CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

202408Orig1s000

OTHER ACTION LETTERS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 202408

RESCIND COMPLETE RESPONSE

Fera Pharmaceuticals, LLC
Attention: John D'Angelo, M.S., R.Ph.
Vice President Regulatory Affairs
134 Birch Hill Road
Locust Valley, NY 11560

Dear Mr. D'Angelo:

Please refer to your New Drug Application (NDA) dated and received, May 31, 2013, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Avaclyr (acyclovir ophthalmic ointment) 3%. We also refer to our letters dated March 31, 2014, and June 24, 2016, informing you that we completed our review of this application. Upon further review of this application, we have determined that our letters were issued in error.

This application is now under review. Once our review is complete, we will issue an action letter. We remind you that this drug product may not be legally marketed or promoted until you have been notified in writing that this application is approved.

If you have any questions, call Lois Almoza, M.S., Regulatory Health Project Manager, at (301) 796-1600.

Sincerely,

{See appended electronic signature page}

Wiley A. Chambers, M.D.
Deputy Director
Division of Transplant and Ophthalmology Products
Office of New Drugs
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

WILEY A CHAMBERS
03/28/2019 06:51:02 PM

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 202408

COMPLETE RESPONSE

Fera Pharmaceuticals, LLC
Attention: John D'Angelo, M.S., R.Ph.
Vice President Regulatory Affairs
134 Birch Hill Road
Locust Valley, NY. 11560

Dear Mr. D'Angelo:

Please refer to your New Drug Application (NDA) dated May 31, 2013, received May 31, 2013, and your amendments, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Avaclyr (acyclovir ophthalmic ointment) 3.0%.

We acknowledge receipt of your amendment dated December 24, 2015, which constituted a complete response to our March 31, 2014, action letter.

We also acknowledge your amendment dated June 22, 2016. This amendment was not reviewed for this action. You may incorporate applicable sections of the amendment by specific reference as part of your response to the deficiencies cited in this letter.

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 reason for this action below and, where possible, our recommendations to address this issue.

You have not provided a sufficient scientific bridge between your product and the one used in the published clinical studies. While we acknowledge you have addressed a number of the items requested in our March 31, 2014, Complete Response letter, you need to address the following remaining items or follow other options, such as conducting a controlled clinical trial with Avaclyr.

Quality and Performance Tests/In Vitro Release Testing

1. We acknowledge that you have developed an in vitro release testing (IVRT) procedure (b) (4) (b) (4) as described in USP<1724>, in an attempt to demonstrate the suitability of the IVRT method and to establish the scientific bridge between your drug product and the comparator product (Zovirax) (*In-Vitro Release Testing Report to Support Acyclovir Release Rate Comparisons from Acyclovir Ophthalmic Ointment Formulations*). However, based on the data provided, the IVRT method is found to be inadequately validated for the following reasons:

a. The method failed [redacted] Provide the investigational report and description of the final method based on any improvements.

b. Provide a full validation report of the final IVRT method, after addressing (a). Close attention should be paid to the sensitivity of the method, which is the ability to detect changes in the release rate as a function of drug concentration in the formulation.

c. It is unclear if polymorphism of the drug substance has an influence on the IVRT results (refer to Comment #2). Provide solubility data as well as intrinsic dissolution rate (as per USP <1087> Apparent Intrinsic Dissolution) for acyclovir drug substance used in your product, in Zovirax and in the [redacted] formulations. Compare this data to the literature reports, if available, for the various polymorphs of acyclovir.

Acyclovir Polymorphisms

2. We acknowledge your finding [redacted] between your drug product and the currently marketed UK Zovirax.

[redacted]

[1] Lutker, K.M. et al. Polymorphs and Hydrates of Acyclovir. J. Pharm.Sci. 2011;100 (3): 949-963.

Other Options

Alternatively, you may also propose other options, such as conducting a controlled clinical trial using your Avaclyr (acyclovir ophthalmic ointment) 3%. We encourage you to request a meeting with the division to discuss further development of your product.

LABELING

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

PROPRIETARY NAME

Please refer to correspondence dated, April 8, 2016 which addresses the proposed proprietary name, Avaclyr. 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 Lois Almoza, M.S., Regulatory Project Manager, at (301) 796-1600.

Sincerely,

{See appended electronic signature page}

Renata Albrecht, M.D.
Director
Division of Transplant and Ophthalmology Products
Office of Antimicrobial Products
Office of New Drugs
Center for Drug Evaluation and Research

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

/s/

RENATA ALBRECHT
06/24/2016

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 202408

COMPLETE RESPONSE

Fera Pharmaceuticals, LLC
Attention: John D'Angelo, M.S., R.Ph.
Vice President, Regulatory Affairs
134 Birch Hill Road
Locust Valley, NY 11560

Dear Mr. D'Angelo:

Please refer to your New Drug Application (NDA) dated May 31, 2013, received May 31, 2013, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Avaclyr (acyclovir ophthalmic ointment) 3.0%.

We acknowledge receipt of your amendments dated:

June 7, 2013 (2)	September 19, 2013	February 26, 2014
June 13, 2013	November 27, 2013	March 10, 2014
July 2, 2013	December 31, 2013	March 12, 2014
July 24, 2013	January 27, 2014	March 18, 2014
August 27, 2013	February 13, 2014	March 19, 2014
August 30, 2013	February 20, 2014	March 25, 2014 (2)

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 reason for this action below and, where possible, our recommendations to address this issue.

An application submitted under 505(b)(2) needs to provide a scientific "bridge" between the proposed product and the product used in the clinical studies submitted to the application. The information submitted to your application on July 24, 2013, March 12 and 25, 2014, is insufficient to establish a scientific "bridge" between the proposed product and the product used in the published clinical trials which are needed for the determination of the safety and efficacy of acyclovir ophthalmic ointment in the proposed indication of acute herpetic keratitis (dendritic ulcers).

To address this deficiency:

We recommend that the characterization of the 3 lots of Fera's acyclovir ophthalmic ointment 3% be compared with 3 lots (if available) of the Zovirax acyclovir ophthalmic ointment 3% product that may serve as the nominal RLD, and that the variation for measured product quality attributes fall within the variability observed for the nominal RLD.

Petrolatum

1. Petrolatum is a heterogeneous mixture of hydrocarbons that may contain varied amounts of saturated alkanes and cycloalkanes as well as unsaturated compounds, individual species of which may be liquid or solid in their purified forms. The unique heterogeneous mixture of these compounds can influence the properties of the resultant material and the performance of the dosage form. This compositional heterogeneity may be indirectly characterized as qualities of the drug product such as melting point, viscosity profile, specific gravity, etc. The specifications constrained by the tests for White Petrolatum, USP provide minimum criteria for inclusion within a grade, and are not sufficient to support a scientific bridge for product quality and performance. Further characterization of the petrolatum by the comparison of specific quality and performance attributes of the nominal RLD with Fera's acyclovir ophthalmic ointment 3% are required.

Viscosity

2. It is known that formulations of White Petrolatum, USP can exhibit non-Newtonian (shear-thinning) behavior (e.g., see Park & Song (2010) *Rheological evaluation of petroleum jelly as a base material in ointment and cream formulations with respect to rubbing onto the human body*, Korea-Australia Rheology Journal 22(4) 279-289). As such, to support a scientific bridge, we recommend that comparative viscosity profile measurements be made not only to determine the linear viscoelastic response but also to investigate the nonlinear viscosity behavior over a range of shear rates.

Quality and Performance Tests

3. We recommend that the scientific bridge be supported by the collective weight of evidence from tests representing the physical qualities as well as the performance behavior of the ophthalmic ointment. These tests of the drug product are recommended to include relevant USP methods for Melting Temperature (Class III) <741>, pH <791>, Specific Gravity <841>, Ophthalmic Ointments <771>, and Drug Release <1724>. The In Vitro Release Test (IVRT) test method for measuring drug release, performed as described in <1724>, should be validated to demonstrate the reproducibility and discrimination sensitivity of the IVRT method. Discrimination sensitivity may be demonstrated by testing of the 3% ophthalmic ointment, compared with altered (e.g., 2% and 4%) ophthalmic ointments of otherwise comparable composition, to demonstrate the sensitivity of the IVRT method to monitoring the proportionality of the release rates as a function of drug concentration, and to demonstrate the ability of the IVRT method to

detect inequivalence of the altered formulations' drug release rates to that measured for the 3% ophthalmic ointment, using the statistical methodology described in <1724>. The receptor solution may be composed of a buffer representing artificial tears, provided that adequate solubility for acyclovir exists so as not to compromise the linearity of the IVRT method, and that the method is appropriately discriminating.

Acyclovir Particle Size

5. The description of acyclovir particle size is inadequate. Because ophthalmic ointments are intended for application to the eye, special precautions must be taken in their preparation, to be free of large particles. As such, the drug substance is ideally added to the ointment base either as a solution or as a micronized powder. To support a scientific bridge, we recommend that the comparative particle size analysis be performed as a 3-tier analysis, reporting the D10, D50 and D90 particle sizes, compared for the nominal RLD and Fera's acyclovir ophthalmic ointment 3%.

Acyclovir Polymorphisms

6. We recommend that Fera characterize the polymorphic form(s) of acyclovir in the nominal RLD, and demonstrate that Fera's manufacturing process has consistently produced a drug product with a comparable polymorphic composition of acyclovir in Fera's acyclovir ophthalmic ointment 3%.

To address this deficiency, you may also propose other options, such as conducting a controlled clinical trial using your acyclovir ophthalmic ointment 3%. If you would like to discuss this or other proposed options, you may request a meeting with the Division.

LABELING

We reserve comment on the proposed labeling until the application is otherwise adequate. If you revise labeling, 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.

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Under 21 CFR 314.102(d), you may request a meeting or telephone conference 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 the FDA and Sponsors or Applicants," May 2009 at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM153222.pdf.

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Sincerely,

{See appended electronic signature page}

Renata Albrecht, M.D.
Director
Division of Transplant and Ophthalmology Products
Office of Antimicrobial Products
Office of New Drugs
Center for Drug Evaluation and Research

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/s/

RENATA ALBRECHT
03/31/2014