**From:** Tanya D. Clayton, BS Regulatory Project Manager
Company: US Agent for Norgine International Limited	Division of Gastroenterology Products
Fax number: 858-759-8384	**Fax number:** 301-796-9905
Phone number:	**Phone number:** 301-796-0871

Subject: NDA 21-881 (Moviprep) Information Request

Total no. of pages including cover: 2

Comments:
Please find attached an Information Request, per our clinical reviewer.

Document to be mailed: YES √NO

Please respond to the following:

1) Provide a Safety update.

2) Provide a detailed synopsis of your Phase 3 German Study (2:1 randomization, 240 Moviprep exposures).

3) We recommend you propose a CLINICAL STUDIES section for your MOVIPREP label that includes the design and the results of your two submitted phase 3 trials (Studies 01/2001 and 02/2001)."

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications

Predecisional Agency Information

Date: February 9, 2006
From: Michael Brony, DDMAC
To: Tanya Clayton, GI and Coagulation Drug Products
Re: NDA 21-881 Moviprep (PEG 3350, sodium sulfate, sodium chloride, potassium chloride, sodium ascorbate and ascorbic acid) for oral solution draft labeling review

- The last line of the CLINICAL PHARMACOLOGY section of the draft product labeling (PI), states:

  "..., *results in* [redacted] *no net absorption or excretion of ions or water* [redacted]"

  Is there substantial evidence to support the claim, [redacted] If there is not, DDMAC recommends deleting this claim.

- In the ADVERSE REACTIONS section of the draft PI states:

  [redacted]

  Because phrases such as, [redacted] and [redacted] minimize the risks associated with Moviprep use, DDMAC recommends that these phrases be deleted. In place of those phrases, DDMAC recommends displaying the incidence of the adverse reactions.

DDMAC has no comments at this time on the Pouch A, Pouch B, Mixer, and Carton labels.

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/s/

Michael Brony
2/9/2006 03:05:58 PM
CSO

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RESULT	OK

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation III

FACSIMILE TRANSMITTAL SHEET

DATE: December 12, 2005

To: Marilyn R. Carlson, D.M.D., M.D., RAC	**From:** Tanya D. Clayton, BS Regulatory Project Manager
Company: US Agent for Norgine International Limited	Division of Gastrointestinal and Coagulation Drug Products
Fax number: 858-759-8384	**Fax number:** 301-796-9905
Phone number:	**Phone number:** 301-796-0871

Subject: NDA 21-881 (Moviprep) Information Request

Total no. of pages including cover: 2

Comments:
Please find attached an Information Request, per our clinical reviewer.

Document to be mailed: YES √NO

Please respond to the following:

1) In Study NRL994-01/2001 (the German, phase 3 study), is the assessment of the primary efficacy endpoint (overall quality of gut cleansing) based on the protocol (Volume 43.1) or the final study report (Volume 37.1)?

2) In Study NRL994-02/2001 (the French, phase 3 study), is the assessment of the primary efficacy endpoint (overall quality of gut cleansing) based on the protocol (Volume 62.1) or the final study report (Volume 61.1)?

OFFICE OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS

NEW DRUG APPLICATION FILING AND REVIEW FORM

1. General Information About the Submission

	Information		Information
NDA Number		Brand Name	Moviprep
OCPB Division (I, II, III)	DCPB III	Generic Name	PEG 3350 & Electrolytes plus +VitaminC
Medical Division	GI and Dermatology	Drug Class	
OCPB Reviewer	Tien-Mien Chen, Ph.D.	Indication(s)	Bowel Cleansing prior to [redacted], Colonoscopy,
OCPB Team Leader	Dennis Bashaw Pharm.D.	Dosage Form	powder
		Dosing Regimen	
Date of Submission	06/07/05	Route of Administration	Oral
Estimated Due Date of OCPB Review	02/25/06	Sponsor	Norgine B. V.
Medical Division Due Date	02/27/06	Priority Classification	Standard
PDUFA Due Date	04/10/06		

(a) Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	X			
HPK Summary	X			
Labeling	X			
Reference Bioanalytical and Analytical Methods	X			
I. Clinical Pharmacology	[redacted]			
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
HEALTHY VOLUNTEERS-				
single dose:				
multiple dose:				
PATIENTS-				
single dose:				
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				

renal impairment:				
hepatic impairment:				
PD:				
Phase 2:				
Phase 3:				
PK/PD:				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability:				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies:				
Dissolution:				
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies	[redacted]	0	0	
(a)				

(b) Filability and QBR comments

	"X" if yes	*(i) Comments*
Application filable ?	X	Reasons if the application is not filable (or an attachment if applicable) For example, is clinical formulation the same as the to-be-marketed one?
Comments sent to firm ?		Comments have been sent to firm (or attachment included). FDA letter date if applicable.
QBR questions (key issues to be considered)	None	
Other comments or information not included above	**Two pivotal clinical studies were conducted, but no human PK studies were done. As concluded by the reviewing chemists in GI division, this NDA for bowel cleansing preparation prior to [redacted] using PEG 3350 and electrolytes plus Vitamin C is considered as a combination drug product application.** **It was concluded within OCPB that the above NDA is fileable. Further, no additional PK studies were needed to address the combination drug issues since PEG 3350 is known to act locally within the GI lumen and is minimally absorbed into systemic circulation and Vitamin C is not considered as a drug.**	
Primary reviewer Signature and Date	Tien-Mien Chen, Ph.D.	
Secondary reviewer Signature and Date		

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/s/

Tien-Mien Chen
11/21/2005 12:26:30 PM
BIOPHARMACEUTICS

Per OCPB internal discussion, a memo to file was submitted to DFS to address OCPB point of view regarding PEG 3350 and electrolytes plus Vitamin C being considered as a combinaiton drug product.

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TX/RX NO	0262
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TIME USE	00'28
PAGES SENT	2
RESULT	OK

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation III

FACSIMILE TRANSMITTAL SHEET

DATE: October 18, 2005

To: Marilyn R. Carlson, D.M.D., M.D., RAC	**From:** Tanya D. Clayton, BS Regulatory Project Manager
Company: US Agent for Norgine International Limited	Division of Gastrointestinal and Coagulation Drug Products
Fax number: 858-759-8384	**Fax number:** 301-796-9905
Phone number:	**Phone number:** 301-796-0871

Subject: NDA 21-881 (Moviprep) Information Request

Total no. of pages including cover: 2

Comments:
Please find attached an Information Request, per our clinical reviewer.

Document to be mailed: YES √NO

Please answer the following questions and please refer us to the exact section of the protocol that confirms your answer.

1) In Study 02/2001, whose assessment will be used in the primary efficacy analysis for the primary efficacy endpoint?

A) One of the four gastroenterology experts on the expert panel (refer to Volume 61, Section 14.3, Page 27/40 of the protocol)
B) The "majority judgment" between one of the four gastroenterology experts, the investigator, and another gastroenterology expert on the panel (refer to Volume 61, Section 10.5, Page 22/40 and Section 11.1, Page 23/40 of the protocol) or
C) Other people or rules not described by A and B.

2) In Study 02/2001, is the primary efficacy endpoint based on the poorer of the two assessments during colonoscopy (during introduction of the colonoscopy and during withdrawal of the colonoscopy as defined in Study 01/2001)?

3) In Study 02/2001, is the per protocol statistical analysis of the investigator's assessment of the overall quality of the cleansing solution [success (A or B)/failure (C or D)], a co-primary or a secondary analysis of the primary efficacy endpoint? (Refer to Volume 61, Section 14.3, Page 27/40 of the protocol or Volume 61, Section 9.8.3.2, Page 45 of the Study Report.)

4) Is the confirmatory analysis using MITT patient population for the expert's assessment of the overall quality of the cleansing solution [success (A or B)/failure (C or D)] a co-primary or a secondary analysis of the primary efficacy endpoint? (Refer to Volume 61, Section 14.3, Page 27/40 of the protocol or Volume 61, Section 9.8.3.2, Page 45 of the Study Report.)

5) In Study 01/2001, who makes the assessment of the primary efficacy endpoint on the three member gastroenterologist expert panel?

A) Only one gastroenterologist on the panel or
B) Two out of three gastroenterologists on the panel or
C) Other people or rules not described by A and B.

6) In Study 02/2001, clarify if the overall quality of each preparation as rated by the investigator is on a 0 mm (excellent) to 100 mm (very bad) VAS scale (refer to Volume 61, Section 9.5.1.6, Page 38/110 in the Study Report) or a 0 mm to 100 mm (perfectly clean) VAS scale (refer to Volume 61, Section 11.1, Page 23/40 in the Protocol).

7) In Study 02/1001, identify the statistical analysis population for the patient acceptability efficacy endpoint (refer to Volume 61, Section 14.3, Page 27/40).

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation III

FACSIMILE TRANSMITTAL SHEET

DATE: October 17, 2005

To: Marilyn R. Carlson, D.M.D., M.D., RAC	**From:** Tanya D. Clayton, BS Regulatory Project Manager
Company: US Agent for Norgine International Limited	Division of Gastrointestinal and Coagulation Drug Products
Fax number: 858-759-8265	**Fax number:** 301-443-9285
Phone number: 858-759-8384	**Phone number:** 301-827-4005

Subject: NDA 21-881 (Moviprep) Information Request

Total no. of pages including cover: 2

Comments:
Please find attached an Information Request, per our clinical reviewer.

Document to be mailed: YES √NO

Please answer the following questions and please refer us to the exact section of the protocol that confirms your answer.

1) In Study 02/2001, whose assessment will be used in the primary efficacy analysis for the primary efficacy endpoint?

A) One of the four gastroenterology experts on the expert panel (refer to Volume 61, Section 14.3, Page 27/40 of the protocol)
B) The "majority judgment" between one of the four gastroenterology experts, the investigator, and another gastroenterology expert on the panel (refer to Volume 61, Section 10.5, Page 22/40 and Section 11.1, Page 23/40 of the protocol) or
C) Other people or rules not described by A and B.

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5) In Study 01/2001, who makes the assessment of the primary efficacy endpoint on the three member gastroenterologist expert panel?

A) Only one gastroenterologist on the panel or
B) Two out of three gastroenterologists on the panel or
C) Other people or rules not described by A and B.

Clayton, Tanya

From: He, Ruyi
Sent: Monday, October 17, 2005 5:54 PM
To: Brodsky, Eric
Cc: Chen, Wen Jen; Clayton, Tanya
Subject: RE: MOVIPREP information request

It is fine for me. Thanks. Ruyi

-----Original Message-----
From: Brodsky, Eric
Sent: Monday, October 17, 2005 5:29 PM
To: He, Ruyi
Cc: Chen, Wen Jen; Clayton, Tanya
Subject: MOVIPREP information request

Hey Ruyi,

I talked to Wen Jen regarding the primary statistical analysis for the primary efficacy endpoint for the French phase III study for MOVIPREP (Study 02/2001). We both feel that the protocol is equivocal and we have several questions. I want to show you this email before I ask Tanya to send this to the sponsor as an information request.

Please answer the following questions and please show us the exact section of the protocol that confirms your answer.

1) In Study 02/2001, whose assessment will be used in the primary efficacy analysis for the primary efficacy endpoint?

A) One of the four gastroenterology experts on the expert panel (refer to Volume 61, Section 14.3, Page 27/40 of the protocol)
B) The "majority judgment" between one of the four gastroenterology experts, the investigator, and another gastroenterology expert on the panel (refer to Volume 61, Section 10.5, Page 22/40 and Section 11.1, Page 23/40 of the protocol) or
C) Other people or rules not described by A and B.

2) In Study 02/2001, is the primary efficacy endpoint based on the poorer of the two assessments during colonoscopy (during introduction of the colonoscopy and during withdrawal of the colonoscopy as defined in Study 01/2001)?

3) In Study 02/2001, is the per protocol statistical analysis of the investigator's assessment of the overall quality of the cleansing solution [success (A or B)/failure (C or D)], a co-primary or a secondary analysis of the primary efficacy endpoint? (Refer to Volume 61, Section 14.3, Page 27/40 of the protocol or Volume 61, Section 9.8.3.2, Page 45 of the Study Report.)

4) Is the confirmatory analysis using MITT patient population for the expert's assessment of the overall quality of the cleansing solution [success (A or B)/failure (C or D)] a co-primary or a secondary analysis of the primary efficacy endpoint? (Refer to Volume 61, Section 14.3, Page 27/40 of the protocol or Volume 61, Section 9.8.3.2, Page 45 of the Study Report.)

5) In Study 01/2001, who makes the assessment of the primary efficacy endpoint on the three member gastroenterologist expert panel?

A) Only one gastroenterologist on the panel or
B) Two out of three gastroenterologists on the panel or
C) Other people or rules not described by A and B.

Thanks.

Appears This Way
On Original

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation III

FACSIMILE TRANSMITTAL SHEET

DATE: August 9, 2005

To: Ramona Krailler, Ph.D.	**From:** Tanya D. Clayton, BS Regulatory Project Manager
Company: US Agent for Norgine International Limited	Division of Gastrointestinal and Coagulation Drug Products
Fax number: 011-44-1895-453-711	**Fax number:** 301-443-9285
Phone number: 011-44-7795-005-484	**Phone number:** 301-827-4005

Subject: NDA 21-881 (Moviprep) Information Request

Total no. of pages including cover: 2

Comments:
Please find attached an Information Request, per our statistical reviewer

Document to be mailed: YES √NO

Please provide the following information for Study# NRL994-01/2001 and Study# NRL994-02/2001:

1) Please provide justification on the choice for the non-inferiority margin of 15% used in the analysis of the primary efficacy endpoint (frequency with grade A or B in the overall quality assessment of gut cleansing).

2) Please provide the algorithm for testing the interaction between treatment and center stated in the section 11.4.2 "Statistical/ Analysis Issues" of Volume 23.1.

3) Please provide data for both Studies NRL994-01/2001 and Study# NRL994-02/2001 in electronic format consistent with the guidance, *Regulatory Submissions in Electronic Format; General Considerations.* It is suggested that the following variables be included:

   - Study number;
   - Investigator or Center code;
   - Patient number/name;
   - Treatment name;
   - Intent-to-treat population (Yes or No) - ITT;
   - Modified Intent-to-treat population (Yes or No) - mITT;
   - Per Protocol population (Yes or No) - PP;
   - Patient used in the primary analysis (Yes or No);
   - Patient used in the secondary analysis (Yes or No);
   - Gender ;
   - Age (year);
   - Race;
   - Weight (kg);
   - Overall quality assessment of gut cleansing (from A to D) – Primary endpoint;
   - Degree of gut cleansing by the physician performing the endoscopic procedure (from 4 to 0);
   - Degree of gut cleansing by a blinded and independent expert panel on the basis of videotapes recorded during colonoscopy (from 4 to 0);
   - Classification of the overall quality of gut cleansing (from A to D) based on the assessment of the physician performing the endoscopic procedure;
   - Mean degree of gut cleansing by averaging all segmental scores based on the physician performing the endoscopic procedure;
   - Mean degree of gut cleansing by averaging all segmental scores based on a blinded and independent expert panel on the basis of videotapes recorded during colonoscopy;

- Global quality of colonic cleansing as assessed on a VAS ranging from 0 (dirty) to 100 mm (perfectly clean) by the physician performing the endoscopic procedure;
- Global quality of colonic cleansing as assessed on a VAS ranging from 0 (dirty) to 100 mm (perfectly clean) by a blinded and independent expert panel on the basis of videotapes recorded during colonoscopy;
- Overall easiness (convenience) to perform the colonoscopy as rated by the investigator on a 3-level VRS (verbal rating scale) with ranks I (easy), 2 (with some difficulties), and 3 (difficult);
- Evaluation of taste of the first and the second dose of the gut cleansing solution by the patient on a VAS ranging from 0 (very good) to 100 mm (very bad);
- Global evaluation of taste of the gut cleansing solution by the patient on a VRS with ranks acceptable, satisfactory, and not acceptable;
- Degree of patient 's satisfaction with the gut cleansing regimen as assessed on a VAR ranging from 0 (excellent) to 100 mm (very bad);
- Overall patient's acceptability of the gut cleansing regimen as assessed on a VAS ranging from 0 (excellent) to 100 mm (very bad);
- Patient's problems with drinking the entire volume of the gut cleansing solution as assessed on a 3-level VRS with ranks none, some, many;
- Patient's complying with the necessary diet as assessed on a 4-level VRS with ranks easy, acceptable, hard, very hard;
- Amount of additional clear fluid ingested;
- Time to first bowel movement after start of intake;

NDA REGULATORY FILING REVIEW
(Including Memo of Filing Meeting)

NDA # 21-881 Supplement # N/A Efficacy Supplement Type SE- N/A

Trade Name: Moviprep
Established Name: PEG 3350, NAS, NACL, KCL, NA
Strengths: 100g, 7.500g, 2.691g, 1.015g, 5.900g, 4.700g

Applicant: Norgine B.V.
Agent for Applicant: Marilyn Carlson, D.M.D., M.D., RAC

Date of Application: June 7, 2005
Date of Receipt: June 10, 2005
Date clock started after UN:
Date of Filing Meeting: August 1, 2005
Filing Date: August 9, 2005
Action Goal Date (optional): User Fee Goal Date: April 10, 2006

Indication(s) requested:

Type of Original NDA: (b)(1) ☒ (b)(2) ☐
OR
Type of Supplement: (b)(1) ☐ (b)(2) ☐

NOTE:

(1) If you have questions about whether the application is a 505(b)(1) or 505(b)(2) application, see Appendix A. 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). If the application is a (b)(2), complete Appendix B.

(2) If the application is a supplement to an NDA, please indicate whether the NDA is a (b)(1) or a (b)(2) application:

☒ NDA is a (b)(1) application OR ☐ NDA is a (b)(2) application

Therapeutic Classification: S ☒ P ☐
Resubmission after withdrawal? ☐ Resubmission after refuse to file? ☐
Chemical Classification: (1,2,3 etc.) 4 and 5
Other (orphan, OTC, etc.)

Form 3397 (User Fee Cover Sheet) submitted: YES ☒ NO ☐

User Fee Status: Paid ☒ Exempt (orphan, government) ☐
Waived (e.g., small business, public health) ☐

NOTE: *If the NDA is a 505(b)(2) application, and the applicant did not pay a fee in reliance on the 505(b)(2) exemption (see box 7 on the User Fee Cover Sheet), confirm that a user fee is not required. The applicant is required to pay a user fee if: (1) the product described in the 505(b)(2) application is a new molecular entity or (2) the applicant claims a new indication for a use that that has not been approved under section 505(b). Examples of a new indication for a use include a new indication, a new dosing regime, a new patient population, and an Rx-to-OTC switch. The best way to determine if the applicant is claiming a new indication for a use is to compare the applicant's proposed labeling to labeling that has already been approved for the product described in the application. Highlight the differences between the proposed and approved labeling.*

If you need assistance in determining if the applicant is claiming a new indication for a use, please contact the user fee staff.

- Is there any 5-year or 3-year exclusivity on this active moiety in an approved (b)(1) or (b)(2) application? YES ☐ NO ☒
  If yes, explain:

- Does another drug have orphan drug exclusivity for the same indication? YES ☐ NO ☒

- If yes, is the drug considered to be the same drug according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]? YES ☐ NO ☐

  If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007).

- Is the application affected by the Application Integrity Policy (AIP)? YES ☐ NO ☒
  If yes, explain:

- If yes, has OC/DMPQ been notified of the submission? YES ☐ NO ☐

- Does the submission contain an accurate comprehensive index? YES ☒ NO ☐

- Was form 356h included with an authorized signature? YES ☒ NO ☐
  If foreign applicant, both the applicant and the U.S. agent must sign.

- Submission complete as required under 21 CFR 314.50? YES ☒ NO ☐
  If no, explain:

- If an electronic NDA, does it follow the Guidance? N/A ☒ YES ☐ NO ☐
  If an electronic NDA, all forms and certifications must be in paper and require a signature.
  Which parts of the application were submitted in electronic format?

  Additional comments:

- If an electronic NDA in Common Technical Document format, does it follow the CTD guidance? N/A ☐ YES ☐ NO ☐

- Is it an electronic CTD (eCTD)? N/A ☒ YES ☐ NO ☐
  If an electronic CTD, all forms and certifications must either be in paper and signed or be electronically signed.

  Additional comments:

- Patent information submitted on form FDA 3542a? YES ☒ NO ☐

- Exclusivity requested? YES, _____ Years NO ☒
  NOTE: *An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.*

- Correctly worded Debarment Certification included with authorized signature? YES ☐ NO ☒
  If foreign applicant, both the applicant and the U.S. Agent must sign the certification.

NOTE: *Debarment Certification should use wording in FD&C Act section 306(k)(1) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as "To the best of my knowledge . . . ."*

- Financial Disclosure forms included with authorized signature? YES ☒ NO ☐
  (Forms 3454 and 3455 must be included and must be signed by the APPLICANT, not an agent.)
  NOTE: *Financial disclosure is required for bioequivalence studies that are the basis for approval.*

- Field Copy Certification (that it is a true copy of the CMC technical section)? Y ☒ NO ☐

- PDUFA and Action Goal dates correct in COMIS? YES ☒ NO ☐
  If not, have the document room staff correct them immediately. These are the dates EES uses for calculating inspection dates.

- Drug name and applicant name correct in COMIS? If not, have the Document Room make the corrections. Ask the Doc Rm to add the established name to COMIS for the supporting IND if it is not already entered.

- List referenced IND numbers: 63,268

- End-of-Phase 2 Meeting(s)? Date(s) _____ NO ☒
  If yes, distribute minutes before filing meeting.

- Pre-NDA Meeting(s)? Date(s) July 18, 2004 NO ☐
  If yes, distribute minutes before filing meeting.

Project Management

- Was electronic "Content of Labeling" submitted? YES ☒ NO ☐
  If no, request in 74-day letter.

- All labeling (PI, PPI, MedGuide, carton and immediate container labels) consulted to DDMAC? YES ☒ NO ☐

- Risk Management Plan consulted to ODS/IO? N/A ☒ YES ☐ NO ☐

- Trade name (plus PI and all labels and labeling) consulted to ODS/DMETS? Y ☒ NO ☐

- MedGuide and/or PPI (plus PI) consulted to ODS/DSRCS? N/A ☒ YES ☐ NO ☐

- If a drug with abuse potential, was an Abuse Liability Assessment, including a proposal for scheduling, submitted?
  N/A ☒ YES ☐ NO ☐

If Rx-to-OTC Switch application:

- OTC label comprehension studies, all OTC labeling, and current approved PI consulted to ODS/DSRCS? N/A ☒ YES ☐ NO ☐

- Has DOTCDP been notified of the OTC switch application? YES ☐ NO ☐

Clinical

- If a controlled substance, has a consult been sent to the Controlled Substance Staff? YES ☐ NO ☐

Chemistry

- Did applicant request categorical exclusion for environmental assessment? YES ☒ NO ☐
  If no, did applicant submit a complete environmental assessment? YES ☐ NO ☐
  If EA submitted, consulted to Florian Zielinski (HFD-357)? YES ☐ NO ☐
- Establishment Evaluation Request (EER) submitted to DMPQ? YES ☒ NO ☐
- If a parenteral product, consulted to Microbiology Team (HFD-805)? YES ☐ NO ☐

ATTACHMENT

MEMO OF FILING MEETING

DATE: August 1, 2005

BACKGROUND: Moviprep is indicated for bowel cleansing prior to colonoscopy

(Provide a brief background of the drug, e.g., it is already approved and this NDA is for an extended-release formulation; whether another Division is involved; foreign marketing history; etc.)

ATTENDEES: Tanya Clayton, Brian Harvey, Jasti Choudary, Ruyi He, Eric Brodsky, Marie Kowblansky for Liang Zhou and Ramesh Raghavarchi, Ke Zhang, Wen Jen, Albert Chen

ASSIGNED REVIEWERS (including those not present at filing meeting) :

Discipline	**Reviewer**
Medical:	Eric Brodsky
Secondary Medical:	
Statistical:	Wen Jen Chen
Pharmacology:	Ke Zhang
Statistical Pharmacology:	
Chemistry:	Ramesh Raghavarchi
Environmental Assessment (if needed):	
Biopharmaceutical:	Albert Chen
Microbiology, sterility:	
Microbiology, clinical (for antimicrobial products only):	
DSI:	Khairy Malek
Regulatory Project Management:	Tanya Clayton
Other Consults:	DDMAC, DMETS,

Per reviewers, are all parts in English or English translation? YES ☒ NO ☐
If no, explain:

CLINICAL FILE ☒ REFUSE TO FILE ☐

- Clinical site inspection needed? YES ☒ NO ☐
- Advisory Committee Meeting needed? YES, date if known _____ NO ☒
- If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? N/A ☐ YES ☐ NO ☐

CLINICAL MICROBIOLOGY N/A ☒ FILE ☐ REFUSE TO FILE ☐

STATISTICS N/A ☐ FILE ☒ REFUSE TO FILE ☐

BIOPHARMACEUTICS FILE ☒ REFUSE TO FILE ☐

- Biopharm. inspection needed? YES ☐ NO ☒

PHARMACOLOGY N/A ☐ FILE ☒ REFUSE TO FILE ☐

- GLP inspection needed? YES ☐ NO ☐

CHEMISTRY FILE ☒ REFUSE TO FILE ☐

- Establishment(s) ready for inspection? YES ☐ NO ☐
- Microbiology YES ☐ NO ☒

ELECTRONIC SUBMISSION:
Any comments:

REGULATORY CONCLUSIONS/DEFICIENCIES:
(Refer to 21 CFR 314.101(d) for filing requirements.)

☐ The application is unsuitable for filing. Explain why:

☒ The application, on its face, appears to be well-organized and indexed. The application appears to be suitable for filing.

- ☐ No filing issues have been identified.
- ☐ Filing issues to be communicated by Day 74. List (optional):

ACTION ITEMS:

1. ☐ If RTF, notify everybody who already received a consult request of RTF action. Cancel the EER.
2. ☐ If filed and the application is under the AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
3. ☒ Convey document filing issues/no filing issues to applicant by Day 74.

Sponsor is submitting amendment to application with signed debarment certification. Original debarment certification is not signed.

Tanya Clayton, B.S.
Regulatory Project Manager, HFD-180

Appendix A to NDA Regulatory Filing Review

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

(1) it relies on literature to meet any of the approval requirements (unless the applicant has a written right of reference to the underlying data)
(2) it relies on the Agency's previous approval of another sponsor's drug product (which may be evidenced by reference to publicly available FDA reviews, or labeling of another drug sponsor's drug product) to meet any of the approval requirements (unless the application includes a written right of reference to data in the other sponsor's NDA)
(3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)
(4) it seeks approval for a change from a product described in an OTC monograph and relies on the monograph to establish the safety or effectiveness of one or more aspects of the drug product for which approval is sought (see 21 CFR 330.11).

Products that may be likely to be described in a 505(b)(2) application include combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations), OTC monograph deviations, new dosage forms, new indications, and new salts.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, please consult with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007).

Appendix B to NDA Regulatory Filing Review
Questions for 505(b)(2) Applications

1. Does the application reference a listed drug (approved drug)? YES ☐ NO ☐

   *If "**No**," skip to question 3.*

2. Name of listed drug(s) referenced by the applicant (if any) and NDA/ANDA #(s):

3. The purpose of this and the questions below (questions 3 to 5) is to determine if there is an approved drug product that is equivalent or very similar to the product proposed for approval and that should be referenced as a listed drug in the pending application.

   (a) Is there a pharmaceutical equivalent(s) to the product proposed in the 505(b)(2) application that is already approved?

   YES ☐ NO ☐

   (***Pharmaceutical equivalents*** are drug products in identical dosage forms that: **(1)** contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; **(2)** do not necessarily contain the same inactive ingredients; **and** **(3)** meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates. (21 CFR 320.1(c))

   *If "**No**," skip to question 4. Otherwise, answer part (b).*

   (b) Is the approved pharmaceutical equivalent(s) cited as the listed drug(s)? YES ☐ NO ☐
   (The approved pharmaceutical equivalent(s) should be cited as the listed drug(s).)

   *If "**Yes**," skip to question 6. Otherwise, answer part (c).*

   (c) Have you conferred with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (ORP) (HFD-007)? YES ☐ NO ☐

   *If "**No**," please contact the Director, Division of Regulatory Policy II, ORP. Proceed to question 6.*

4. (a) Is there a pharmaceutical alternative(s) already approved? YES ☐ NO ☐

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

   *If "**No**," skip to question 5. Otherwise, answer part (b).*

   (b) Is the approved pharmaceutical alternative(s) cited as the listed drug(s)? YES ☐ NO ☐
   (The approved pharmaceutical alternative(s) should be cited as the listed drug(s).)

   NOTE: *If there is more than one pharmaceutical alternative approved, consult the Director, Division of*

Regulatory Policy II, Office of Regulatory Policy (ORP) (HFD-007) to determine if the appropriate pharmaceutical alternatives are referenced.

*If "**Yes**," skip to question 6. Otherwise, answer part (c).*

(c) Have you conferred with the Director, Division of Regulatory Policy II, ORP? YES ☐ NO ☐

*If "**No**," please contact the Director, Division of Regulatory Policy II, ORP. Proceed to question 6.*

5. (a) Is there an approved drug product that does not meet the definition of "pharmaceutical equivalent" or "pharmaceutical alternative," as provided in questions 3(a) and 4(a), above, but that is otherwise very similar to the proposed product? YES ☐ NO ☐

*If "**No**," skip to question 6.*

*If "**Yes**," please describe how the approved drug product is similar to the proposed one and answer part (b) of this question. Please also contact the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007), to further discuss.*

(b) Is the approved drug product cited as the listed drug? YES ☐ NO ☐

6. Describe the change from the listed drug(s) provided for in this (b)(2) application (for example, "This application provides for a new indication, otitis media" or "This application provides for a change in dosage form, from capsules to solution").

7. Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? (Normally, FDA will refuse-to-file such NDAs (see 21 CFR 314.101(d)(9)). YES ☐ NO ☐

8. Is the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action less than that of the reference listed drug (RLD)? (See 314.54(b)(1)). If yes, the application should be refused for filing under 21 CFR 314.101(d)(9)). YES ☐ NO ☐

9. Is the rate at which the product's active ingredient(s) is absorbed or otherwise made available to the site of action unintentionally less than that of the RLD (see 21 CFR 314.54(b)(2))? If yes, the application should be refused for filing under 21 CFR 314.101(d)(9). YES ☐ NO ☐

10. Are there certifications for each of the patents listed for the listed drug(s)? YES ☐ NO ☐

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

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

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

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

☐ 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted. (Paragraph IV certification)
Patent number(s):

NOTE: *IF FILED, and if the applicant made a "Paragraph IV" certification [21 CFR 314.50(i)(1)(i)(A)(4)], the applicant must* ***subsequently*** *submit a signed certification stating that the NDA holder and patent owner(s) were notified the NDA was filed [21 CFR 314.52(b)]. The applicant must also submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)].*

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

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

☐ 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above).
Patent number(s):

☐ Written statement from patent owner that it consents to an immediate effective date upon approval of the application.
Patent number(s):

12. Did the applicant:

- Identify which parts of the application rely on information (e.g. literature, prior approval of another sponsor's application) that the applicant does not own or to which the applicant does not have a right of reference?

  YES ☐ NO ☐

- Submit a statement as to whether the listed drug(s) identified has received a period of marketing exclusivity?

  YES ☐ NO ☐

- Submit a bioavailability/bioequivalence (BA/BE) study comparing the proposed product to the listed drug?

  N/A ☐ YES ☐ NO ☐

- Certify that it is seeking approval only for a new indication and not for the indications approved for the listed drug if the listed drug has patent protection for the approved indications and the applicant is requesting only the new indication (21 CFR 314.54(a)(1)(iv).?

  N/A ☐ YES ☐ NO ☐

13. If the (b)(2) applicant is requesting 3-year exclusivity, did the applicant submit the following information required by 21 CFR 314.50(j)(4):

- Certification that at least one of the investigations included meets the definition of "new clinical investigation" as set forth at 314.108(a).

  YES ☐ NO ☐

- A list of all published studies or publicly available reports that are relevant to the conditions for which the applicant is seeking approval.

  YES ☐ NO ☐

- EITHER

  The number of the applicant's IND under which the studies essential to approval were conducted.

  IND# _____ NO ☐

  OR

  A certification that the NDA sponsor provided substantial support for the clinical investigation(s) essential to approval if it was not the sponsor of the IND under which those clinical studies were conducted?

  YES ☐ NO ☐

14. Has the Associate Director for Regulatory Affairs, OND, been notified of the existence of the (b)(2) application?

YES ☐ NO ☐

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

/s/

Tanya Clayton
9/28/2005 04:40:16 PM
CSO

DSI CONSULT: Request for Clinical Inspections

Date: August 2, 2005

To: Malek Khairy, GCPB Reviewer/HFD-46

From: Tanya Clayton, B.S., Regulatory Health Project Manager, HFD-180

Subject: **Request for Clinical Inspections**
NDA 21-881
Norgine B.V.
Moviprep, (PEG 3350, sodium sulfate, sodium chloride, potassium chloride, sodium ascorbate and ascorbic acid) for oral solution.

Site Identification:

The following sites essential for approval have been identified for inspection:

Indication	Phase 3 Protocol #	Site (Name and Address)	Number of Subjects
Bowel cleansing prior to colonoscopy			
Bowel cleansing prior to colonoscopy			

Note: International inspection requests or requests for five or more inspections require sign-off by the ORM Division Director and forwarding through the Director, DSI.

Goal Date for Completion:

We request that the inspections be performed and the Inspection Summary Results be provided by (inspection summary goal date) **January 6, 2006**. We intend to issue an action letter on this application by (action goal date) **April 10, 2006**.

Contact Information:

The contact person for this NDA is as follows:

Marilyn R. Carlson, D.M.D., M.D., RAC (US Agent)
1229 Caminito Graciela
Encinitas, California 92024
858-759-8265 (phone)
858-759-8384 (fax)

Should you require any additional information, please contact Tanya Clayton at 301-827-4005.

Concurrence: (if necessary)

Ruyi He, M.D. (Team Leader)
Brian E. Harvey, M.D., Ph.D. (Division Director)

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

/s/

Tanya Clayton
8/2/05 05:16:22 PM

Brian Harvey
8/3/05 08:26:03 AM

****
*** TX REPORT ***
****

TRANSMISSION OK

TX/RX NO	4802
CONNECTION TEL	9011441895453711
CONNECTION ID	
ST. TIME	07/06 10:14
USAGE T	00'21
PGS. SENT	2
RESULT	OK

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation III

FACSIMILE TRANSMITTAL SHEET

DATE: July 6, 2005

To: Ramona Krailler, Ph.D.	**From:** Tanya D. Clayton, BS Regulatory Project Manager
Company: US Agent for Norgine International Limited	Division of Gastrointestinal and Coagulation Drug Products
Fax number: 011-44-1895-453-711	**Fax number:** 301-443-9285
Phone number: 011-44-7795-005-484	**Phone number:** 301-827-4005

Subject: NDA 21-881 (Moviprep) Information Request

Total no. of pages including cover: 2

Comments:
Please find attached an Information Request, per our statistical reviewer

Document to be mailed: YES √NO

Please provide the following information electronically:

- Volumes 23, 24, 37, and 38 for Study NRL994-01/2001;

- Volumes 50, 51, 61, 62, and 63 for Study NRL994-02/2001.

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DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION	**REQUEST FOR CONSULTATION**

'Division/Office):	FROM:
Scott Dallas and Diane Smith, HFD-420 Parklawn 9C-15	Tanya Clayton, Regulatory Health Project Manager Parklawn, 6B-45

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
July 6, 2005		21-881	Tradename Review	June 10, 2005

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Moviprep	Standard	Laxative	February 10, 2006

NAME OF FIRM: Norgine International Limited

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE--NDA MEETING
- ☐ END OF PHASE II MEETING
- ☐ RESUBMISSION
- ☐ SAFETY/EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☒ OTHER *(SPECIFY BELOW)*: See comments below.

COMMENTS/SPECIAL INSTRUCTIONS:

This is a type 1New Drug Application that is indicated for bowel cleansing prior to colonoscopy
'he sponsor is proposing Moviprep as the tradename. The PDUFA goal date is 04/10/06. I'm attaching a copy of the proposed labeling. Also, please te that the package insert was submitted electronically, consequently, it may be found on the EDR pathway – N 21881/10June2005/labeling. Please let ıne know if you require additional information. Thank you in advance.
Tanya Clayton – 827-4005.

SIGNATURE OF REQUESTER	METHOD OF DELIVERY (Check one) ☐ MAIL ☒ HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

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/s/

Tanya Clayton
7/6/05 10:40:30 AM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO *(Division/Office)*:
Shannon Benedetto and Elaine Hu,
HFD-42, Parklawn Building, Room 17B-17

FROM:
Tanya Clayton (Regulatory Health Project Manager)
GI and Coagulation Drug Products, HFD-180,
PKLN 6B-45

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
July 5, 2005		21-881	New Drug Application	June 7, 2005

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Moviprep	Standard	Laxative	February 10, 2006

NAME OF FIRM: Norgine International Limited

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE-NDA MEETING
- ☐ END OF PHASE II MEETING
- ☐ RESUBMISSION
- ☐ SAFETY/EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☒ OTHER *(SPECIFY BELOW)*: Labeling Review

COMMENTS/SPECIAL INSTRUCTIONS:

This is a type 1New Drug Application that is indicated for bowel cleansing prior to colonoscopy [redacted]. The PDUFA goal date is 03/10/06. I'm attaching a copy of the proposed package and PI labeling. Also, please note that the labeling was submitted electronically, consequently, it may be found on the EDR pathway – N 21881/7June2005 . Please let me know if you require additional information.

Thank you in advance.

Tanya Clayton – 827-4005.

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SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

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/s/

Tanya Clayton
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DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Food and Drug Administration
Rockville, MD 20857

NDA 21-881

Norgine International Limited
Attention: Marilyn R. Carlson, D.M.D., M.D., RAC
US Agent
entreMeDica, Inc.
1229 Caminito Graciela
Encinitas, California 92024

Dear Dr. Carlson:

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

Name of Drug Product:	Moviprep (PEG 3350, sodium sulfate, sodium chloride, potassium chloride, sodium ascorbate and ascorbic acid) for oral solution
Review Priority Classification:	Standard (S)
Date of Application:	June 7, 2005
Date of Receipt:	June 10, 2005
Our Reference Number:	NDA 21-881

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 August 9, 2005 in accordance with 21 CFR 314.101(a). If the application is filed, the user fee goal date will be April 10, 2006.

Under 21 CFR 314.102(c), you may request a meeting with this Division (to be held approximately 90 days from the above receipt date) for a brief report on the status of the review but not on the ultimate approvability of the application. Alternatively, you may choose to receive a report by telephone.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We note that you have not fulfilled the requirement. We acknowledge receipt of your request for a deferral of pediatric studies for this application. Once the application has been filed, we will notify you whether we have deferred the pediatric study requirement for this application.

Please cite the NDA number listed above at the top of the first page of any communications concerning this application. Send all electronic or mixed electronic and paper submissions to the Central Document Room at the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Central Document Room (CDR)
5901-B Ammendale Road
Beltsville, MD 20705-1266

If your submission only contains paper, send it to one of the following address:

Courier/Overnight Mail/U.S. Postal Service:
Center for Drug Evaluation and Research
Division of Gastrointestinal and Coagulation Drug Products, HFD-180
Attention: Division Document Room, 8B-45
5600 Fishers Lane
Rockville, Maryland 20857

If you have any questions, call me, Regulatory Health Project Manager, at (301) 827-4005.

Sincerely,

{See appended electronic signature page}

Tanya D. Clayton, B.S.
Regulatory Health Project Manager
Division of Gastrointestinal and Coagulation
Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

Tanya Clayton
6/17/05 03:10:06 PM

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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

PIND 63,268

Norgine International, Limited
Attention: Ramona E. Krailler,
U.S. Regulatory Affairs Specialist
3751 Frondorf Avenue
Cincinnati, OH 45211

Dear Ms. Krailler:

Please refer to the meeting between representatives of your firm and the FDA on October 29, 2004. The purpose of the meeting was to discuss the protocol for establishing essential similarity of European Phase III clinical trial comparators to U.S. approved products.

The official minutes of that meeting are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 443-8017.

Sincerely,

{See appended electronic signature page}

Ryan Barraco, B.A., B.S.
Consumer Safety Officer
Division of Gastrointestinal & Coagulation Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure

MEMORANDUM OF MEETING MINUTES

MEETING DATE: October 29, 2004

TIME: 2:00 PM – 3:00 PM

LOCATION: Parklawn Building, 6B-45 Conference Room (Teleconference)

APPLICATION: PIND 63,268
Moviprep® (PEG 3350, sodium sulfate ——— , ascorbic acid, sodium ascorbate, sodium chloride and potassium chloride for oral solution)

TYPE OF MEETING: Type C

MEETING CHAIR: Dr. Ramesh Raghavachari

MEETING RECORDER: Ryan Barraco

FDA ATTENDEES, TITLES, AND OFFICE/DIVISION

Name of FDA Attendee	Title	Division Name & HFD#
1. Dr. Kathy Robie-Suh	Acting Deputy Division Director	Division of Gastrointestinal and Coagulation Drug Products (DGCDP) (HFD-180)
2. Dr. Ruyi He	Gastrointestinal Medical Officer Team Leader	DGCDP (HFD-180)
3. Dr. Sushanta Chakder	Pharmacologist	DGCDP (HFD-180)
4. Mr. Ryan Barraco	Consumer Safety Officer	DGCDP (HFD-180)
5. Dr. Eric Duffy	Director	Division of New Drug Chemistry II (DNDCII) (HFD-820)
6. Dr. Liang Zhou	Chemistry Team Leader	DNDCII (HFD-820)
7. Dr. Ramesh Raghavachari	Chemist	DNDCII (HFD-820)
8. Dr. Suresh Doddapaneni	Pharmaceutics Team Leader	Office of Clinical Pharmacology and Biopharmaceutics, Division of Pharmaceutical Evaluation II (HFD-870)

EXTERNAL CONSTITUENT (Norgine International Limited) ATTENDEES AND TITLES:

External Attendee	Title	Representing
Dr. Ramona Krailler	U.S. Regulatory Consultant	Norgine International Limited
Mr. Ian Cox	Project Manager	Norgine International Limited
Ms. Dawn Padfield	Technical Service Manager	Norgine International Limited

BACKGROUND:

Norgine International Limited submitted a Meeting Request (MR) on August 11, 2004, received August 18, 2004, for a Type C meeting for Moviprep® (PEG 3350, sodium sulfate ———— , ascorbic acid, sodium ascorbate, sodium chloride and potassium chloride for oral solution). The sponsor submitted two questions addressed to the Agency. The sponsor requested the Type C meeting to discuss the protocol for establishing essential similarity of European Phase III clinical trial comparators to U.S. approved products.

MEETING OBJECTIVES:

To reach an agreement with the Agency on the responses to the questions posed in the sponsor's background package, submitted August 11, 2004.

DISCUSSION POINTS:

In response to the sponsor's questions in their background package for the meeting, the following agreements were reached after discussion. The format provides for the sponsor's questions, followed by the Agency's responses in bold lettering.

IND 63,268/Moviprep
Norgine International, Limited
CMC Telecon

Questions and Responses:

1. Does the Division Chemistry review team agree that the proposed protocol for establishing the essential similarity of the European and US products based on USP monograph testing is adequate?

   Agency Response:

   We would consider these products to be pharmaceutically equivalent based upon formulation comparisons (quantitative/qualitative). Provide verification of formulations for GoLytely, PhospoSoda and the comparator.

2. In the event the Division Chemistry and Biopharmaceutics Review Teams DO NOT agree that the protocol is sufficient, what are the primary areas of concern and what other information would be required to demonstrate sufficient similarity?

Agency Response:

See response to question 1.

Additional Comments:

Regarding Moviprep:

- **It is not clear that ascorbic acid and sodium ascorbate are inactive ingredients. We view these as active ingredients unless you provide data to the contrary. CMC information should be provided for all active drug substances (PEG 3350, Na_2SO_4, NaCl, KCl, ascorbic acid and sodium ascorbate) or alternatively you need to cross reference appropriate DMF(s). Please refer to '*Guideline for Submitting Supporting Documentation in Drug Applications for the Manufacture of Drug Substances*,' 1987.**
    - **The sponsor stated that ascorbic acid and sodium ascorbate are active ingredients.**
- **Identify the lemon flavor, aspartame and acesulfame K manufacturer(s), and provide Certificate of Analysis (COA), and reference appropriate federal regulation for Food and Drug additives. Alternatively, provide a DMF reference with a letter of authorization.**
- **Clarify why the ascorbic acid and sodium ascorbate are to be co-packaged.**
    - **The sponsor stated that ascorbic acid and sodium ascorbate were incompatible with the rest of the ingredients.**
- **Please submit the background package from the July, 28 2004 meeting.**

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/s/

Ryan Barraco
11/19/04 08:42:06 AM

Ramesh Raghavachari
11/19/04 09:38:34 AM

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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

PIND 63,268

Norgine International Limited
Attention: Ramona Krailler, Ph.D.
Keaton House, Widewater Place
Moorhall Road
Harefield, Uxbridge, Middlesex
UB9 6NS, United Kingdom

Dear Dr. Krailler:

Please refer to your Pre-Investigational New Drug Application (PIND) file for Moviprep® (PEG 3350, Sodium Sulfate, Ascorbic Acid, Sodium Ascorbate, Sodium Chloride and Potassium Chloride for Oral Solution).

We also refer to the meeting between representatives of your firm and the FDA on July 28, 2004. The purpose of the meeting was to discuss the upcoming proposed NDA to be submitted for Moviprep®, which is indicated for use in bowel cleansing before colonoscopy [redacted].

The official minutes of that meeting are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 827-4005.

Sincerely,

{See appended electronic signature page}

Tanya Clayton, B.S.
Regulatory Project Manager
Division of Gastrointestinal and Coagulation
Drug Products, HFD-180
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure

MEMORANDUM OF MEETING MINUTES

Meeting Date: July 28, 2004

Time: 1:00-2:30 PM

Location: Parklawn Building, Conference Room C

Application: Pre-IND 63,268

Type of Meeting: Type B, Pre-NDA meeting

Meeting Chair: Hugo Gallo-Torres, M.D., Ph.D, PNS

Meeting Recorder: Tanya Clayton, B.S.

FDA Attendees, Titles, and Office/Division:

Division of Gastrointestinal and Coagulation Drug Products

Robert Justice, M.D., MSc.	Division Director
Joyce Korvick, M.D.	Deputy Director
Hugo Gallo Torres, M.D.,	Medical (GI) Team Leader
Robert Prizont, M.D.	Medical Reviewer
Jasti Choudary, Ph.D., B.V.Sc.	Supervisory Pharmacologist
Ke Zhang, Ph.D.	Pharmacology Reviewer
Stella Grosser, Ph.D.	Biometrics Team Leader
Ramesh Raghavachari, Ph.D.	Chemistry Reviewer
Tanya Clayton, B.S.	Regulatory Project Manager

External Constituent Attendees and Titles:

Norgine International Limited

Dr. Marc Halphen	Medical Director
Dr. Raymond Buck	Senior Vice President, Statistics & Data Services
Dr. Marilyn Carlson	Medical Consultant
Dr. Hillary Sheevers	Director
Norman Barras	Scientific Director
Dr. Hans-Jurgen Gruss	Medical Director, R&D Division
Ian Cox	Project Manager, R&D Division
Dr. Ramona Krailler	US Regulatory Affairs Consultant

Background:

On March 30, 2004, the previous Sponsor, [redacted], requested a type B, pre-NDA meeting for the purpose of discussing the upcoming proposed NDA to be submitted for Moviprep, which is indicated for use in bowel cleansing before colonoscopy [redacted]

A subsequent June 28, 2004 background package was submitted, which contained 4 questions for discussion.

On July 9, 2004 [redacted] faxed correspondence stating their transfer of responsibilities for this PIND to Norgine International Limited. On July 13, 2004 Norgine International Limited faxed a general correspondence accepting the transfer of responsibilities as well as provided an updated list of the attendees and agenda. The questions for discussion remained the same.

Following introductions, the Sponsor provided a brief clinical and pharmacology/toxicology presentation. After the presentation, the Sponsor agreed to proceed directly to the questions for discussion.

Discussion Points: (bullet format):

Clinical

1) Will the two European Phase 3 clinical studies be adequate to support the submission and review of a New Drug Application in the US? If the Division believes the studies are not adequate in either the quantity or quality of data please explain why and discuss in detail specific areas of concern.

   If the Division believes the European clinical studies are not adequate in either the quantity or quality of data please provide detailed recommendations on the quantity and type of data expected for an additional clinical study to be conducted in the United States, including the design of such a study, choice of control, equivalence margin, endpoints, statistical methods, and sample size.

   Agency's Response

   Phase III efficacy results based on non-inferiority analyses generally require a comparator control approved in the US. Norgine proposes to provide a full analytical bridge between the products used in the studies and the approved US products. This will be discussed further at a meeting that will include CMC and biopharm. If the comparator is not approved in the US or is not sufficiently similar to the US products, efficacy results should be based on statistical superiority of the test article over the comparator. Positive results may be the basis for submission to the Agency. Two trials are needed to show replication of efficacy results. The use of different comparators is acceptable.

2) The endoscopy studies in both European trials were recorded on videotape by the principal investigators. The primary efficacy variable in both studies was the quality of the bowel cleansing determined by a reviewer, blinded to the bowel cleansing preparation. Will the agency review team require the sponsor to submit copies of the videotape records of the endoscopies?

Agency's Response

There is no requirement for initial submission of videotapes of colonoscopies. If needed, videotapes may be requested during the review process to clarify unresolved issues.

Nonclinical Toxicology and Pharmacology

3) The Nonclinical Pharmacology and Toxicology information to be submitted in the NDA will be drawn from the published literature as well as other unpublished sources. No additional nonclinical pharmacology or toxicology studies will be conducted. Will this be adequate to support the submission and review of a New Drug Application in the US?

Agency's Response

- **No. Please refer to "Guidance for industry - M3 Nonclinical safety studies for the conduct of human clinical trials for pharmaceuticals" published in July 1997. To support your NDA submission, the following toxicity studies are needed: (1) 2 week repeated dose toxicity studies in rodents and nonrodents. The sponsor has proposed a single study in rats. The division will consider this proposal and respond to the sponsor at a later time.**

- **The following studies will not be required of Moviprep due to the fact that the sponsor has performed these studies with Movicol and will submit these studies and the literature on other components: (2) genotoxicity studies including an Ames test, an in vitro chromosomal aberration test, and an in vivo chromosomal aberration test, and (3) reproductive toxicity studies: Segment II teratology studies in rats and rabbits.**

NDA Content and Format

4) The sponsor proposes to submit the NDA in the format of the Common Technical Document. The NDA could be submitted in either electronic or paper form. Please advise your preference for the physical form of the NDA submission. Further, please advise if there are any special circumstances or requirements for such a submission. The format of tables displaying the primary efficacy and safety variables will be similar to those provided in the Meeting Information Package. Please comment or advise on additional display formats and datasets that would be useful for the review.

Agency's Response

We prefer an electronic submission.

Please clarify if you plan to submit an electronic CTD (eCTD) or a NDA in CTD format submitted in accordance with the 1999 guidance documents for electronic submissions (Regulatory Submissions in electronic Format: General Considerations and NDAs). If you plan to submit an electronic CTD (eCTD) in accordance with M2 eCTD: Electronic Common Technical Document Specification, April 2003, you will need to submit a sample for validation to the electronic document room (edr). This sample would need to be submitted prior to the submission of the NDA. If you are submitting an NDA in CTD format according to the 1999 guidance documents, please do not refer to the application as an "eCTD" or the edr will reject the submission upon receipt. Refer to the submission as a "NDA submitted according to the Guidance for Industry: Regulatory Submissions in Electronic Format".

Chemistry, Manufacturing and Controls (CMC)

At this time the sponsor has no questions related to CMC issues. If this should change during the preparation, submission or review of the NDA we may contact the Division for additional guidance and recommendations.

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/s/

Tanya Clayton
8/24/04 12:17:51 PM

Hugo Gallo Torres
8/25/04 01:55:56 PM

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NDA 21-881
Moviprep

Non-clinical Inspection Review Summary

This section is not applicable.

Tanya Clayton 3/23/06

Tanya Clayton, B.S.
Regulatory Health Project Manager

NDA 21-881
MoviPrep

Statistical Review (carcinogenicity)

This section is not applicable.

Tanya Clayton, B.S.
Regulatory Health Project Manager

NDA 21-881
MoviPrep

CAC/ECAC Report

This section is not applicable.

Tanya Clayton, B.S.
Regulatory Health Project Manager

Methods Validation

Please refer to the Chemistry Review dated April 6, 2006

NDA 21-881
MoviPrep

Stability Review (Stability)

This section is not applicable.

Tanya Clayton, B.S.
Regulatory Health Project Manager

NDA 21-881
MoviPrep

Micro Review (Validation of Sterilization)

This section is not applicable.

Tanya Clayton, B.S.
Regulatory Health Project Manager

NDA 21-881
MoviPrep

Facilities Inspection

Please refer to the Chemistry Review dated April 6, 2006

NDA 21-881
Moviprep

Abuse Liability Review

This section is not applicable.

Tanya Clayton, B.S.
Regulatory Health Project Manager

NDA 21-881
MoviPrep

Safety Update Review(s)

Please refer to the Clinical Review Memo date March 30, 2006 under the Clinical Review(s) Section of this Action Package.

Marlene G. Swider, M.H.S.A.
Regulatory Health Project Manager

NDA 21-881
Moviprep

Advisory Committee Meeting

This section is not applicable.

Tanya Clayton, B.S.
Regulatory Health Project Manager

NDA 21-881
Moviprep

Federal Register Notice(s)

This section is not applicable.

Tanya Clayton, B.S.
Regulatory Health Project Manager

NDA 21-881
Moviprep

Foreign Labeling

This section is not applicable.

Tanya Clayton 3/23/06
Tanya Clayton, B.S.
Regulatory Health Project Manager

Class Labeling

This section is not applicable.

Tanya Clayton, B.S.
Regulatory Health Project Manager

Post marketing Commitments

This section is not applicable. The Agency is not requesting Post marketing Commitments.

Tanya Clayton, B.S.
Regulatory Health Project Manager