

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**208352Orig1s000**

**OTHER ACTION LETTERS**



NDA 208352

**COMPLETE RESPONSE**

Evoform, Inc.  
Attention: John Fair  
Chief Operating Officer  
12400 High Bluff Drive, Suite 600  
San Diego, CA 92130

Dear Mr. Fair:

Please refer to your New Drug Application (NDA) dated and received July 2, 2015, and your amendments, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Amphora (lactic acid 1.76 %, citric acid 1%, and potassium bitartrate 0.4%) vaginal gel.

We have completed our review of this application, as amended, and have determined that we cannot approve this application in its present form. We have described our reasons for this action below and, where possible, our recommendations to address these issues.

**CLINICAL**

Based on the marked disparities in pregnancy, discontinuation, loss to follow-up, and adverse event reporting rates between the US and Russian cohorts in the study, we have determined that the Russian data are not generalizable to the US target population and have therefore based our approvability decision solely on the US data. As a result, and due also to the high proportion of non-evaluable cycles and the high premature discontinuation rate, the study did not provide sufficient cycles (i.e., < the 5,000 cycles we requested) for the analysis of safety and efficacy.

Throughout the course of the review, we have expressed concerns about the analyses you conducted, and indicated that we did not agree with the definition you used for on-treatment pregnancies, with the manner in which you computed “compressed cycles” for analysis after excluding non-evaluable cycles, and with your inclusion of cycles of extremely varying duration (including lengths inconsistent with ovulatory cycles) in your efficacy analysis.

We are in agreement with the revised analysis you provided in response to our communication of February 26, 2016 (Table 14.2.41 of your March 7, 2016 submission). Based on the results in the US population in this efficacy analysis, you have not provided sufficient evidence of efficacy for Amphora gel for the prevention of pregnancy, as this analysis failed to meet your prespecified non-inferiority criterion.

In terms of study conduct, we have the following two comments:

- We had advised you during review of the protocol that we were concerned that the requirement that the gel be applied no earlier than an hour before intercourse will result in a pregnancy rate that is unlikely to be achieved in actual use, when women are likely to

be less rigorous in the timing of application prior to intercourse. We recommended that a range of acceptable dosing times prior to intercourse be specified in the protocol to improve the generalizability of the results. This was not done. Further, your sensitivity analysis of efficacy according to “dosing deviations” did not address our request for efficacy data stratified by the interval between gel application and intercourse.

- The decision to avoid classifying mild genitourinary symptoms that last no more than one hour after product use as adverse events limits the conclusions that can be drawn about expected side effects with use of Amphora gel.

To address these deficiencies, you will need to conduct a new non-inferiority trial to evaluate the pregnancy rate in women using Amphora versus a nonoxynyl-9 gel. The majority of the data should come from the US population and any foreign data submitted should be generalizable to the US population (i.e., should be comparable in terms of efficacy results, rates of study completion, adverse event reporting, etc.). The statistical analysis plan should be pre-specified and submitted for review and comment prior to locking the database. Evaluable cycles should include only cycles in which trial subjects are at risk of pregnancy. Ovulatory cycles should be well-defined and cycles that fall outside of the range consistent with ovulatory cycles should be excluded from efficacy analysis.

Particular attention should be paid to obtaining detailed information on dates of menstrual cycles, intercourse and use of study drug and alternative methods of contraception, so that it can be clearly determined when women are (or are not) at risk for pregnancy. This information will allow cycles to be clearly defined for the determination of whether they are evaluable or non-evaluable. Use of an electronic diary is strongly encouraged to help minimize the amount of missing or possibly unreliable data.

### **FACILITY INSPECTIONS**

During a recent inspection of the (b) (4) manufacturing facility for this application, our field investigator conveyed deficiencies to the representative of the facility. Satisfactory resolution of these deficiencies is required before this application may be approved.

### **CENTER FOR DEVICES AND RADIOLOGICAL HEALTH**

#### **Device Description**

1. The materials of the pre-filled applicator are not consistently stated throughout the submission. There are references to (b) (4). Similarly, the Drug Master File from (b) (4) also references (b) (4). Confirm that the pre-filled applicator intended for use with Amphora gel is constructed from (b) (4).

#### **Biocompatibility**

2. In lieu of biocompatibility testing, you have referenced the wide-spread use of the applicators manufactured by (b) (4) for the past 15 years and the biocompatibility testing conducted on these materials. When comparing the materials and suppliers listed in the NDA to the information provided in the Drug Master File for the pre-filled

applicator, we note differences in the material suppliers. In addition, when reviewing the information provided in the Drug Master File, there is no biocompatibility testing on the final, finished device. Therefore, the information provided in the NDA is not sufficient to demonstrate the biocompatibility of the applicator. In order to demonstrate the biocompatibility of the final, finished device, provide the results of testing in accordance with ISO 10993, as previously requested in our comments to the pre-NDA. Commercial use of the pre-filled applicator may be leveraged to reduce the testing requirements, if (b) (4) can provide information on the number of vaginal applicators sold that are constructed of the same materials from the same suppliers proposed in the NDA and an analysis of product complaints/adverse events related to their use.

3. Similarly, a review of the master file for the disposable applicator also reveals a difference in the material supplier for the (b) (4) when compared to the NDA. In addition, the material safety information is limited to a statement that the material conforms to FDA requirements for food contact. This information is not sufficient to demonstrate the biocompatibility of the disposable applicator. As indicated above for the pre-filled applicator, biocompatibility testing in accordance with ISO 10993 should be provided disposable applicator. Also as indicated above, commercial experience with the same material from the same supplier may be leveraged to reduce the testing requirements.

#### Bench Testing

4. You have provided the results of testing that evaluated the force to deliver the gel and the force required to separate the plunger from the unit for both the pre-filled and disposable applicators. With respect to the separation forces, there was a wide range of values recorded for both applicators. While we understand that there is no unintended clinical consequence associated with separation of the plunger for the pre-filled applicator due to its design with a piston, a minimum force is necessary for the disposable applicator. Identify the minimum force that is necessary to ensure proper and accurate filling of the disposable applicator and incorporate it as a design specification. Also address the maximum acceptable force for the delivery of the gel for the disposable applicator and the pre-filled applicator.
5. You have provided testing that evaluated the compatibility of the Amphora gel with polyisoprene condoms. In the test report provided by (b) (4) dated March 5, 2015, the condom samples were not conditioned at 40° C for 60 minutes prior to testing as identified in the standard referenced in the test report (ASTM D7661) or as requested in the comments provided to the pre-NDA. Repeat the testing using samples that have been conditioned as previously requested.

#### Stability/Shelf Life

6. The stability testing for the pre-filled applicator does not include any assessments of the applicators. Testing should include an evaluation of the key performance specifications, e.g., frictional force between barrel/plunger and barrel/plunger separation force, to demonstrate that they are not adversely over the intended shelf life of the product.

Provide the results of testing that demonstrates that the performance of the pre-filled applicator is not adversely affected by aging.

7. You have conducted stability testing

(b) (4)

### **ADDITIONAL COMMENTS**

We have the following comments/recommendations that are not approvability issues:

### **CLINICAL**

You submitted an *in vitro* study (Protocol EFM-COOO 1-GMPOO 16.00) to evaluate Amphora gel when used with other common vaginal products. The test conditions in this study included temperature of ~ 25°C; you should address the impact of temperature on the stated results and justify the applicability of these results to likely *in vivo* effects at body temperature.

### **PRESCRIBING INFORMATION**

We reserve comment on the proposed labeling until the application is otherwise adequate. We encourage you to review the labeling review resources on the [PLR Requirements for Prescribing Information](#) and [Pregnancy and Lactation Labeling Final Rule](#) websites, including regulations and related guidance documents and the Selected Requirements for Prescribing Information (SRPI) – a checklist of important format items from labeling regulations and guidances.

If you revise labeling, use the SRPI checklist to ensure that the prescribing information conforms with format items in regulations and guidances. Your response must include updated content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>

### **CARTON AND CONTAINER LABELING**

Submit draft carton and container labeling revised as follows when you respond to the application deficiencies:

#### **A. Container Label (5 gram pre-filled applicators)**

1. To minimize confusion regarding the appropriate drug name, active ingredients, route of administration, and strengths, revise this information to read as follows:

Amphora  
(lactic acid, citric acid, and potassium bitartrate)  
Vaginal Gel  
1.76 %/1 %/0.4 %

2. Add a barcode to the immediate container in accordance with 21 CFR 201.25(c)(2)

3. To minimize confusion, relocate the net quantity (e.g., “5 g”) away from the route of administration (e.g., “For Vaginal Use Only”).

B.

(b) (4)

C. Carton Labeling (5 gram pre-filled applicators)

(b) (4)

1. See A.1 Above.
2. Add the intended NDC number for our review and comment. Ensure that the NDC appears on the principal display panel (PDP) and that the package codes (last 2 digits) are different between the container sizes.
3. To minimize confusion, relocate the net quantity statement to the bottom third of the label away from the product name, dosage form and strength statements.
4. Wherever it appears, revise the strength statement so that terminal zeros are not present. Specifically, revise “1.00 %” and “0.40 %” to read “1 %” and “0.4 %”, respectively, as the decimal point may be overlooked and cause confusion.
5. Add the route of administration to the Dosage and Administration Statement to minimize the risk of wrong route errors.

**PROPRIETARY NAME**

Refer to correspondence dated, September 2, 2015, which addresses the proposed proprietary name, Amphora. This name was found acceptable pending approval of the application in the current review cycle. Please resubmit the proposed proprietary name when you respond to the application deficiencies.

**SAFETY UPDATE**

When you respond to the above deficiencies, include a safety update as described at 21 CFR 314.50(d)(5)(vi)(b). The safety update should include data from all nonclinical and clinical studies/trials 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/clinical trials 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.
3. Present a retabulation of the reasons for premature trial discontinuation by incorporating the drop-outs from the newly completed trials. Describe any new trends or patterns identified.
4. Provide case report forms and narrative summaries for each patient who died during a clinical trial or who did not complete a trial because of an adverse event. In addition, provide narrative summaries for serious adverse events.
5. Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original NDA data.
6. Provide updated exposure information for the clinical studies/trials (e.g., number of subjects, person time).
7. Provide a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug marketed in other countries.
8. Provide English translations of current approved foreign labeling not previously submitted.

## **OTHER**

Within one year after the date of this letter, you are required to resubmit or take other actions available under 21 CFR 314.110. If you do not take one of these actions, we may consider your lack of response a request to withdraw the application under 21 CFR 314.65. You may also request an extension of time in which to resubmit the application. A resubmission must fully address all the deficiencies listed. A partial response to this letter will not be processed as a resubmission and will not start a new review cycle.

You may request a meeting or teleconference with us to discuss what steps you need to take before the application may be approved. If you wish to have such a meeting, submit your meeting request as described in the FDA Guidance for Industry, "Formal Meetings Between FDA and Sponsors or Applicants," May 2009 at

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM153222.pdf>.

The drug product may not be legally marketed until you have been notified in writing that this application is approved.

If you have any questions, call Charlene Williamson, Regulatory Project Manager, at (301) 796-1025.

Sincerely,

*{See appended electronic signature page}*

Audrey Gassman, M.D.  
Deputy Director  
Division of Bone, Reproductive and Urologic Products  
Office of Drug Evaluation III  
Center for Drug Evaluation and Research



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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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AUDREY L GASSMAN  
04/28/2016