CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

202408Orig1s000

CLINICAL REVIEW(S)
### Summary Review #2 for Regulatory Action

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<thead>
<tr>
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<td>From</td>
<td>Renata Albrecht, MD</td>
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<td>Division of Transplant and Ophthalmology Products</td>
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<tr>
<td>Subject</td>
<td>Division Director Summary Review #2</td>
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<tr>
<td>NDA Number</td>
<td>NDA 202408</td>
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<tr>
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<td>Applicant Name</td>
<td>Fera Pharmaceuticals, LLC</td>
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<td>Date of Submission</td>
<td>May 31, 2013</td>
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<td>Date of Receipt</td>
<td>May 31, 2013</td>
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<tr>
<td>PDUFA Goal Date #1</td>
<td>March 31, 2014</td>
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<tr>
<td>Complete Response Letter</td>
<td>March 31, 2014</td>
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<td>Resubmission</td>
<td>December 24, 2015</td>
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<td>PDUFA Goal Date #2</td>
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<td>Proprietary Name / Established (USAN) Name</td>
<td>Avaclyr</td>
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<td>Formulation</td>
<td>ophthalmic ointment, 3%</td>
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**Proposed Indication(s):** treatment of acute herpetic keratitis (dendritic ulcers) in patients with herpes simplex (HSV-1 and HSV-2)  

**Action for Application:** Complete Response
NDA 202408, acyclovir ophthalmic ointment 3%
Proposed indication: treatment of acute herpetic keratitis (dendritic ulcers) in patients with herpes simplex (HSV-1 and HSV-2)

NOTE to the Reader:
The current review is only addressing the information reviewed during the resubmission of this application. The Division Director Summary Review dated 3/31/2014, along with other primary and secondary reviews should be consulted for the background and history of the application.

<table>
<thead>
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<td>Martin Nevitt, William Boyd</td>
<td>6/13/2016</td>
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<td>Pharmacology/Toxicology Review</td>
<td>Aaron Ruhland, Lori Kotch</td>
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<td>Product Quality Manufacturing Review</td>
<td>Manar Al-Ghabeish DPQR/OTR/OPQ</td>
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<td>Xiaoming Xu DPQR/OTR/OPQ</td>
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<td>Balajee Shanmugam, ATL, ONDP/OPQ</td>
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<td>Otto Townsend, Yelena Maslov</td>
<td>3/31/2016</td>
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<td>Todd Bridges</td>
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<td>Pediatric Review Committee</td>
<td>Orphan Designation – PREA does not apply</td>
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<tr>
<td>Project Manager</td>
<td>Lois Almoza</td>
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CDTL=Cross-Discipline Team Leader
OSI/DGCPC=Office of Scientific Investigations/Division of Good Clinical Practice Compliance
(formerly Division of Scientific Investigation (DSI)
OSE= Office of Surveillance and Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
OPDP/DPDP=Office of Prescription Drug Promotion/Division of Professional Drug Promotion;
formerly, DDMAC=Division of Drug Marketing, Advertising and Communication
OC = Office of Compliance
OPQ = Office of Product Quality
NDA 202408, acyclovir ophthalmic ointment 3%
Proposed indication: treatment of acute herpetic keratitis (dendritic ulcers) in patients with herpes simplex (HSV-1 and HSV-2)

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1. Summary and Recommendations

NDA 202408 is a 505(b)(2) application submitted by Fera Pharmaceuticals, LLC for Avaclyr (acyclovir ophthalmic ointment) 3% for the treatment of acute herpetic keratitis (dendritic ulcers). The applicant obtained orphan drug designation for the indication “treatment of acute herpetic keratitis associated with Herpes Simplex Virus type 1 and type 2.”

This review covers the resubmission to NDA 202408 dated December 24, 2015, with a PDUFA goal date of June 24, 2016. For complete background and summary of the findings during the first review cycle, the Division Director Summary Review dated May 31, 2014, along with reviews by all the disciplines should be consulted.

As a result of the first review cycle, the applicant was issued a Complete Response (CR) letter on March 31, 2014. Although the published studies were considered to provide evidence of safety and effectiveness, and other disciplines also found the submission to support approval of the Fera product, the deficiency consisted of the absence of a scientific “bridge.” In this 505(b)(2) application, there were no data provided in normal volunteers or patients to link the proposed Fera acyclovir ophthalmic ointment 3% to the Zovirax ophthalmic ointment 3% that was used in the 5 published clinical studies submitted to support the efficacy and safety of the product. Since four of the published studies stated the product was from Burroughs-Wellcome, now GlaxoSmithKline (GSK), FDA requested that a scientific “bridge” between the Fera and GSK product based on the physicochemical properties and in-vitro release testing on three batches of each product. In the CR letter, the applicant was advised that other approaches may be acceptable, including the conduct of a controlled clinical study with the Avaclyr product.

The May 31, 2014 CR letter made the following recommendations:

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

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1 NDA 202408, electronic document room submission dated March 12, 2014, contains all the names and a complete chronology of the mergers, showing how Burroughs Wellcome is related to GlaxoSmithKline.
NDA 202408, acyclovir ophthalmic ointment 3%
Proposed indication: treatment of acute herpetic keratitis (dendritic ulcers) in patients with herpes simplex (HSV-1 and HSV-2)

*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**
4. 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**
5. 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.

As summarized in the OPQ/OGD review dated June 17, 2016, based on the applicant’s response and comparison of 3 lots of their product and 3 lots of the UK Zovirax product, the testing results for viscosity, specific gravity, pH, melting temperature and particle size were considered acceptable. This addressed the Petrolatum, Viscosity, a portion of the Quality and Performance Tests, and Acyclovir Particle Size items from the CR letter.

However, Fera was not able to adequately address the Quality and Performance Tests/In-Vitro Release Testing and Acyclovir Polymorphism items and OPQ/OGD concluded that the scientific bridge has not been established. Therefore, the application will be issued a Complete Response action letter.

### 2. Background

Please see reviews from the first review cycle for this NDA 202408 for details.
The applicant held a pre-NDA meeting with the agency on December 6, 2010 during which the application content was discussed. During the meeting the agency advised that,

*The application needs to include adequate and well controlled studies either directly or by reference. Additional studies (clinical or non-clinical) are not expected to be needed as long as you are able to reference the Agency’s findings through a 505(b)(2) application and can link your product to the products in previous studies.*

**Scientific “Bridge” Between Fera’s Product, Listed Drugs, and Published Studies**

Following the first review cycle, Fera was issued a Complete Response (CR) letter requesting that a scientific “bridge” between the Fera and the Zovirax product used in the clinical studies be established.

Because the Fera product has not been evaluated in clinical studies and is a topical product that does not lend itself to bioequivalence studies, a scientific “bridge” based on the products’ physicochemical characteristics was recommended. This approach was able to address some of the 5 recommendations in the CR letter but did not successfully address the in vitro release testing and acyclovir polymorphism items.

**Experience in the Office of Generic Drugs**

During the first review cycle, OGD provided advice on scientific bridging based on physicochemical properties, as was done by OGD for the approval of Mylan’s ANDA 202459 for topical acyclovir ointment 5%. The Mylan product was judged to have the same properties as Zovirax® (acyclovir topical ointment) 5%, the reference listed product approved for treatment of initial genital herpes and in limited non-life-threatening mucocutaneous Herpes simplex virus infections in immunocompromised patients. Zovirax® is now licensed by Valeant; NDA 18604.

The Division Director Summary Review dated March 31, 2014 includes a discussion of these issues, including the ANDA and the related Citizen Petition FDA-2012-P-0799 from Valeant, dated July 18, 2012 and the FDA response dated December 14, 2012.

### 3. CMC/Product Quality Microbiology

See complete CMC reviews of the Fera product in the first review cycle for details. The drug substance (by reference to DMF [b] [4]) and drug product manufactured by [b] [4] were reviewed during the first cycle, and found acceptable, Compliance recommended an overall acceptable finding for the manufacturing facilities, and the CMC reviewers recommended the product for approval.

During the second review cycle, it was determined by OPQ that the December 24, 2015, submission would be reviewed by a team represented by OPQ offices (ONDP, OLDP, OPPQ and OTR) and OGD chemists, and the review would evaluate whether Fera was able to establish a scientific bridge to the GSK product based on physicochemical properties and in vitro release-testing. The following is a brief summary of their findings and recommendations (see complete review dated June 17, 2016).
NDA 202408, acyclovir ophthalmic ointment 3%
Proposed indication: treatment of acute herpetic keratitis (dendritic ulcers) in patients with herpes simplex (HSV-1 and HSV-2)

Fera’s response to the Complete Response letter of March 31, 2014, was responsive to the five items in the letter, and included additional CMC information characterizing GSK’s currently marketed European Zovirax product and comparing it to their own product. Several quality attributes such as viscosity, specific gravity, pH, melting temperature, particle size were tested by comparing three lots of Fera’s product with three lots of European marketed Zovirax. The review team concludes that the results of the characterization of the above mentioned attributes comparing the two products are acceptable.

Issues surrounding in-vitro release testing (IVRT) and Acyclovir Polymorphism testing remained outstanding. The IVRT method was determined to be inadequate and therefore a bridge between Fera’s product and the nominal RLD Zovirax (acyclophphalmic ointment), 3% was not established.

X-Ray Powder Diffraction (XRD) data presented in the resubmission found that 

A literature survey indicates that there are different polymorphs of acyclovir². The reported polymorphs include several anhydrous and hydrate forms. The XRD finding prompted the question which polymorphic form of acyclovir was used in the five clinical studies cited in Fera’s NDA; however, this information or information on other physical properties of the drug is not provided in the application.

Overall, based on [REDACTED] and the lack of a validated IVRT method, the Product Quality review team determined the NDA resubmission was deficient and recommended a Complete Response action.

4. Nonclinical Pharmacology/Toxicology

For details, see the complete Pharmacology/Toxicology reviews from the first review cycle, which included labeling revisions and recommended approval.

During the second review cycle, the reviewer clarified that the applicant now only references NDA 18604 to support nonclinical information in labeling. Nonclinical carcinogenicity studies supporting labeling are derived from the literature. This second review also provides for PLLR labeling revisions.

5. Clinical Pharmacology/Biopharmaceutics

No clinical pharmacology studies were submitted. The Clinical Pharmacology Reviewers recommended approval and labeling revisions that were incorporated.

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simplex (HSV-1 and HSV-2)

6. Clinical Microbiology/Immunology

The virology consult from DAVP recommended labeling revisions that have been incorporated
in Section 12.4 of the package insert.

7. Clinical/Statistical-Efficacy

There were no clinical studies submitted which tested the safety and efficacy of the Fera
acyclovir ophthalmic ointment 3%. The clinical studies submitted were from the published
literature. Five publications were submitted and outcomes are summarized in the table below:

Results for five double-blind, randomized studies of acyclovir versus idoxuridine;
Study 002 results are for dendritic and geographic ulcers while results for Studies 003, 004, 005 and
006 are for dendritic ulcers only

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<tr>
<th>Reference</th>
<th>FP-ACV-002</th>
<th>FP-ACV-003</th>
<th>FP-ACV-004</th>
<th>FP-ACV-005</th>
<th>FP-ACV-006</th>
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<td>Healing rates</td>
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<td></td>
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<td>Day 7</td>
<td></td>
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<td>ACV</td>
<td>19/25 (76%)</td>
<td>29/30 (97%)</td>
<td>27/28 (96%)</td>
<td>8/10 (80%)</td>
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<td>6/30 (20%)</td>
<td>22/26 (85%)</td>
<td>5/10 (50%)</td>
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<tr>
<td>ACV-IDU (95%CI)</td>
<td>+35% (+8%, +60%)</td>
<td>+77% (+57%, +88%)</td>
<td>+12% (-5%, +32%)</td>
<td>+30% (-15%, +67%)</td>
<td>-3.8% (-30%, +23%)</td>
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<td>ACV</td>
<td>23/25 (92%)</td>
<td>30/30 (100%)</td>
<td>28/28 (100%)</td>
<td>10/10 (100%)</td>
<td>22/26 (85%)</td>
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<td>IDU</td>
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<td>22/30 (73%)</td>
<td>26/26 (100%)</td>
<td>10/10 (100%)</td>
<td>24/26 (92%)</td>
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1 The healing rates were extracted from the literature and study reports. When 7 day results were not available, the applicant interpolated the 7 day results from a graph of time to healing found in the publication; this reviewer checked the interpolation.
2 The high rate of 85% for IDU in this study is for a dosage of 1% for IDU compared to 0.5% in the rest of the studies.
3 Risk differences were computed by the statistical reviewer and are based on an exact test to compare proportions. Positive risk differences favor ACV.

The clinical and statistical reviewers recommended revisions to labeling and approval in the first cycle.

During the second cycle, the DTOP Deputy Director wrote a review disagreeing that an in vitro release test (IVRT) was needed to establish a scientific “bridge” between the two drug products as recommended by the CMC reviewers and described in the Complete Response letter. For details please see the review dated 6/21/2016. Briefly the main points from that review are:
NDA 202408, acyclovir ophthalmic ointment 3%
Proposed indication: treatment of acute herpetic keratitis (dendritic ulcers) in patients with herpes
simplex (HSV-1 and HSV-2)

- The review makes statements that the Fera and GSK products should be considered to be bridged.
  
  **Comment:**
  This is not consistent with the findings by the CMC reviewers. Data to support the statement are not provided. To quote the recommendations from the CMC reviewers, “the current submission contains insufficient information to establish a bridge between the proposed product and the referenced product.”

- The CMC information in the application for the Fera product was acceptable and Compliance recommended that manufacturing facilities were overall acceptable.
  
  **Comment:**
  The review does not, however, clarify that the Fera product has not been tested in either normal volunteers or patients, and has not shown to be alike to the currently marketed UK Zovirax product or the Burroughs-Wellcome product used in the published studies.

- The ointment is placed in direct contact with the site where the disease occurs.
  
  **Comment:**
  However, the review does not provide data how the acyclovir is released from the 3% ointment, and how the product enters the corneal epithelial cells in order to impede herpes virus replication. Specifically, the mechanism of action of acyclovir is that it needs to be converted by viral thymidine kinase to acyclovir monophosphate, which is then converted by host cell guanine kinase to acyclovir diphosphate, and then by cellular enzymes (e.g., phosphoglycerate kinase, nucleoside diphosphate kinase, phosphoenol pyruvate kinase) to acyclovir triphosphate (ACV-TP). The ACV-TP, in turn, competitively inhibits and inactivates HSV-specified DNA polymerases preventing further viral DNA synthesis.

In a letter dated 6/21/2016, the DTOP Deputy Director contacted the Director of the Office of Pharmaceutical Quality expressing disagreement with the OPQ recommendation and requesting re-consideration. The OPQ Director responded, thanked the DTOP Deputy Director for the memorandum, and clarified that the OPQ decision was based on a thorough assessment of all quality-related information in the submission. The OPQ Director noted that if the quality team decided that the memo presented new information that should be considered in an updated recommendation, a separate memo will be finalized. The OPQ recommendation is a complete response action for NDA 202408.

8. Safety

The adverse reaction information is based on the submitted publications. The most common adverse reactions reported in >1% of patients were punctuate keratitis, eye pain (burning, stinging), follicular conjunctivitis, and increase lacrimation.

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9. Advisory Committee Meeting

An Advisory Committee meeting was not held for this 505(b)(2) application.

10. Pediatrics

The applicant has orphan designation for the indication “treatment of acute herpetic keratitis associated with Herpes Simplex Virus type 1 and type 2,” therefore the Pediatric Research Equity Act requirements are not applicable to this NDA.

11. Other Relevant Regulatory Issues

Compliance Inspection
Overall the Office of Compliance found manufacturing facilities acceptable.

Office of Scientific Investigation (OSI) Audits
No OSI inspections were conducted on the published clinical studies.

Debarment Certification
Fera certified that they have not and will not use in any capacity the services of any person debarred under the Federal Food Drug and Cosmetic Act, Section 306(k)(1).

Financial Disclosure
Fera states they have not conducted any clinical studies.

12. Labeling

Labeling was reviewed by the Division, DAVP (virology), DMEPA and OPDP and recommendation considered and included as applicable.

• Package insert (PI): PLR format
• Carton and Container Labels: Labels finalized
• Proprietary Name: DMEPA concluded that the proposed proprietary name Avaclyr is provisionally acceptable in the letter dated September 6, 2013 and April 21, 2016.

13. Decision/Action/Risk Benefit Assessment

Regulatory Action
A complete response will be issued, identifying the need to submit sufficient information to establish the scientific “bridge” between the Fera product and the Burroughs Wellcome product used in the published clinical trials, or to conduct a controlled clinical study with the Avaclyr product.

The following advice will be included in the CR letter:
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 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 to...

      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 formulations. Compare this data to the literature reports, if available, for the various polymorphs of acyclovir.

**Acyclovir Polymorphisms**

2. We acknowledge your finding between your drug product and the currently marketed UK Zovirax.
NDA 202408, acyclovir ophthalmic ointment 3%
Proposed indication: treatment of acute herpetic keratitis (dendritic ulcers) in patients with herpes simplex (HSV-1 and HSV-2)

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.

Risk Benefit Assessment
Acute herpetic keratitis is a viral infection that affects over 20,000 patients yearly and is the leading cause of corneal blindness in the United States and the most common source of infectious blindness in the Western world.

Acyclovir ophthalmic ointment 3% was shown to be safe and effective for the treatment of patients with herpetic keratitis (dendritic ulcers) in published clinical studies with Burroughs Wellcome/GSK product. The GSK product, Zovirax® is approved in Europe, has been marketed for decades, and is listed on the WHO list of essential medications. There is no acyclovir ophthalmic ointment approved in the US. Availability of the product would provide another treatment option.

Recommendation for other Postmarketing Requirements (PRMs) and Commitments (PMCs)
None at this time

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

/s/

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RENATA ALBRECHT
06/24/2016
1. Introduction

Acyclovir is a synthetic nucleoside analog active against herpes viruses. The drug substance is a white crystalline powder with the molecular formula of \( C_8H_7N_3O_3 \) and a molecular weight of 225.2. The maximum solubility in water at 37°C is 1.41 mg/mL. The pKa’s of acyclovir are 2.52 and 9.35.

The chemical name of acyclovir is 2-amino-1,9-dihydro-9-[(2-hydroxyethoxy)methyl]6H-purin-6-one, it has the following chemical structure:

![Chemical structure of acyclovir]

Avacyr is a sterile ointment for topical administration. Each gram of ointment contains 30 mg of acyclovir in a white petrolatum base.

2. Background

Acyclovir has been shown to be active against HSV and HZV in human clinical studies.

Acyclovir ophthalmic ointment 3% (Zovirax) has been marketed in Europe and many countries around the world for several decades. Acyclovir Ophthalmic Ointment 3% is included on the WHO List of Essentials Medicines as the first line therapy of an Ophthalmological anti-infective agent.

On December 6, 2010, a Pre-NDA meeting with the FDA was held to discuss the requirements for filing the NDA submission as a 505(b)(2) submission.
Acyclovir ophthalmic ointment, 3% was granted Orphan drug Designation on December 13, 2010.

This is a 505(b)(2) application. Zovirax (acyclovir) Ointment 5% (NDA 18-604) is claimed as the listed drug. In this application, acyclovir has been formulated for topical ophthalmic use for a new indication, i.e., treatment of acute herpetic keratitis (dendritic ulcers). The literature provided in the application describes the use of acyclovir ophthalmic ointment, 3% for this proposed ocular indication.

The application references both a listed drug (Zovirax Ointment) and published literature. Zovirax (acyclovir) Ointment 5% (NDA 18-604) is a listed drug since it was approved in 1982 and has not been withdrawn. The clinical safety and efficacy studies which supported the approval of Zovirax are not relevant to the evaluation of Avaclyr. The applicant has therefore provided literature in the form of adequate and well controlled studies which demonstrate the safety and efficacy of acyclovir ophthalmic ointment 3%.

There is no listed drug which is or has been approved that includes acyclovir in an ophthalmic dosage form.

The studies published in the literature are applicable to the proposed drug product because they were conducted with a drug product which contains, to the extent that can be determined, the same active and inactive ingredients. The proposed drug product includes acyclovir uniformly distributed throughout the drug product (as documented in the Chemistry/Manufacturing Review). No absorption or transport of the active ingredient is necessary for the drug product to reach the infected cells since the disease being treated affects only the outermost layer of the cornea. The drug product will be placed in direct contact with the site where the disease occurs (on the corneal epithelium). There is no known interaction between the active ingredient and the base ingredient of the formulation. The drug substance has been shown in vitro to be incorporated into cells infected with herpes simplex virus when the drug is placed in direct contact with the cells.

See Medical Officer’s review dated 2/18/14 and the CDTL memorandum dated 3/28/14.

On March 31, 2014, a Complete Response Letter was issued to NDA 202408. The Complete Response Letter states as the single deficiency that the application is lacking a scientific “bridge” between the proposed product and the product used in the clinical studies submitted to the application. The letter further states that the information submitted in the application was considered insufficient to establish a scientific “bridge” between the proposed product and the product used in the published clinical trials. The “bridge” was described as being needed for the determination of the safety and efficacy of acyclovir ophthalmic ointment in the proposed indication of acute herpetic keratitis (dendritic ulcers).

A Class 2 Resubmission was received on 12/24/15.
3. CMC

The original primary Chemistry Review finalized 2/24/2014 did not recommend approval “until finalized of the post approval stability protocol and completion of the label by the project team.”

The primary Chemistry addendum dated 3/13/2014 recommended approval, stating, “…The post approval studies protocol is now acceptable. The NDA has provided sufficient CMC information to assure the identity, strength, purity and quality of the drug product. The labeling is finalized by the team. Therefore, from CMC perspective, the application is recommended for approval.”

The primary Chemistry memorandum dated 3/27/2014 recommended approval, stating, “…Three new amendments, Sequence #18, 19 and 20, were submitted March 19-25, 2014. The new amendments are reviewed below. The risk of leachables from the container closure system is found to be minimal. The overall conclusion recommending approval of NDA 202408 from a CMC perspective remains unchanged.”

The tertiary Chemistry review dated 3/31/2014 recommended approval, stating:

…The 27 MAR-2014 Memorandum to Chemistry Review #1 provides updated review comments for amendments #18-20 and confirms that the previous approval recommendation remains unchanged. The memorandum also summarized scientific bridging information requested in a 14-MAR-2014 Information Request. The primary reviewer states that “Overall, from the product quality consideration, the test results of the Fera and Zovirax drug product attributes evaluated appear to be similar.”

It is important to note that the provided CMC data are preliminary and do not sufficiently establish a bridge between the Fera and Zovirax products. Accordingly, there is no confirmation of CMC equivalence and/or comparability (or lack thereof) between the Fera and Zovirax products. It is also important to note that the reviewer’s assessment of “similarity” is very specific to the test results only, and no inference of comparability and/or equivalence between the two products can be assumed based solely on the similarity of those test results.

I concur with the findings of the CMC review team. Based on the information provided, the overall CMC recommendation remains as an approval recommendation for this NDA.

From the Office of Generic Drugs consult dated 3/31/2014:

The Director of the Division of Transplant and Ophthalmology Products (OAP/OND/CDER/FDA) requested a consult from the Office of Generic Drugs OGD regarding “whether the comparative information provided by Fera, comparing the Glaxo/Burroughs Wellcome product used in the published clinical trials and the Fera-manufactured product in this NDA, is sufficient to conclude that Fera has established a scientific “bridge” between these two products needed to support this 505(b)(2) application, or whether Fera needs to provide any additional information.”
The OGD general comments and the comments regarding viscosity, quality performance tests, and acyclovir particle size and acyclovir polymorphism were utilized to craft the Complete Response Letter dated 3/31/2014.

From the primary Chemistry Review of this Class 2 Resubmission finalized 6/17/2016:

...In response to addressing the recommendations provided in the Complete Response, the applicant submitted additional CMC information characterizing GSK’s currently marketed Zovirax and comparing it to their own product. Several quality attributes such as viscosity, specific gravity, pH, melting temperature, particle size were tested by comparing three lots of Fera’s product with three lots of U.K. marketed Zovirax. The review team concludes that the results of the characterization of the above mentioned attributes comparing the two products are acceptable (details in the review section below). Issues still surrounding IVRT and Polymorphism are discussed below.

...the in-vitro release testing (IVRT) method has been determined to be inadequate and therefore a bridge between Fera’s product and the nominal RLD Zovirax (acyclovir ophthalmic ointment), 3% has not been established given an inadequate method for in-vitro release testing. During the review cycle, the team generated several IR issues involving the study reports submitted, including IVRT method development. Since Fera has been unable to develop a IVRT method, we requested that they evaluate the impact of several factors in developing a validated IVRT method. As of the review date Fera has not submitted a response.

The Product Quality review team determined the NDA resubmission to be deficient and recommended a Complete Response for the Class 2 Resubmission.

The following comments were provided in the CMC Addendum dated 6/23/2016 for inclusion in the Action Letter:

1. We acknowledge that you have developed an in vitro release testing (IVRT) procedure 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 in developing a validated IVRT method.

Reference ID: 3949333
2. We acknowledge your finding between your drug product and Zovirax.

3. We acknowledge your amendment dated June 22, 2016. However, as it was submitted at a very late stage in the review cycle we are unable to review the information provided.

4. Nonclinical Pharmacology/Toxicology

See the original Pharmacology/Toxicology Review finalized 2/24/2014.

From the Pharmacology/Toxicology Review of this Class 2 Resubmission finalized 5/23/2016:

This review represents a revision to the review of the original NDA application. The original application received a complete response letter regarding CMC issues and was not approved during the first cycle. In this second cycle of review, the applicant only references a single listed drug (NDA 018604: Zovirax topical ointment 5%) for 505(b)(2) approval which no longer allows reference to other approved formulations of acyclovir which describe the lack of carcinogenic potential of acyclovir. A published reference was found, however, and the data which describe carcinogenicity assays can be included in the labeling1. The second cycle of review also allows the opportunity to convert the label to PLLR format.
5. Clinical Pharmacology/Biopharmaceutics

No Clinical Pharmacology Review was completed for this Class2 resubmission.

From the original Clinical Pharmacology Review finalized 2/19/14:

No new clinical pharmacology studies were conducted for this NDA. Acyclovir ophthalmic ointment 3.0% (30 mg/g) is a sterile drug product

6. Product Quality Microbiology

See the original Product Quality Micro Review dated 1/23/14.

7. Clinical/Statistical- Efficacy

See the original Clinical Review dated 2/18/14.

No new clinical studies were conducted for this NDA.

8. Safety

See the original Clinical Review dated 2/18/14.

No new clinical studies were conducted for this NDA.

9. Advisory Committee Meeting

No Advisory Committee Meeting was held. There were no new issues raised in the review of the application which were thought to benefit from an Advisory Committee Meeting.

10. Pediatrics

This drug product has been designated an orphan drug and hence, is exempt from the pediatric assessment requirement under 21 CFR 314.55(d). Safety and efficacy in pediatric patients below the age of 2 years have not been established.

11. Other Relevant Regulatory Issues

BIOSTATISTICS
No Biostatistics Review was completed for this Class 2 resubmission. See the original Biostatistics Review finalized 2/19/14:

DMEPA
The proposed proprietary name, Avaclyr, was found acceptable from both a promotional and safety perspective, and Fera Pharmaceuticals, Inc. was informed in a letter dated 4/8/2016.

DMEPA provided formal labeling comments for the original package insert and carton and container labeling in a review dated 10/24/2013 and for the revised labeling in a review dated 3/31/2016.

OFFICE OF PRESCRIPTION DRUG PROMOTION (OPDP)
OPDP completed a review of the substantially complete labeling on 2/25/14. A number of the suggested revisions could not be made because this application is a literature-based, 505(b)(2) application. A teleconference was held between this reviewer and the OPDP reviewer on 2/26/14 to discuss.

FINANCIAL DISCLOSURE
This is a 505(b)(2) application. There are no covered clinical studies in this application.

OSI
An Office of Scientific Investigations (OSI) audit was not requested; this is a 505(b)(2) application.

12. Labeling

NDA 202408 for Avaclyr (acyclovir ophthalmic ointment) 3%, is recommended for approval for the treatment of treatment of acute herpetic keratitis (dendritic ulcers) with the revised package insert and carton and container labeling submitted by the applicant on 5/25/16.

13. Recommendations/Risk Benefit Assessment
NDA 202408 for Avaclyr (acyclovir ophthalmic ointment) 3%, is recommended for approval for the treatment of treatment of acute herpetic keratitis (dendritic ulcers) with the revised package insert and with the suggested revisions to carton and container labeling found here.

In this opinion of this reviewer, the description of the manufacturing process used to produce the proposed product along with the chemical identity tests and specifications proposed for the product are sufficient to scientifically conclude that the proposed product can be expected to produce clinical results consistent with the product used in the clinical trials.

The characterization of acyclovir ophthalmic ointment as requested in the Complete Response Letter was not performed on the product used in the clinical trials and is not included in the specifications for the marketed Zovirax ophthalmic product. The Zovirax ophthalmic product with which the applicant has been requested to compare their product is not an approved product in the United States. The requests for additional information by Product Quality are inconsistent with the information required during the review of other ophthalmic new drug applications or abbreviated ophthalmic new drug applications accepted for review and/or approved.

1) Specifically, the request for an in-vitro release testing (IVRT) method for this drug product runs counter to United States Pharmacopeia recommendation in Chapter <1771> Ophthalmic Products – Performance Tests:

   …This chapter provides information on performance tests to assess drug release from finished ophthalmic products. These tests are applicable to products that have an extended-release mechanism (beyond 1 day); the dissolution/drug release rate is rate limiting for absorption and is expected to provide a controlled therapeutic response.

   …For products having a localized and immediate response when applied to the eye (e.g., topically applied dosage forms, including dispersed systems, having very short residence time for absorption), a dissolution/drug release test may have no practical value.

2) Specifically, the request to characterize the polymorphic form(s) of acyclovir is inconsistent with the information required during the review of other ophthalmic new drug applications or abbreviated ophthalmic new drug applications accepted for review and/or approved. The polymorphic forms of acyclovir and the available evidence indicates that is not relevant for this indication where the drug product is in direct contact with the cornea and the infecting organism.

There is adequate information in the literature to demonstrate that the active ingredient, acyclovir, a synthetic purine nucleoside analogue antiviral agent, inhibits replication of herpes viruses both in vitro and in vivo. Sensitive human viruses include herpes simplex virus (HSV, types 1 and 2) and varicella-zoster virus (VZV).

The submitted studies in this NDA support a favorable risk benefit profile regarding the safety and efficacy of acyclovir in the treatment of acute herpes simplex keratitis (dendritic ulcer).
The most common adverse events (>1%) were punctate keratitis, and eye pain (burning, stinging), follicular conjunctivitis, and increased lacrimation.
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

WILLIAM M BOYD
06/24/2016

WILEY A CHAMBERS
06/24/2016
1. Introduction
Acyclovir is a synthetic nucleoside analog active against herpes viruses. The drug substance is a white crystalline powder with the molecular formula of \(\text{C}_8\text{H}_{11}\text{N}_2\text{O}_3\) and a molecular weight of 225.2. The maximum solubility in water at \(37^\circ\text{C}\) is 1.41 mg/mL. The pKa’s of acyclovir are 2.52 and 9.35. The chemical name of acyclovir is 2-amino-1,9-dihydro-9-[(2-hydroxyethoxy)methyl]6H-purin-6-one, it has the following chemical structure:

![Chemical structure of acyclovir](image)

Avaclyr is a sterile ointment for topical administration. Each gram of ointment contains 30 mg of acyclovir in a white petrolatum base.

2. Background
Acyclovir ophthalmic ointment 3% was developed in the mid-1980s by Burroughs-Wellcome under IND 13,923. At the same time, Burroughs-Wellcome developed IND 3949056 for Viroptic (trifluridine ophthalmic solution). Burroughs submitted an NDA for Viroptic in the United States, but never submitted an NDA for acyclovir ophthalmic ointment. Burroughs did submit a marketing application in Europe. Following various corporate mergers, GalaxoSmithKline now markets acyclovir ophthalmic ointment in Europe. Based on meetings with the firm, GlaxoSmithKline does not have access to the original studies conducted with the product, although several have been published.

Acyclovir ophthalmic ointment has been marketed in Europe and several countries around the world for over three decades.

There is no evidence that any formulation of acyclovir ophthalmic ointment other than the one proposed for marketing in this application (acyclovir USP mixed with white petrolatum, USP) has been used in any clinical trial or marketed. The manufacturing synthesis of the drug substance, acyclovir, has changed multiple times and it does not appear that any product is currently (or has been for years) manufactured exactly the same way it was manufactured for the clinical trials. Manufacturing differences have not had an impact on this product because there are only two
ingredients in the formulation and the active ingredient is placed in direct contact with the infected tissue.

The present application was submitted as a 505(b)(2) application. Zovirax (acyclovir) Ointment 0.5% (NDA 18-604) was cited as the listed drug. Zovirax (acyclovir) Ointment 5% has a different formulation, a different indication, a different site of use, and a different concentration. It does include the same active ingredient. Zovirax is indicated in the management of initial genital herpes and in limited non-life-threatening mucocutaneous Herpes simplex virus infections in immunocompromised patients. Zovirax is not approved in the United States as an ophthalmic dosage form; however it is approved in other dosage forms such as tablets, capsules, suspension, cream, ointment, and injectable.

Zovirax ointment with its different formulation is intended for use on the skin, but not the eye. In this application, acyclovir has been formulated for topical ophthalmic use for a new indication, i.e., treatment of acute herpetic keratitis (dendritic ulcers). The application references studies in the literature to support the safety and efficacy of acyclovir ophthalmic ointment, 3% for this proposed ocular indication.

3. Product Quality

The original CMC review recommended approval. The drug substance information for Acyclovir is referenced through Drug Master File (DMF) and a letter of authorization was provided in the NDA on January 25, 2012. The DMF holder is

Acyclovir, USP is purchased from

Microbiological control of the drug

substance includes

(b)(4)

(b)(4)

(b)(4)
The container/closure system that will be used for the commercial drug product is a 3.5 g pre-printed tin tube with a black low density polyethylene cap. The tubes are purchased from [Redacted].

Validation of drug product container/closure (C/C) integrity was demonstrated via microbial challenge by Altana Inc. Pharmaceutical Group, and reported in Validation Study # V-N-0000-16.12, dated October 20, 2003.

Product development of the acyclovir formula and dosage form was undertaken by [Redacted] on behalf of Fera Pharmaceuticals. The drug product is an [Redacted] above the label claim.

Ophthalmic products are required to list all active and inactive ingredients.

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Amount/gm</th>
<th>Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acyclovir, USP</td>
<td>30 mg</td>
<td>Active</td>
</tr>
<tr>
<td>White petrolatum, USP</td>
<td></td>
<td>Base</td>
</tr>
</tbody>
</table>

**Drug Product Specifications:**

**Test**                      | **Acceptance Criteria**                                                                 |
---                            |------------------------------------------------------------------------------------------|
Description                   | Soft white ointment without visible discoloration                                         |
ID                             | Retention time of major peak is same for std and sample                                  |
ID IR                          | IR absorption spectrum of the preparation of the test preparation exhibits maxima only at the same wavelengths as that of a similar preparation of the reference standard. |
Assay (30 mg/g)                | % label claim                                                                            |

**Related Substances and Impurities**

<table>
<thead>
<tr>
<th></th>
<th>NMT %</th>
<th>NMT %</th>
<th>NMT %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Individual unknown</td>
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<td></td>
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<tr>
<td>Total known and unknown</td>
<td>NMT</td>
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<td></td>
</tr>
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</table>
## Deputy Division Director Review

**Wiley A. Chambers, M.D.**

**NDA 202408**

**Avacyr (acyclovir ophthalmic ointment) 3%**

<table>
<thead>
<tr>
<th>Test</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minimum Fill</td>
<td>NMT</td>
</tr>
<tr>
<td>Metal Particles</td>
<td>NMT</td>
</tr>
<tr>
<td>Leak Test</td>
<td>No leakage in tubes</td>
</tr>
<tr>
<td>Sterility</td>
<td>Complies with USP &lt;71&gt;</td>
</tr>
<tr>
<td>Particle size</td>
<td></td>
</tr>
<tr>
<td>Less than [10]μm</td>
<td>NLT [8]%</td>
</tr>
<tr>
<td>Less than [8]μm</td>
<td>NLT [9]%</td>
</tr>
<tr>
<td>Kinematic viscosity</td>
<td>[4] cSt</td>
</tr>
<tr>
<td>Residual solvents</td>
<td>Complies with USP 467</td>
</tr>
<tr>
<td>Homogeneity</td>
<td></td>
</tr>
<tr>
<td>Assay</td>
<td>[59]% label claim</td>
</tr>
</tbody>
</table>

**INSPECTIONS:**

The Office of Compliance has made an “Overall Acceptable” recommendation for the manufacturing sites.

### 4. 505(b)(2) Bridging

The present application was submitted as a 505(b)(2) application. The application references both a listed drug (Zovirax Ointment) and published literature. Zovirax (acyclovir) Ointment 0.5% (NDA 18-604) is a listed drug since it was approved in 1982 and has not been withdrawn. The clinical safety and efficacy studies which supported the approval of Zovirax are not relevant to the evaluation of Avacyr. The applicant has therefore provided literature in the form of adequate and well controlled studies which demonstrate the safety and efficacy of acyclovir ophthalmic ointment 3%.

There is no listed drug which is or has been approved that includes acyclovir in an ophthalmic dosage form.
Deputy Division Director Review
Wiley A. Chambers, M.D.
NDA 202408
Avaclyr (acyclovir ophthalmic ointment) 3%

The studies published in the literature are applicable to the proposed drug product because they were conducted with a drug product which contains, to the extent that can be determined, the same active and inactive ingredients \(^{(b)(4)}\). The proposed drug product includes acyclovir uniformly distributed throughout the drug product (as documented in the Chemistry/Manufacturing Review). No absorption or transport of the active ingredient is necessary for the drug product to reach the infected cells since the disease being treated affects only the outermost layer of the cornea. The drug product will be placed in direct contact with the site where the disease occurs (on the corneal epithelium). There is no known interaction between the active ingredient and the base ingredient of the formulation. The drug substance has been shown \textit{in vitro} to be incorporated into cells infected with herpes simplex virus when the drug is placed in direct contact with the cells.

The Office of Product Quality does not recommend approval of the application. In response to the recommendations provided in the Complete Response issued for this application, the applicant submitted additional CMC information characterizing GSK’s currently marketed Zovirax and comparing it to their own product. Several quality attributes such as viscosity, specific gravity, pH, melting temperature, particle size were tested by comparing three lots of Fera’s product with three lots of U.K. marketed Zovirax. The OPQ review team concluded that the results of the characterization of the above mentioned attributes comparing the two products are acceptable, however issues still remained surrounding IVRT and Polymorphism. The in-vitro release testing (IVRT) method has been determined to be inadequate and therefore OPQ review team concluded that a bridge between Fera’s product and the nominal RLD Zovirax (acyclovir ophthalmic ointment), 3% has not been established given an inadequate method for in-vitro release testing. During the review cycle, the OPQ team generated several IR issues involving the study reports submitted, including IVRT method development. Since Fera has been unable to develop a IVRT method, the OPQ review team requested that they evaluate the impact of several factors \(^{(b)(4)}\) in developing a validated IVRT method. As of the review date Fera has not submitted a response.

I disagree with the OPQ review because the reviewer’s recommendations:

a) conflict with the United States Pharmacopeia chapter <1771>,

b) conflict with prior Agency actions on at least 40 anti-infective ophthalmic ointment ANDAs,

c) proposes to compare the drug product’s absorption through an IVRT model which is not applicable to ophthalmic drugs products, does not measure the active drug substance at the site of action, does not mimic the method of administration or the in vivo conditions and has never been correlated with the ability to predict in vivo performance.

Bacterial or viral conjunctivitis are bacterial and viral infections of the conjunctival surface, respectively. Bacterial, fungal or viral keratitis are bacterial, fungal or viral infections of the cornea surface. Each of these ocular surface infections is treated with a topical anti-infective applied directly to the surface of the cornea or conjunctiva. Ophthalmic ointments are dosage formulations designed to place an anti-infective drug substance in close proximity to the infecting organism so that the drug substance can interfere with the life cycle of the infecting organism and assist the body in resolving the infection. For example, in herpes keratitis, the infected cells are shown by green arrows on the surface of the cornea.
The United States Pharmacopeia has two chapters on Performance Tests. One is titled Ophthalmic Products- Performance Tests <1771> and the other is titled Semisolid Drug Products- Performance Tests <1724>. Chapter <1771> is the newer chapter and was written to distinguish the special considerations for ophthalmic products. Chapter <1771> states, “For products having a localized and immediate response when applied to the eye (e.g., topically applied dosage forms, including dispersed systems, having very short residence time for absorption), a dissolution/drug release test may have no practical value. Application of a dissolution/drug release test to assess performance as a surrogate for in vivo testing should be considered only with appropriately validated in vivo-in vitro correlations.”

The OPQ review team has concluded that a scientific bridge in the case of Acyclovir Ophthalmic Ointment cannot be made because the applicant has not been able to develop a validated In Vitro Release Test (IVRT) following <1724> of the USP. The request to follow <1724> for an ophthalmic drug product is not consistent with the USP because it is not the correct chapter for an ophthalmic product. Chapter <1771> would be the appropriate chapter, and it does not recommend the use of a drug release test for a topically applied dosage form such as an anti-infective ophthalmic ointment.

The requirement to develop and validate an IVRT test for an ophthalmic drug product is not consistent with prior reviews and approvals of ophthalmic drug products. There are no validated IVRTs for any ophthalmic products. There is no approved ophthalmic product with an IVRT. Abbreviated new drug applications (ANDAs) for anti-infective ophthalmic drug products which are currently approved include:

<table>
<thead>
<tr>
<th>ANDA Number</th>
<th>Active Ingredient(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>060687</td>
<td>BACITRACIN</td>
</tr>
<tr>
<td>060734</td>
<td>BACITRACIN</td>
</tr>
<tr>
<td>061212</td>
<td>BACITRACIN</td>
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<td>062158</td>
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<tr>
<td>062453</td>
<td>BACITRACIN</td>
</tr>
<tr>
<td>061229</td>
<td>BACITRACIN ZINC;POLYMIXIN B SULFATE</td>
</tr>
<tr>
<td>062430</td>
<td>BACITRACIN ZINC;POLYMIXIN B SULFATE</td>
</tr>
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<td>BACITRACIN ZINC;POLYMIXIN B SULFATE</td>
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<td>BACITRACIN ZINC;POLYMIXIN B SULFATE</td>
</tr>
<tr>
<td>065022</td>
<td>BACITRACIN ZINC;POLYMIXIN B SULFATE</td>
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<tr>
<td>062167</td>
<td>BACITRACIN-NEOMYCYCN-POLYMIXIN</td>
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</tr>
<tr>
<td>061648</td>
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</tr>
</tbody>
</table>
Deputy Division Director Review
Wiley A. Chambers, M.D.
NDA 202408
Avaclyr (acyclovir ophthalmic ointment) 3%

061187  CHLORAMPHENICOL
062439  CHLORAMPHENICOL
062446  ERYTHROMYCIN
062447  ERYTHROMYCIN
062481  ERYTHROMYCIN
064030  ERYTHROMYCIN
064067  ERYTHROMYCIN
062443  GENTAMICIN SULFATE
062501  GENTAMICIN SULFATE
065024  GENTAMICIN SULFATE
064093  GENTAMICIN SULFATE
060442  NEOMYCIN SULFATE
061045  NEOMYCIN SULFATE
062566  NEOMYCIN SULFATE
060478  NEOMYCIN SULFATE
060610  NEOMYCIN SULFATE
060932  NEOMYCIN SULFATE; GRAMICIDIN
060647  NEOMYCIN SULFATE; POLYMYXIN B SULFATES; BACITRACIN ZINC
060764  NEOMYCIN SULFATE; POLYMYXIN B SULFATES; BACITRACIN ZINC
062386  NEOMYCIN SULFATE; POLYMYXIN B SULFATES; BACITRACIN ZINC
064064  NEOMYCIN SULFATE; POLYMYXIN B SULFATES; BACITRACIN ZINC
065088  NEOMYCIN SULFATE; POLYMYXIN B SULFATES; BACITRACIN ZINC
061291  NEOMYCIN SULFATE; POLYMYXIN B SULFATES; BACITRACIN ZINC
061048  NEOMYCIN SULFATE; POLYMYXIN B SULFATES; BACITRACIN
061015  OXYTETRACYCLINE HYDROCHLORIDE; POLYMYXIN B SULFATE
060696  PENICILLIN G POTASSIUM
080029  SULFACETAMIDE SODIUM
084015  SULFACETAMIDE SODIUM
080021  SULFACETAMIDE SODIUM
088000  SULFACETAMIDE SODIUM
080023  SULFISOXAZOLE DIOLAMINE

Although most of these products were reviewed for their approved indications under the Drug Efficacy Study Implementation (DESI); the approval for Erythromycin Ophthalmic Ointment for the prevention of Ophthalmia Neonatorum was not reviewed under DESI and is the most common use of Erythromycin Ophthalmic Ointment. All of these applications were approved without an IVRT comparison (bridge). All of the comparisons between the drug product proposed in the ANDA application and the innovator product were performed on the basis of a chemical identification and quantification of the active and inactive ingredients. There were no required tests of chemical or physical properties of the drug products to establish a bridge.

The IVRT models proposed in the USP <1724> are based on the following theory:

“A thick layer of the semisolid product under evaluation is placed in contact with a medium in a reservoir, and the latter acts as a receptor when the drug substance diffuses through the formulation, across the membrane, and into the reservoir. Diffusion occurs across an inert, highly permeable support membrane. The membrane is intended to keep the product and the receptor medium separate and distinct. Membranes should offer the least possible diffusional resistance and should not be rate controlling. Samples are withdrawn from the receptor chamber, typically at 1-h intervals over a 4–6 h period. After a short lag period, release of drug from the semisolid dosage form is kinetically described.
by diffusion of a chemical out of a semi-infinite medium into a sink. The momentary release rate tracks the depth of penetration of the forming gradient within the semisolid.”

In contrast to settings on the skin or on other mucous membranes where the stationary placement of the drug product under a patch or with the aid of gravity allows a diffusion gradient to develop, eyelid motion and ocular movement create a setting where there is frequent mixing of the ointment and significant sheer forces. Every few seconds, the lids push and then pull a new thin layer of the ointment over the cornea and conjunctiva. In addition, the orientation of the diffusion gradient is not necessarily vertical in the eye. Movement of the head may lead to vertical, horizontal or intermediate orientations. The chances that any of the models described in the USP could correctly distinguish clinically significant formulation and/or manufacturing differences between products is remote.

Anti-infective ophthalmic ointments do not require diffusion for the drug product to have an effect. Ophthalmic ointments can physically hold the drug substance at the site of action, in contact with the offending infective organisms. The drug substance may become absorbed through the cornea or conjunctiva, but it is not required to do so in order to have an effect on the site of infection. Absorbed drug product in the eye is replaced on the corneal and conjunctival surface by eyelid action. The concentration applied directly to the site is much higher than that needed to have a clinical effect. The concentration of all of the ophthalmic anti-infective products is orders of magnitude greater than the typical minimal inhibitory concentration needed to kill or inhibit the source of the infection.

While it is recognized that an IVRT does not necessarily need to be able to predict in vivo performance to be a useful test, USP <1771> states that “test conditions should reasonably mimic the method of administration of the product and in vivo conditions to establish, if possible, an in vivo-in vitro correlation that can be used to predict in vivo performance of the product.” Tests described in chapter <1724> do not mimic the method of administration of any ophthalmic anti-infective ointment.

For these reasons, there is a disagreement with the requirement to use an IVRT method to establish a bridge between formulations of topical ophthalmic anti-infective ointments. It is recommended that anti-infective ophthalmic ointments which have their intended site of action on the surface of the cornea or conjunctiva be considered to be bridged if their active and inactive ingredients are qualitatively and quantitatively the same based on chemical identification and assay tests.

5. Nonclinical Pharmacology/Toxicology

All nonclinical data were derived from the referenced drug or published literature reports. The published literature is applicable because it includes the same active ingredient. While the relevant literature is not limited to studies with the current formulation, the regulations permit reference to nonclinical studies conducted with different dosage forms and different drug products including different concentrations. The literature referenced by the applicant supports previous findings detailed in the labeling for the listed acyclovir drug products. Systemic exposure following topical
ocular administration is minimal, particularly when compared to the approved intravenous dose. Systemic toxicity following topical ophthalmic administration was not observed. In neonatal rats administered acyclovir subcutaneously, lower body weight gain, injection site reactions and findings related to renal pathology including increased BUN and cellular debris in the collecting ducts and Loop of Henle were observed in animals treated in rats treated with 80 mg/kg/day. Intravenous acyclovir is approved in neonates at a dose of 10 mg/kg infused at a constant rate over 1 hour, every 8 hours for 10 days.

6. Clinical Pharmacology/Biopharmaceutics

No new clinical pharmacology studies were conducted for this NDA.

7. Clinical/Statistical - Efficacy

A total of 5 published clinical studies were presented. The control in these trials was idoxuridine ophthalmic solution (IDU). IDU was the subject of several approved new drug applications for the treatment of herpes simplex keratitis. The new drug applications for IDU were supported by adequate and well controlled studies which demonstrated the superiority of IDU over its vehicle.

The original results of the acyclovir ophthalmic ointment studies demonstrated the safety and efficacy of Acyclovir Ophthalmic Ointment 3% for the treatment of acute herpetic keratitis (dendritic ulcers) in patients with herpes simplex virus. The dosage regimen, patient demographics and study objectives and endpoints were consistent across the 5 studies. One or more of the following efficacy endpoints in the original publications included:

- Time to ulcer healing
- Ulcer healing rate at Day 7
- Ulcer healing rate at the end of the study

Since the healing rate at Day 7 is considered to be an important endpoint for the proposed indication and not all of the original publications provided an analysis at this time point, all studies were reanalyzed to confirm the Day 7 healing rate.

Analysis of Primary Endpoint(s)

The primary efficacy endpoint used in the review of this NDA is cure rate (healed ulcers) at Day 7.

<table>
<thead>
<tr>
<th>First Author</th>
<th>Year</th>
<th>Control</th>
<th>Acyclovir Cures n/N (%)</th>
<th>IDU Cures n/N (%)</th>
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</thead>
<tbody>
<tr>
<td>Colin</td>
<td>1981</td>
<td>IDU</td>
<td>19/25 (76)</td>
<td>11/27 (41)</td>
</tr>
<tr>
<td>Collum</td>
<td>1980</td>
<td>IDU</td>
<td>29/30 (97)</td>
<td>6/30 (20)</td>
</tr>
<tr>
<td>Coster</td>
<td>1980</td>
<td>IDU</td>
<td>27/28 (96)</td>
<td>22/26 (85)</td>
</tr>
<tr>
<td>Klauber</td>
<td>1982</td>
<td>IDU</td>
<td>8/10 (80)</td>
<td>5/10 (50)</td>
</tr>
<tr>
<td>McCulley</td>
<td>1982</td>
<td>IDU</td>
<td>16/26 (62)</td>
<td>17/26 (65)</td>
</tr>
<tr>
<td>Average (95% CI)</td>
<td>IDU</td>
<td>99/119 (83) (76% - 90%)</td>
<td>60/119 (50) (41% - 59%)</td>
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Source: Fera Section 2.5 Table 1

Acyclovir 3% is superior to IDU for the treatment of dendritic ulcers in the Day 7 ulcer healing rates in all of the studies.
Results for five double-blind, randomized studies of acyclovir versus idoxuridine; Study 002 results are for dendritic and geographic ulcers while results for Studies 003, 004, 005 and 006 are for dendritic ulcers only

<table>
<thead>
<tr>
<th>Reference</th>
<th>FP-ACV-002</th>
<th>FP-ACV-003</th>
<th>FP-ACV-004</th>
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<td>IDU</td>
<td>ACV</td>
<td>IDU</td>
<td>ACV</td>
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<td>Colin, 1981</td>
<td>19/25 (76%)</td>
<td>11/27 (41%)</td>
<td>29/30 (97%)</td>
<td>6/30 (20%)</td>
<td>27/28 (96%)</td>
</tr>
<tr>
<td>Collum, 1980</td>
<td>29/30 (97%)</td>
<td>6/30 (20%)</td>
<td>27/28 (96%)</td>
<td>22/26 (85%)²</td>
<td>8/10 (80%)</td>
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<td>Coster, 1980</td>
<td>+35% (+8%, +60%)</td>
<td>+77% (+57%, +88%)</td>
<td>+12% (-5%, +32%)</td>
<td>+30% (-15%, +67%)</td>
<td>-3.8% (-30%, +23%)</td>
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<td>Risk Difference³</td>
<td>ACV-IDU (95%CI)</td>
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<tr>
<td>Colin, 1981</td>
<td>+35% (+8%, +60%)</td>
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<tr>
<td>Collum, 1980</td>
<td>+77% (+57%, +88%)</td>
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<tr>
<td>Coster, 1980</td>
<td>+12% (-5%, +32%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Klauber, 1982</td>
<td>+30% (-15%, +67%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>McCulley, 1982</td>
<td>-3.8% (-30%, +23%)</td>
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<tr>
<td>End of study</td>
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<td>IDU</td>
<td>ACV</td>
<td>IDU</td>
<td>ACV</td>
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<tr>
<td>Colin, 1981</td>
<td>23/25 (92%)</td>
<td>30/30 (100%)</td>
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<td>26/28 (100%)</td>
<td>10/10 (100%)</td>
</tr>
<tr>
<td>Collum, 1980</td>
<td>22/27 (81%)</td>
<td>22/30 (73%)</td>
<td>26/28 (100%)</td>
<td>10/10 (100%)</td>
<td>24/26 (92%)</td>
</tr>
</tbody>
</table>

¹The healing rates were extracted from the literature and study reports. When 7 day results were not available, the applicant interpolated the 7 day results from a graph of time to healing found in the publication; this reviewer checked the interpolation.

² The high rate of 85% for IDU in this study is for a dosage of 1% for IDU compared to 0.5% in the rest of the studies.

³Risk differences were computed by the statistical reviewer and are based on an exact test to compare proportions. Positive risk differences favor ACV.

Analysis of Secondary Endpoints(s)
Time to ulcer cure was used as a supportive efficacy endpoint.

Acyclovir vs IDU – Time to Ulcer Healing

<table>
<thead>
<tr>
<th>First Author</th>
<th>Year</th>
<th>Control</th>
<th>Acyclovir (days)</th>
<th>IDU (days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colin</td>
<td>1981</td>
<td>IDU</td>
<td>7.5</td>
<td>9</td>
</tr>
<tr>
<td>Collum</td>
<td>1980</td>
<td>IDU</td>
<td>4.4</td>
<td>8.7</td>
</tr>
<tr>
<td>Coster</td>
<td>1980</td>
<td>IDU</td>
<td>Data not reported</td>
<td>Data not reported</td>
</tr>
<tr>
<td>Klauber</td>
<td>1982</td>
<td>IDU</td>
<td>50% in 5-6 days</td>
<td>50% in 10-12 days</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Epithelial and stromal</td>
<td>Epithelial and stromal</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>50% in 3-4 days</td>
<td>50% in 7 days</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Epithelial only</td>
<td>Epithelial only</td>
</tr>
<tr>
<td>McCulley</td>
<td>1982</td>
<td>IDU</td>
<td>6.4 Dendritic only</td>
<td>6.6 Dendritic only</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>5.9 Dendritic and geographic</td>
<td>7.2 Dendritic and geographic</td>
</tr>
</tbody>
</table>

Source: Fera Section 2.7.3 Table 3

The literature describing adequate and well-controlled clinical trials demonstrate that acyclovir ophthalmic ointment 3% is superior to IDU for the treatment of dendritic ulcers in the Day 7 ulcer healing rates. The time to ulcer healing provides additional evidence that Acyclovir 3% is effective in treating dendritic ulcers.
8. Safety
The major sources of clinical data utilized included:

- Two single center randomized, double-masked clinical trials – Klauber et al 1982 and Coster et al 1980 (Note: Coster study did not report adverse events and is not included in the safety database)
- Worldwide marketing experience

274 patients were included in the 5 clinical studies. Since no adverse events were reported in Coster et al 1980, the overall safety assessment is based on 214 patients exposed to either ACV 3% (n=103) and or IDU 0.5% (n=111).

Both ACV and IDU were dosed 5 times daily initially for 7 days. At the point of ulcer healing treatment was either withdrawn or reduced to 3 times daily for a further treatment period. Hence treatment durations varied considerably between patients and studies ranging from 2 to 17 days.

Acyclovir 3%, AEs reported with a frequency greater than 1% include punctuate keratitis, eye pain (burning and stinging on instillation) and follicular conjunctivitis. Those AEs occurring at a rate greater than 5% include punctuate keratitis and eye pain (burning and stinging on instillation).

9. Advisory Committee Meeting
No Advisory Committee Meeting was held. There were no new issues raised in the review of the application which were thought to benefit from an Advisory Committee Meeting.

10. Pediatrics
This drug product has been designated an orphan drug and hence, is exempt from the pediatric assessment requirement under 21 CFR 314.55(d). Safety and efficacy in pediatric patients below the age of 2 years have not been established.

11. Other Relevant Regulatory Issues

DMEPA
The proposed proprietary name, Avaclyr, was found acceptable from both a promotional and safety perspective, and Fera Pharmaceuticals, Inc.

FINANCIAL DISCLOSURE
There are no covered clinical studies in this application.

OSI
An Office of Scientific Investigations (OSI) audit was not requested.
12. **Labeling**

The proposed labeling for NDA 202408 for Avaclyr (acyclovir ophthalmic ointment) 3%, has been revised. The revised package insert with suggested revisions to carton and container labeling can be found in the Cross Discipline Team Leader review (CDTL) and at the end of this review.

13. **Recommendations/Risk Benefit Assessment**

NDA 202408 for Avaclyr (acyclovir ophthalmic ointment) 3%, is recommended for approval for the treatment of acute herpetic keratitis (dendritic ulcers) with the revised package insert and revisions to carton and container labeling found at the end of this review.

There are no risk management activities recommended beyond the routine monitoring and reporting of all adverse events. There are no recommended Postmarketing Requirements or Phase 4 Commitments.

3 Pages of Draft Labeling have been Withheld in Full as B4 (CCI/TS) immediately following this page
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/s/

WILEY A CHAMBERS
06/21/2016
1. Introduction

Acyclovir is a synthetic nucleoside analog active against herpes viruses. The drug substance is a white crystalline powder with the molecular formula of C₈H₈N₄O₃ and a molecular weight of 225.2. The maximum solubility in water at 37°C is 1.41 mg/mL. The pKa’s of acyclovir are 2.52 and 9.35.

The chemical name of acyclovir is 2-amino-1,9-dihydro-9-[(2-hydroxyethoxy)methyl]6H-purin-6-one, it has the following chemical structure:

![Chemical Structure of Acyclovir](image)

Avaclyr is a sterile ointment for topical administration. Each gram of ointment contains 30 mg of acyclovir in a white petrolatum base.

2. Background

Acyclovir has been shown to be active against HSV and HZV in human clinical studies.

Acyclovir ophthalmic ointment 3% (Zovirax) has been marketed in Europe and many countries around the world for several decades. Acyclovir Ophthalmic Ointment 3% is included on the WHO List of Essentials Medicines as the first line therapy of an Ophthalmological anti-infective agent.

On December 6, 2010, a Pre-NDA meeting with the FDA was held to discuss the requirements for filing the NDA submission as a 505(b)(2) submission.
Acyclovir ophthalmic ointment, 3% was granted Orphan drug Designation on December 13, 2010.

This is a 505(b)(2) application. Zovirax (acyclovir) Ointment 5% (NDA 18-604) is claimed as the listed drug. In this application, acyclovir has been formulated for topical ophthalmic use for a new indication, i.e., treatment of acute herpetic keratitis (dendritic ulcers). The literature provided in the application describes the use of acyclovir ophthalmic ointment, 3% for this proposed ocular indication.

The application references both a listed drug (Zovirax Ointment) and published literature. Zovirax (acyclovir) Ointment 5% (NDA 18-604) is a listed drug since it was approved in 1982 and has not been withdrawn.

The clinical safety and efficacy studies which supported the approval of Zovirax are not relevant to the evaluation of Avacyl. The applicant has therefore provided literature in the form of adequate and well controlled studies which demonstrate the safety and efficacy of acyclovir ophthalmic ointment 3%.

There is no listed drug which is or has been approved that includes acyclovir in an ophthalmic dosage form.

The studies published in the literature are applicable to the proposed drug product because they were conducted with a drug product which contains, to the extent that can be determined, the same active and inactive ingredients. The proposed drug product includes acyclovir uniformly distributed throughout the drug product (as documented in the Chemistry/Manufacturing Review). No absorption or transport of the active ingredient is necessary for the drug product to reach the infected cells since the disease being treated affects only the outermost layer of the cornea. The drug product will be placed in direct contact with the site where the disease occurs (on the corneal epithelium). There is no known interaction between the active ingredient and the base ingredient of the formulation. The drug substance has been shown in vitro to be incorporated into cells infected with herpes simplex virus when the drug is placed in direct contact with the cells.

See Medical Officer’s review dated 2/18/14 and the CDTL memorandum dated 3/28/14.

On March 31, 2014, a Complete Response Letter was issued to NDA 202408. The Complete Response Letter states as the single deficiency that the application is lacking a scientific “bridge” between the proposed product and the product used in the clinical studies submitted to the application. The letter further states that the information submitted in the application was considered insufficient to establish a scientific “bridge” between the proposed product and the product used in the published clinical trials. The “bridge” was described as being needed for the determination of the safety and efficacy of acyclovir ophthalmic ointment in the proposed indication of acute herpetic keratitis (dendritic ulcers).
A Class 2 Resubmission was received on 1/26/16.

3. Recommendations

NDA 202408 for Avaclyr (acyclovir ophthalmic ointment) 3%, is recommended for approval for the treatment of treatment of acute herpetic keratitis (dendritic ulcers) with the revised package insert and with the suggested revisions to carton and container labeling found here.

The description of the manufacturing process used to produce the proposed product along with the chemical identity tests and specifications proposed for the product are sufficient to scientifically conclude that the proposed product can be expected to produce clinical results consistent with the product used in the clinical trials.

There is adequate information in the literature to demonstrate that the active ingredient, acyclovir, a synthetic purine nucleoside analogue antiviral agent, inhibits replication of herpes viruses both in vitro and in vivo. Sensitive human viruses include herpes simplex virus (HSV, types 1 and 2) and varicella-zoster virus (VRZ).

The submitted studies in this NDA support a favorable risk benefit profile regarding the safety and efficacy of acyclovir in the treatment of acute herpes simplex keratitis (dendritic ulcer).

The most common adverse events (>1%) were punctuate keratitis, and eye pain (burning, stinging), follicular conjunctivitis, and increased lacrimation.

4. Labeling

NDA 202408 for Avaclyr (acyclovir ophthalmic ointment) 3%, is recommended for approval for the treatment of treatment of acute herpetic keratitis (dendritic ulcers) with the revised package insert and carton and container labeling submitted by the applicant on 5/25/16.

6 Pages of Draft Labeling have been Withheld in Full as B4 (CCI/TS) immediately following this page
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/s/

---------------------------------------------
MARTIN P NEVITT
06/13/2016

WILLIAM M BOYD
06/13/2016

Reference ID: 3945017
NDA 202408, acyclovir ophthalmic ointment 3%
Proposed indication: treatment of acute herpetic keratitis (dendritic ulcers) in patients with herpes simplex (HSV-1 and HSV-2)

## Summary Review for Regulatory Action

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<tr>
<td>Date of Submission</td>
<td>May 31, 2013</td>
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Reference ID: 3481057
NDA 202408, acyclovir ophthalmic ointment 3%
Proposed indication: treatment of acute herpetic keratitis (dendritic ulcers) in patients with herpes simplex (HSV-1 and HSV-2)

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<td>Martin Nevitt, William Boyd 2/18/2014</td>
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<td>Lois Almoza</td>
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CDTL=Cross-Discipline Team Leader
OSI/DGCPC=Office of Scientific Investigations/Division of Good Clinical Practice Compliance (formerly Division of Scientific Investigation (DSI)
OSE= Office of Surveillance and Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
OPDP/DPDP=Office of Prescription Drug Promotion/Division of Professional Drug Promotion; formerly, DDMAC=Division of Drug Marketing, Advertising and Communication
OC = Office of Compliance
NDA 202408, acyclovir ophthalmic ointment 3%
Proposed indication: treatment of acute herpetic keratitis (dendritic ulcers) in patients with herpes simplex (HSV-1 and HSV-2)

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1. Summary and Recommendations

NDA 202408 is a 505(b)(2) application submitted by Fera for acyclovir ophthalmic ointment 3% for the treatment of acute herpetic keratitis (dendritic ulcers). The applicant obtained orphan drug designation for the indication “treatment of acute herpetic keratitis associated with Herpes Simplex Virus type 1 and type 2.”

In the US, acyclovir is approved as a topical cream, topical ointment, tablet, capsule, and injection for the treatment of herpes infections; these products are made by GlaxoSmithKline (GSK) and Fera is relying on these applications in part to support their NDA. The applicant notes that an acyclovir ophthalmic ointment 3% is not approved in the US, and that the GSK Zovirax (acyclovir ophthalmic ointment) 3% is approved in the UK, and in many other countries around the world, has been marketed for more than 30 years, and is on the World Health Organization (WHO) Essential Medicines List.

The application included complete CMC and manufacturing information on the Fera product, and this information is judged acceptable by the chemists and the Office of Compliance.

The nonclinical and clinical studies submitted in the application are from the published literature. The applicant writes that as discussed at the pre-NDA meeting, clinical data are from the scientific literature comparing acyclovir ophthalmic ointment to idoxuridine in the treatment of herpetic keratitis, otherwise the application relies on FDA’s previous finding of safety and effectiveness of the FDA-approved products (source: reviewer guide, NDA section 1.2).

- For non-clinical data, Fera can rely on the FDA’s findings in the approved labeling for the oral and injection forms (and possibly the 5% topical formulations) because the levels achieved by systemic administration exceed levels achieved by topical ophthalmic administration, therefore the non-clinical information can be bridged from these FDA approved products.
- However, there is no approved US acyclovir ophthalmic ointment 3% to serve as a listed drug. A 505(b)(2) application needs to include a scientific “bridge” between the proposed NDA product and the listed product and specify what information is being relied on to which the applicant does not have right of reference.
- The only clinical data for the acute herpetic keratitis indication in the NDA are five published clinical studies which were conducted in the 1980’s and four identify the source as Burroughs Wellcome (now GSK). A scientific “bridge” between the product used in the clinical trials and the Fera product submitted in July 27, 2013 was not adequate, and became a topic of discussions in various internal meetings, at the 505(b)(2) committee meeting, and at the OND Director Briefing on March 19, 2014. These groups confirmed the need for a scientific “bridge,” as discussed in Section 2.

The lack of an adequate scientific “bridge” to link the clinical data to the Fera product is a deficiency for this application that precludes approval during this review cycle. Specific

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1 NDA 202408, electronic document room submission dated March 12, 2014, contains all the names and a complete chronology of the mergers, showing how Burroughs Wellcome is related to GlaxoSmithKline.
NDA 202408, acyclovir ophthalmic ointment 3%
Proposed indication: treatment of acute herpetic keratitis (dendritic ulcers) in patients with herpes simplex (HSV-1 and HSV-2)

deficiencies/outstanding issues have been identified by OGD and OPS/OTR colleagues after review of the March 12 and March 25, 2014 submissions.

The other disciplines recommend approval. The CMC of the product is found to be acceptable and Office of Compliance has provided a recommendation of acceptable for manufacturing facilities. The statistical and clinical reviewers recommend that the clinical studies conducted with the Burroughs Wellcome product demonstrate safety and efficacy, however, as already noted there are no clinical studies with the Fera product and data establishing an adequate scientific “bridge” between the two products is lacking. Other disciplines recommend approval based on FDA’s listed drugs: the pharmacology/toxicology, virology and clinical pharmacology disciplines are relying on the FDA approved listed products, to the extent this information is available and applicable to this 505(b)(2) application.

1.1 Deficiencies

- Under 505(b)(2) the applicant needs to provide a scientific “bridge” between a listed drug and the NDA product. Although the application relies on listed drugs (injection, oral) for non-clinical information, there is no “bridge” to link the NDA product to the clinical trials published in the literature that used product manufactured by GSK (Burroughs Wellcome).
- The NDA does not contain any clinical trials done with the Fera product, which could constitute direct evidence of safety and efficacy of the Fera product. The application does not include any other in vivo information, for example, a pharmacokinetic or pharmacodynamic comparison on the activity, safety and/or efficacy of the Fera product (such studies with topical products may not be considered reliable).
- Because of the applicant’s statement that their product is virtually identical to the GSK product used in the clinical trials, the applicant was asked to provide a side-by-side comparison of the physicochemical properties of these two drugs. The rationale behind requesting a bridge based on the product characteristics is based on the recent experience and success in the Office of Generic Drugs (OGD) where Q1/Q2/Q3 comparability between the Zovirax® topical ointment 5% and generic Mylan acyclovir topical ointment 5% was evaluated; and led to the approval of Mylan’s ANDA 202459.
- Fera submitted information on the comparison between their product and the reference GSK product on March 12 and March 25, 2014. Based on the review of this information, the reviewers in the OGD and Office of Pharmaceutical Science/Office of Testing and Research (OPS/OTR) the applicant provide characterization of 3 lots of Fera’s product and 3 lots of Zovirax product, and perform testing of petrolatum, viscosity, quality and performance tests, acyclovir particle size and acyclovir polymorphism (see Appendix A for complete recommendations):

1.2 Post-Marketing Studies:
Not applicable at this time

1.3 Other Issues
None at this time
2. **Background**

**Approved Products**
(Information from DARRTS and Drugs@FDA)

- Zirgan (gancyclovir ophthalmic gel) 0.15%, NDA 22211, Sirion Therapeutics, approved 9/15/2009, for the treatment of acute herpetic keratitis (dendritic ulcers).
- Viroptic (trifluridine ophthalmic solution) 1%, NDA 18299, approved 4/10/1980, for treatment of primary keratoconjunctivitis and recurrent epithelial keratitis due to herpes simplex virus, types 1 and 2.

**Not Marketed**
- Herplex (idoxuridine sterile ophthalmic solution) 0.1%, NDA 13935, Allergan Pharmaceuticals, approved 6/11/1963 (Allergan requested withdrawal of approval of their NDA on 9/26/2002 and submitted a letter on 12/6/2002 to rescind the request to withdraw approval of the NDA, and updated the Allergan contact information for NDA 13935 on 2/21/2014).
- Dendrid (idoxuridine ophthalmic solution), 0.1%, NDA 14169, Alcon Laboratories, approved 6/28/1963 (the annual report submitted 12/19/2013 states the product is no longer manufactured or marketed).

**Disease**

As reported in the submission, herpes simplex virus (HSV) keratitis is the leading cause of corneal blindness in the United States and the most common source of infectious blindness in the Western world.

Patients with HSV keratitis may complain of pain, photophobia, blurred vision, tearing, and redness. The earliest sign of active viral replication in the corneal epithelium is the development of small, raised, clear vesicles. These coalesce as the virus spreads from cell to cell, to form dendrites. Dendritic ulcers (also called epithelial keratitis) are the most common presentation of HSV keratitis. Prominent features of a dendritic ulcer include a linear branching pattern with terminal bulbs, swollen epithelial borders, and central ulceration through the basement membrane. The dendritic ulcers may resolve in 1 to 2 weeks or they may develop into geographic ulcers.

A geographic ulcer is typically formed by coalescence of several dendritic ulcer, is large superficial irregularly shaped, with scalloped margins. If the infection becomes advanced, it may lead to stromal ulcers.

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2 Trifluridine ophthalmic solution was developed under IND 90822, Glaxo Wellcome. The NDA was submitted 4/18/1979 and approved 4/10/1980 (DARRTS). The current applicant listed in DARRTS is Monarch Pharmaceuticals.
Proposed indication: treatment of acute herpetic keratitis (dendritic ulcers) in patients with herpes simplex (HSV-1 and HSV-2)

Stromal keratitis (disciform keratitis) may lead to scarring and decreased vision; there may be associated localized inflammation of the corneal endothelium.

The diagnosis is based on clinical findings and can be confirmed by staining, immunostaining and/or culture of the corneal scrapings.

Since most cases of HSV epithelial keratitis resolve spontaneously within 3 weeks, the rationale for treatment is to minimize stromal damage and scarring. Gentle epithelial débridement may be performed to remove infectious virus and viral antigens that may induce stromal keratitis. Antiviral therapy, topical or oral, is an effective treatment for epithelial herpes infection. Prompt treatment is necessary to limit subepithelial and stromal scarring, and to reduce the risk for vision loss. The prognosis is generally favorable with aggressive treatment.

The direct effect of the virus, and more importantly, the potent immune response to the viral proteins trigger ingrowth of blood vessels, infiltration of leukocytes, and damage to the corneal stroma and endothelium that combine to promote corneal opacity and edema. The inflammation clears, usually aided by topical corticosteroids, but often with some degree of scar tissue deposition (Jones, 1958; Wilhelmus, 1987). Repeated bouts of HSK can lead to progressive irreversible corneal scarring and blindness.3

Approximately 20,000 new cases (as well as more than 28,000 reactivations) of ocular HSV occur annually in the United States.

2.1 Regulatory History and Considerations

The applicant held a pre-NDA meeting with the agency on December 6, 2010 during which the application content was discussed. During the meeting the agency advised that, 

*The application needs to include adequate and well controlled studies either directly or by reference. Additional studies (clinical or non-clinical) are not expected to be needed as long as you are able to reference the Agency’s findings through a 505(b)(2) application and can link your product to the products in previous studies.*

NDA 202408 was submitted May 31, 2013 and the applicant stated they were relying on the following US-approved listed drugs. All of these are different from the Fera product in terms of formulation, strength, indication, and site of action.

- **NDA 18604** – topical ointment 5%
  - Approved for initial genital herpes and in limited non-life-threatening mucocutaneous Herpes simplex virus infections in immunocompromised patients
- **NDA 21478** – topical cream 5%
  - Approved for the treatment of recurrent herpes labialis (cold sores) in adults and adolescents (12 years of age and older).
- **NDA 18828** – capsule 200mg

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NDA 202408, acyclovir ophthalmic ointment 3%
Proposed indication: treatment of acute herpetic keratitis (dendritic ulcers) in patients with herpes
simplex (HSV-1 and HSV-2)

- **Herpes Zoster Infections:** ZOVIRAX is indicated for the acute treatment of herpes zoster
  (shingles).
- **Genital Herpes:** ZOVIRAX is indicated for the treatment of initial episodes and the management
  of recurrent episodes of genital herpes.
- **Chickenpox:** ZOVIRAX is indicated for the treatment of chickenpox (varicella).

- **NDA 19909 — suspension 200mg/5mL**
  - Same indications as Capsule
- **NDA 20089 — tablets, 400 mg and 800 mg**
  - Same indications as Capsule
- **NDA 08603 — injection (discontinued 2006)**
  - **Herpes Simplex Infections in Immunocompromised Patients:** ZOVIRAX for Injection is
    indicated for the treatment of initial and recurrent mucosal and cutaneous herpes simplex (HSV-1
    and HSV-2) in immunocompromised patients.
  - **Initial Episodes of Herpes Genitalis:** ZOVIRAX for Injection is indicated for the treatment of
    severe initial clinical episodes of herpes genitalis in immunocompetent patients.
  - **Herpes Simplex Encephalitis:** ZOVIRAX for Injection is indicated for the treatment of herpes
    simplex encephalitis.
  - **Neonatal Herpes Simplex Virus Infection:** ZOVIRAX for Injection is indicated for the
    treatment of neonatal herpes infections.
  - **Varicella-Zoster Infections in Immunocompromised Patients:** ZOVIRAX for Injection
    is indicated for the treatment of varicella-zoster (shingles) infections in immunocompromised
    patients.

The applicant also submitted the labeling for the UK-approved Zovirax ophthalmic ointment 3%
and in section 1.14.3.1 in the “Table of Annotations,” writes that the source of information for
the Indication and Usage, Dosage and Administration, and Dosage Forms and Strengths section
of the package insert is “based on the Zovirax® UK Product Labeling – Approved by EMA.”

### 2.2 Orphan Designation

The applicant obtained orphan drug designation (ODD# 10-3250) on December 13, 2010 for the
indication, “treatment of acute herpetic keratitis associated with Herpes Simplex Virus type 1
and type 2.” [NDA 202408, section 1.3.5.3.]

### 2.3 Scientific “Bridge” Between Fera’s Product, Listed Drugs, Published Studies

At the filing meeting for this application, it was noted that Fera had not submitted a scientific
“bridge” between their product and the product used in the clinical studies. Following a request
for information, on July 24, 2013, Fera submitted a 2-page narrative and 1-page diagram on “a
comparison of Fera’s and Glaxo’s (approved in EU) European drug products.

This information was considered insufficient; the application did not contain data that could bridge the Fera product to
the product used in the clinical studies.

**Comment:**
The review of this application has been challenging because of the differences in opinion
between the need for a scientific “bridge” for this 505(b)(2) application, and differences in
NDA 202408, acyclovir ophthalmic ointment 3%
Proposed indication: treatment of acute herpetic keratitis (dendritic ulcers) in patients with herpes simplex (HSV-1 and HSV-2)

Scientific opinion among reviewers about what constitutes a scientific “bridge” and what information is needed to “bridge” the Fera product to the clinical data showing the safety and efficacy of the GSK-identified product in the published clinical studies.

Such information is necessary as summarized below:

The FDA guidance on 505(b)(2) applications states that:
- Studies necessary to support the change or modification from the listed drug or drugs (if any). Complete studies of safety and effectiveness may not be necessary if appropriate bridging studies are found to provide an adequate basis for reliance upon FDA’s finding of safety and effectiveness of the listed drug(s).
- Before submitting the application, the applicant should submit a plan to the appropriate new drug evaluation division identifying the types of bridging studies that should be conducted. The applicant should also identify those components of its application for which it expects to rely on FDA’s finding of safety and effectiveness of a previously approved drug product. The division will critique the plan and provide guidance.

The FDA 505(b)(2) Assessment form states:
- Reliance on information regarding another product (whether a previously approved product or from published literature) must be scientifically appropriate. An applicant needs to provide a scientific “bridge” to demonstrate the relationship of the referenced and proposed products. Describe how the applicant bridged the proposed product to the referenced product(s). (Example: BA/BE studies)

Comment:
Of note, no precedent has been identified where the absence of a bridge nevertheless led to approval of a 505(b)(2) application. Examples were cited during internal discussions as not having a bridge [mycophenolic acid, quinine, tinidazole, nitrogen mustard, erythromycin ophthalmic ointment, bacitracin ophthalmic ointment] However, for these examples there was evidence of a bridge based on clinical, clinical pharmacology and/or chemistry data – see below.

a. Myfortic (mycophenolic acid) relied on the FDA’s findings of safety and effectiveness for Cellcept for non-clinical information, and conducted controlled clinical trials to support approval of this 505(b)(2) application.

b. Qualaquin (quinine by Mutual, NDA 21799) was shown to be bioequivalent to GPO quinine, the product used in many controlled clinical trials.

c. Tindamax (tinidazole by Presutti Labs, NDA 21618) was shown to be bioequivalent to Fasigyn, the product used in clinical studies.

d. Erythromycin ophthalmic ointment was approved under the DESI review process under NDA 50-368 (Ilotycin) on June 29, 1964. ANDA 62447 was approved September 26, 1983. The current OGD guidance discusses waiving in vivo bioequivalence for an ANDA based on a recommendation from a clinical ophthalmology consult. (Marketing of Ilotycin was discontinued and NDA 50-368 was withdrawn per Federal Register on June 16, 2006; ANDA 62447 is now the RLD.)
The 505(b)(2) Committee

The 505(b)(2) committee, chaired by Mary Ann Holovac, includes regulatory and legal experts among its members. After reviewing the Fera 505(b)(2) information, the 505(b)(2) committee asked for clarification about the role of the (European) approved Zovirax® ophthalmic ointment labeling, and about the scientific “bridge” for this application to the listed products and to the published clinical studies.

Foreign labeling

The Division agreed that the UK-approved product and foreign labeling could not serve the role of a listed drug. A listed drug is one that is approved in the US, and can be relied on for general findings of safety and effectiveness. A European product is not considered a listed drug and cannot be relied on for safety and effectiveness.

Although Fera submitted the UK-approved Zovirax® ophthalmic ointment labeling, Fera also submitted five published controlled clinical studies in their application and these are the studies Fera is using to support the safety and efficacy of Fera’s product. As noted in Section 7-Efficacy and Section 8-Safety, below, reviewers concluded that these studies did demonstrate safety and efficacy of acyclovir ophthalmic ointment 3%; however, four studies identified Burroughs Wellcome as the source of the product. No clinical study used the Fera product. Therefore, a bridge between these two products is needed.

Scientific “bridge

By this stage of the review, there were ongoing discussions, which included input from the Division of Dermatologic and Dental Products (DDDP), the 505(b)(2) committee, the Office of Generic Drugs (OGD), the Office of Pharmaceutical Science/Office of Testing and Research (OPS/OTR).

A Briefing with the OND Director was scheduled for March 19, 2014, and attended by representatives from OND, OAP, DTOP, DDDP, ONDQA, OPS/OTR and the 505(b)(2) committee.

After hearing a brief presentation about the lack of a scientific bridge for the Fera NDA 202408, the OND Director stated that based on discussion with Chief Counsel over the past 22 years, a scientific “bridge” was needed for a 505(b)(2) application. The discussion proceeded to cover what bridges have been used and how bridging might be achieved.

The Division of Dermatologic and Dental Products (DDDP) provided a summary of DDDP’s approach to 505(b)(2) applications at the meeting, and further clarification during a subsequent discussion. The DDDP relies on listed drugs for bridging to non-clinical studies, and may use additional clinical PK data to make that bridge. However, DDDP bases efficacy determination of topical dermal products on controlled clinical trials done with the product submitted for approval, and DDDP does not accept published studies that purport to use the same product as the one being reviewed under NDA.

Reference ID: 3481057
The Fera application is for an ophthalmic ointment with no clinical data, therefore in vivo scientific bridge was not provided. However, bridging between drug products using CMC and related information is an area of scientific work that has been addressed by recent work in the Office of Generic Drugs (OGD) and Office of Testing and Research (OTR) in the Office of Pharmaceutical Sciences (OPS), and has included input and consultation from the Office of New Drug Quality Assessment (ONDQA) and the Office of Clinical Pharmacology (OCP), as well as OND. This work has involved use of Q1/Q2/Q3 characteristics of a product to determine similarity.

In addition, CDER addressed the approach of using in vitro data to demonstrate bioequivalence on the basis of Q1/Q2/Q3 in vitro release testing data. Dr. Janet Woodcock, the Center Director, articulated CDER’s position in the December 14, 2012 letter in response to the Citizen Petition submitted July 18, 2012 by Valeant regarding their product Zovirax® (acyclovir) ointment 5%. Sections from this letter are cited and discussed below:

**Experience in the Office of Generic Drugs**

Although ONDQA has consulted with OGD on chemical comparisons between products manufactured by different companies, ONDQA reviewers and precedence committee stated they did not have experience or precedent with establishing a scientific bridge on the basis of chemical attributes of the formulation. Therefore guidance from the OGD and OPS/OTR was sought to address this question.

OGD approved Mylan’s ANDA 202459 for topical acyclovir ointment 5% by way of comparison to Zovirax® (acyclovir topical ointment) 5%, the reference listed product approved for initial genital herpes and in limited non-life-threatening mucocutaneous *Herpes simplex* virus infections in immunocompromised patients. Zovirax® was developed by Glaxo, and is now licensed by Valeant; NDA 18604.

The reviews and consults by OGD and other Offices archived in DARRTS for ANDA 202459 provide a complete history of this application. Additional information on this approach is provided in the December 14, 2012 response to the Citizen Petition (CP) submitted by Valeant to the agency on July 18, 2012. The Valeant CP challenging the proposed use of the “In Vitro option” in the March 2012 OGD “Draft Guidance on Acyclovir.” This guidance states,

To qualify for the in vitro option for this drug product pursuant to 21 CFR 320.24 (b)(6), under which “any other approach deemed adequate by FDA to measure bioavailability or establish bioequivalence” may be acceptable for determining the bioavailability or bioequivalence (BE) of a drug product, all of the following criteria must be met:

i. The test and Reference Listed Drug (RLD) formulations are qualitatively and quantitatively the same (Q1/Q2).

ii. Acceptable comparative physicochemical characterization of the test and RLD formulations.

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4 Draft Guidance on Acyclovir
NDA 202408, acyclovir ophthalmic ointment 3%
Proposed indication: treatment of acute herpetic keratitis (dendritic ulcers) in patients with herpes simplex (HSV-1 and HSV-2)

iii. Acceptable comparative in vitro drug release rate tests of acyclovir from the test and RLD formulations.

The in vitro approach in the draft guidance provides a means to “bridge” two products, ones made by different manufacturers, using in vitro, i.e., non-clinical scientific information.

In the Office of Clinical Pharmacology Consult Review dated 7/14/2011 for the Mylan ANDA 202459, the reviewer summarizes the information provided by the applicant, to characterize the Mylan generic product, addressing the criteria in the “Draft Guidance on Acyclovir: that must be met for the in vitro option:

Mylan submitted a request for a waiver of in vivo bioequivalence (BE) studies for acyclovir ointment, 5%. The basis of this request relies on the composition of the proposed product and the reference listed drug (RLD) demonstrating both qualitative and quantitative sameness (Q1/Q2). In addition, the firm has proposed additional in vitro tests to further demonstrate sameness with respect to physicochemical and drug release characteristics (Q3) between their product and the RLD. From a regulatory standpoint, according to 21 CFR 320.24 (b)(6), an application may be approved without an in vivo BE study if bioequivalence is established by any other approach deemed adequate by FDA to measure bioavailability or establish BE.

The KEY CLINICAL PHARMACOLOGY CONCERNS raised were:

➤ Are the test and reference products formulated similarly such that the release characteristics of acyclovir are the same between the two products? (Will the same amount of drug be available at the site of action?)

➤ Will absorption be the same for the test and reference products? (Will the amount of drug uptake by the skin be affected by differences in formulation and/or manufacturing of the two products?)

REVIEW OF DATA AND PROPOSALS
Q1/Q2
Mylan’s proposed product and the RLD (Zovirax® ointment) are Q1/Q2 identical (contains the same components):

<table>
<thead>
<tr>
<th>Zovirax Acyclovir Ointment 5%</th>
<th>Amount (%)/ 15 gram tube</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ingredient</td>
<td></td>
</tr>
<tr>
<td>Acyclovir, USP</td>
<td>(5.0)</td>
</tr>
<tr>
<td>Polyethylene Glycol</td>
<td>(5.0)</td>
</tr>
<tr>
<td>Total</td>
<td>(10.0)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Mylan’s Proposed Acyclovir Ointment 5%</th>
<th>Amount (%)/ 15 gram tube</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ingredient</td>
<td></td>
</tr>
<tr>
<td>Acyclovir, USP</td>
<td>(5.0)</td>
</tr>
<tr>
<td>Polyethylene Glycol</td>
<td>(5.0)</td>
</tr>
<tr>
<td>Total</td>
<td>(10.0)</td>
</tr>
</tbody>
</table>

Q3
Mylan has also conducted the following tests to establish Q3 sameness:

a. Size Exclusion Chromatography (SEC): used to confirm comparability between the two products with respect to molecular weight distribution and quantity of each component.

b. X-ray Diffraction: used to confirm sameness in active pharmaceutical ingredient (API) polymorphic states between the two products.

c. Laser Light Scattering: used to evaluate the particle size of the API present in the proposed and RLD products.
NDA 202408, acyclovir ophthalmic ointment 3%
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d. Viscosity: compared the viscosity of Mylan’s product in (9) stages of manufacturing against three lots of the RLD product.
e. Franz Diffusion Cell: used to compare the in vitro release of acyclovir between the two products.

The OCP consult review made the recommendation that based on the Q1/Q2/Q3 sameeness; it was “unlikely that the proposed product and the reference product would not be similar in local absorption characteristics and clinical effects.”

The ONDQA consult review by Drs. Miller and Madurawe, dated 8/15/2011, addressed the same Q1/Q2/Q3 points and raised additional points for consideration:
- Product is Q1/Q2 – supported by size-exclusion chromatography results
- Is there assurance that Mylan manufacturing process (9)?
- Is there consistency in particle size?
- Change in viscosity over time – is this likely to have impact on in vitro release characteristics?

Citizen Petition FDA-2012-P-0799 by Valeant, July 18, 2012 and FDA response December 14, 2012

Glaxo originally manufactured Zovirax® and it was approved under NDA 18604. The product is currently licensed to Valeant. Valeant submitted a CP on 7/18/2012 and challenged the agency’s proposal to base approval of a generic acyclovir topical ointment 5% based on in vitro testing.

In the 12/14/2012 response to the CP, the agency explains that products that are not Q1/Q2 and do not show acceptable comparative physicochemical and in vitro release characteristics “would not qualify for use of the in vitro option to demonstrate bioequivalence to Zovirax.”

The CP response notes that “FDA will use release data to confirm that manufacturing processes have not altered product attributes and potentially affected the availability of a formulation Q1/Q2/Q3 to Zovirax.” (CP response, p 12)

Comment: The above statement from the CP indicates that although one may hypothesize that products with the same formulation would have the same release characteristics, the agency would not accept such a hypothesis but would expect scientific evidence to confirm the hypothesis.

The CP notes that, “We agree that Q1/Q2 formulations may still result in different products. Differences in physicochemical properties can alter the availability and release of the drug substance, making the acceptable comparative physicochemical profile (Q3) criterion an important requirement of the recommended in vitro option.” (CP response, p 14)

The CP also notes, “Requiring an acceptable comparative physicochemical characterization of the drug product provides assurance that two products that are Q1/Q2 the same are expected to deliver the same amount of drug at the site of application for absorption based upon the results of the in vitro drug release test. The burden is on the applicant to provide data supporting a Q1/Q2 formulation and data to demonstrate that the products have similar physicochemical
NDA 202408, acyclovir ophthalmic ointment 3%
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characteristics. Whether the data are sufficient for his purpose is an issue to be determined during review of a proposed generic product’s marketing application.” (CP response, p15)

Comment: These statements in the CP response indicate that while Q1/Q2 sameness is necessary, it is not sufficient to make conclusions about the sameness in terms of delivering the same amount of drug at the site of application, which is why other attributes and release testing are needed. Again, although the CP is specifically dealing with generic and RLD products, the principles and approaches appear applicable to supporting a scientific “bridge” between a 505(b)(2) NDA drug and the drug used in the published clinical studies (made by a different company) intended to support the approval of a new indication for the 505(b)(2) drug.

The CP further clarifies that, “But the purpose of bioequivalence testing is not to directly measure safety or therapeutic effect. We do not look to the in vitro release data – or to in vivo data – used to demonstrate bioequivalence for the purpose of establishing the safety or efficacy of the proposed product. Rather, we use such testing only to establish bioequivalence.” (CP response, p17)

Comment: This explanation puts into perspective the role of the testing. The testing is not a surrogate for safety and efficacy, the testing is simply a means to establish bioequivalence - in vitro. So if one could establish bioequivalence, based on in vitro methods as discussed in the CP response, between two products, that bioequivalence might be considered a scientific “bridge” between those products (e.g., Fera and GSK acyclovir ophthalmic ointment 3%). However, as stated in the CP, that bridge would not establish the safety and efficacy of the Fera product, it would just provide a bridge to the Glaxo Zovirax® product. The safety and efficacy of the Burroughs Wellcome acyclovir ophthalmic ointment 3% was demonstrated -- per the clinical and statistical reviewers for NDA 202408 -- in the published clinical trials.

The CP also explains that, “The recommended in vitro option reflects the rate and extent to which acyclovir ointment becomes available for delivery of the drug to the site of action, and release data are used to confirm a formulation’s attributes, not as a surrogate model for diseases skin.” (CP response, page 18)

Comment: This comment again reinforces the purpose of the Q1/Q2/Q3 testing, to make comparisons of in vitro bioequivalence between products, and not to be used as a surrogate model for the disease.

Summary and Discussion

In summary, based on the advice from a broad range of experts in CDER, a scientific “bridge” is needed for a 505(b)(2) application. Based on the experience from OGD in consultation with other Offices, in vitro bioequivalence can be assessed by comparing products using Q1/Q2/Q3 characteristics and in vitro release testing. If adequate data are available, such an approach may be able to provide a scientific “bridge” between the Fera and GSK/Burroughs Wellcome product.

Comment: Based on the discussions of what would constitute such a scientific bridge, including during internal discussions and during the OND Director Briefing on March 19, 2014, it was
NDA 202408, acyclovir ophthalmic ointment 3%
Proposed indication: treatment of acute herpetic keratitis (dendritic ulcers) in patients with herpes simplex (HSV-1 and HSV-2)

clear that the bridge would need to be based on scientific data not on unsupported statements, assertions or beliefs that the bridge was not needed or the bridge existed. The information provided in Appendix A, based on the OGD consult dated 3/31/2014, will be requested from the applicant in the Complete Response letter.

Outstanding Issues

During the March 19, 2014 meeting,

(see excerpts below)
NDA 202408, acyclovir ophthalmic ointment 3%
Proposed indication: treatment of acute herpetic keratitis (dendritic ulcers) in patients with herpes simplex (HSV-1 and HSV-2)

These statements appear inconsistent or contradictory, and would appear to have ramifications beyond this application.

However, the review of this application did not rely on any reference to information in IND. To support approval of this application, the applicant has submitted 5 published clinical trials from the literature, most of these cite the Burroughs Wellcome acyclovir ophthalmic ointment 3% as the product used in the trials. There is a need to bridge between the proposed Fera product in this NDA and the Burroughs Wellcome product used in the trials. Based on the discussions with experts in OGD, OPS/OTR, OND, and others in the center, and also based on the principles articulated in Citizen Petition response dated December 14, 2012 (FDA-2012-P-0799), there is experience in assessing in vitro bioequivalence and using that information to provide the scientific “bridge.”

3. CMC/Product Quality Microbiology

See complete CMC reviews by Drs. Pagay and Madurawe.

3.1 Product Quality -

In the reviewer guide, the applicant states that information regarding the physical attributes, manufacturing processes and impurity characterization of the DS is incorporated by reference to DMF and controls for manufacture, testing and release of the DS and DP are done by

The product includes 3% acyclovir in petrolatum. It is supplied in 3.5 gram tin tubes with a black LDPE cap. Each tube is packaged in an individual carton. The drug specifications, petrolatum specification and drug product specifications are provided in the CMC review.

The CMC reviewer notes that

The CMC review also discusses the initial proposed particle size testing with particle sizes proposed
NDA 202408, acyclovir ophthalmic ointment 3%

Proposed indication: treatment of acute herpetic keratitis (dendritic ulcers) in patients with herpes simplex (HSV-1 and HSV-2)

Dr. Pagay provides the following summary regarding the Fera product: All three primary stability batches were manufactured at the commercial production facility at the commercial scale (3 Kg ointment). The drug product is

The drug product release testing quality attributes include leak test, metal particles, particle size of the dispersed drug in the ointment base and ointment homogeneity; these are also important from patient consideration for an ophthalmic drug delivery system. The assay, impurities etc., are performed to insure that the ointment quality is maintained through the shelf life. Most of the testing is performed by compendial test methods except for assay, impurities, particle size and viscosity. The viscosity of the applicant’s drug is similar to that of the RLD. These 4 tests were developed in-house and validated. The drug product shelf life is 2 years when stored at 20-25°C.

Comment:
The reviews dated 2/24/14 and 3/13/14 incorrectly identify the GlaxoSmithKline (GSK) acyclovir ophthalmic ointment 3% (approved in Europe but not in the US) as the Reference Listed Drug. This has been communicated to CMC.

Viscosity is identified as one of the physicochemical characteristics that contributes to understanding formulation attributes and equivalence. Particle size is considered a critical attribute as well, although no data comparing the GSK product are discussed. The Fera product manufacturing and controls are considered acceptable. Other than viscosity, there is no comparison of the Fera product attributes to the GSK product attributes in the review.

In an additional review dated 3/27/14, the reviewer examined information submitted by Fera 3/25/214 regarding the scientific “bridge” and commented that the product attributes between the two products “appear to be similar.” Further clarification of this observation was provided in the 3/31/14 Memorandum by the supervisor that the similarity is not sufficient to establish a bridge between the Fera and Zovirax products.

3.2 Product Quality Microbiology

Sterilization is achieved

Comment: CMC recommends approval of the application based on the information provided for the Fera product. The Office of Compliance recommends that manufacturing facilities are acceptable. There are no proposed CMC PMC's.

4. Nonclinical Pharmacology/Toxicology

The following is a summary of issues in the nonclinical studies and the Pharmacology/Toxicology review. For more detail, see the complete P/T review by Drs. Ruhland and Kotch.
Proposed indication: treatment of acute herpetic keratitis (dendritic ulcers) in patients with herpes simplex (HSV-1 and HSV-2)

This is a 505(b)(2) application and relies on published nonclinical studies; no studies using the Fera product are submitted. The applicant also relies on the FDA’s findings of general safety for systemic and topical listed drugs. Systemic exposure following topical ocular administration is very low and resultant toxicity is not expected.

Acyclovir was positive in 5 of 16 in vitro and in vivo genetic toxicity assays, however, plasma concentrations following intravenous or topical ophthalmic doses do not reach threshold levels shown to induce genotoxicity in vitro or in vivo.

Dr. Ruhland notes that published non-clinical safety and pharmacokinetic studies showed that acyclovir distributes to the aqueous humor following topical ocular administration. Distribution to other ocular tissues was not explored. In rabbits following topical ocular application, a dose-dependent increase in mild conjunctival irritation was noted following treatment with acyclovir and its white petrolatum base compared to saline control. The irritation was most pronounced following the last dose of the day and was almost completely resolved by the following morning’s dose. No other signs of ocular pathology were noted upon biomicroscopy, funduscropy or histological analysis. A NOAEL was established at 6% acyclovir, 5 times per day (6.3 mg/eye/day) which provides a ~3.25- fold safety margin over the maximum recommended human dose.

Labeling is derived from the listed drugs.

Comment: The Pharmacology/Toxicology (P/T) reviewers provided revisions to the labeling and recommend approval.

5. Clinical Pharmacology/Biopharmaceutics

See Clinical Pharmacology review by Drs. Gieser and Colangelo.

No clinical pharmacology studies were submitted.

Comment: The Clinical Pharmacology Reviewers recommend approval pending resolution of labeling. However, the labeling revisions are not consistent with the PLR format, given that information related to microbiology (virology) belongs in section 12.4. Therefore, the labeling has been revised to be consistent with PRL format.

6. Clinical Microbiology/Immunology

See consult review by Drs. Mishra and O’Rear.

Acyclovir is a synthetic purine nucleoside analogue anti-viral agent. After phosphorylation, acyclovir triphosphate, inhibits replication of herpes viral DNA by competing with nucleotides for binding to viral DNA polymerase, incorporating into DNA and leading to termination of the growing viral DNA chain. The cellular thymidine kinase of normal, uninfected cells does not use acyclovir effectively as a substrate; hence toxicity to mammalian host cells is low. Resistance to herpes simplex virus (HSV) may result from changes in thymidine kinase (TK) and/or DNA and
NDA 202408, acyclovir ophthalmic ointment 3%
Proposed indication: treatment of acute herpetic keratitis (dendritic ulcers) in patients with herpes simplex (HSV-1 and HSV-2)

isolates have been isolated from patients with advanced HIV infection. The current product is intended for treatment of acute herpetic keratitis (dendritic ulcers).

Comment: The virology consult provides recommended revisions to the package insert which have been incorporated in labeling.

7. Clinical/Statistical-Efficacy

The following is a brief summary of key findings and issues. For additional details, see clinical reviews by Drs. Boyd and Chambers, and statistical review by Drs. Mele and Wang.

There were no clinical studies submitted which tested the safety and efficacy of the Fera acyclovir ophthalmic ointment 3%. The clinical studies submitted were from the published literature. Five publications were submitted; five published controlled clinical studies were submitted, four were double masked and one was open label. Three studies were multicenter (Colin 1981, Collum 1980, and McCulley 1982) and two were single center (Coster 1980, Klauber 1982). All but one study were conducted in Europe (London, Dublin, Paris, and Copenhagen); the McCulley study was done in the US (California, Texas, Louisiana, and Tennessee). Four identified the source of the acyclovir product as Burroughs Wellcome. The control drug was idoxuridine ophthalmic ointment 0.5% in all studies except Coster 1980 which used idoxuridine ophthalmic ointment 1.0% as the comparator. Treatment was dosed 5 times daily initially for 7 days. At the point of ulcer healing treatment was either withdrawn or reduced to 3 times daily for a further treatment period.

Dr. Mele notes that no two studies used the same treatment regimen with studies differing by type of concomitant medication used and by duration of treatment (see Table 3.1). The proposed labeling recommends applying the ointment 5 timer per day until healed and then 3 times per day for 7 days. None of the 5 studies used the identical dosing schedule recommended in the applicant’s proposed labeling: the studies used 5 times per day dosing to achieve healing. Additional dosing 3 times per day was reported in two studies. In two studies the maximum duration of treatment was specified as 14 days.
NDA 202408, acyclovir ophthalmic ointment 3%
Proposed indication: treatment of acute herpetic keratitis (dendritic ulcers) in patients with herpes simplex (HSV-1 and HSV-2)

Dr. Mele notes that acyclovir (ACV) was superior to idoxuridine (IDU) 0.5% in Study 3, and Study 4 showed that ACV was non-inferior to IDU 1.0% for the Day 7 endpoint of ulcer healing rates, based on a 12% non-inferiority margin derived by comparing IDU to placebo (see Appendix 5.2 of Statistical Review). For the other three studies (002, 005 and 006): one study does not present data for dendritic ulcers only, a second study was underpowered to show superiority or non-inferiority with only 10 patients in each arm and the third study appears to be inconsistent with the other studies by design (no use of an anticholinergic) and by results (unusually low healing rate for ACV of 62% at Day 7).
Overall, the pooled assessment of outcomes at Day 7 yields a healing rate of 99/119 (83%), 95% CI 76%-90%, for acyclovir and 61/119 (50%), 95% CI 41%-59%, for idoxuridine. It is noted that some studies also included patient with geographic ulcers, a more advanced condition than dendritic ulcers. Average time to healing was generally reported as occurring earlier with acyclovir.

The reviewers conclude that the submitted studies demonstrate safety and efficacy of acyclovir ophthalmic ointment 3%. This conclusion is consistent with the Guidance to Industry document on demonstrating effectiveness based on published clinical trials. These studies, however, demonstrate the safety and effectiveness of Burroughs Wellcome product. For this 505(b)(2) application in which no studies were conducted using the Fera product, a scientific “bridge” is needed between the two products to be able to conclude that if the Fera acyclovir ophthalmic ointment 3% had been used in these trials, it (like the Burroughs Wellcome product) would have been shown to be safe and effective (see Section 2).

Comment: Reviewers recommend revisions to labeling and approval.

8. Safety

The following is a brief summary of the safety issues. For additional information, see clinical reviews by Drs. Nevitt, Boyd and Chambers.

The adverse reaction information is based on the submitted publications. The most common adverse reactions reported in >1% of patients were punctuate keratitis, eye pain (burning, stinging), follicular conjunctivitis, and increase lacrimation.
9. Advisory Committee Meeting

An Advisory Committee meeting was not held for this 505(b)(2) application.

10. Pediatrics

The applicant has orphan designation for the indication “treatment of acute herpetic keratitis associated with Herpes Simplex Virus type 1 and type 2,” therefore the Pediatric Research Equity Act requirements are not applicable to this NDA.

11. Other Relevant Regulatory Issues

11.1 Compliance Inspection
Overall the Office of Compliance found manufacturing facilities acceptable.

11.2 Office of Scientific Investigation (OSI) Audits
No OSI inspections were conducted on the published clinical studies in this 505(b)(2) application.

11.3 Debarment Certification
Fera certified that they have not and will not use in any capacity the services of any person debarred under the Federal Food Drug and Cosmetic Act, Section 306(k)(1) in connection with the application.

11.4 Financial Disclosure
Fera states they have not conducted any clinical studies under their sponsorship but are relying solely on data from the scientific literature to the clinical and non-clinical evaluations to support the safety and efficacy of their product.

11.5 Other Regulatory Issues
For a discussion of 505(b)(2)-related issues, see Section 2 of this review.

12. Labeling

Labeling was reviewed by the Division, DAVP (virology), DMEPA and OPDP and recommendation considered and included as applicable.

- **Package insert (PI):** PLR format
- **Carton and Container Labels:** Labels finalized
- **Proprietary Name:** DMEPA concluded that the proposed proprietary name Avaclyr is provisionally acceptable in the letter dated September 6, 2013. The name will need to be reviewed within 90 days of an action.
13. Decision/Action/Risk Benefit Assessment

13.1 Regulatory Action

A complete response will be issued, identifying the need to submit sufficient information to establish the scientific link between the Fera product and the Burroughs Wellcome product used in the published clinical trials.

13.2 Risk Benefit Assessment

Acute herpetic keratitis is a viral infection that affects over 20,000 patients yearly and is the leading cause of corneal blindness in the United States and the most common source of infectious blindness in the Western world.

Acyclovir ophthalmic ointment 3% was shown to be safe and effective for the treatment of patients with herpetic keratitis (dendritic ulcers) in published clinical studies with Burroughs Wellcome/GSK product. The GSK product, Zovirax® is approved in Europe, has been marketed for decades, and is listed on the WHO list of essential medications. There is no acyclovir ophthalmic ointment approved in the US. Availability of acyclovir ophthalmic ointment 3% would provide another treatment option.

Before the product can be approved, information needs to be provided on the comparability of the Fera and GSK product (see Appendix A for OGD recommendations). This information will be included in the Complete Response letter.

13.3 Recommendation for other Postmarketing Requirements (PRMs) and Commitments (PMCs)

None at this time
APPENDIX A: Text to be included in the Complete Response 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.

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.
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
03/31/2014
Submitted:

Submitted on March 18, 2014, are revised package insert and carton and container labeling. The applicant has accepted all of the Division’s recommended edits from the March 14, 2014, email correspondence to Fera.

Recommendations:

NDA 202408 for Avaclyr (acyclovir ophthalmic ointment) 3%, is recommended for approval for the treatment of acute herpetic keratitis (dendritic ulcers) with the package insert and with the carton and container labeling found here.

William M. Boyd, M.D.
Clinical Team Leader
Division of Transplant and Ophthalmology Products
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

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WILLIAM M BOYD
03/26/2014

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WILEY A CHAMBERS
03/28/2014

Reference ID: 3477814
1. Introduction

Acyclovir is a synthetic nucleoside analog active against herpes viruses. The drug substance is a white crystalline powder with the molecular formula of C₈H₁₁N₅O₃ and a molecular weight of 225.2. The maximum solubility in water at 37°C is 1.41 mg/mL. The pKa’s of acyclovir are 2.52 and 9.35.

The chemical name of acyclovir is 2-amino-1,9-dihydro-9-[(2-hydroxyethoxy)methyl]6H-purin-6-one, it has the following chemical structure:

![Chemical structure of acyclovir](image)

Avaclyr is a sterile ointment for topical administration. Each gram of ointment contains 30 mg of acyclovir in a white petrolatum base.

2. Background

Acyclovir has been shown to be active against HSV and HZV in human clinical studies.

Acyclovir ophthalmic ointment 3% (Zovirax) has been marketed in Europe and many countries around the world for several decades. Acyclovir Ophthalmic Ointment 3% is included on the WHO List of Essentials Medicines as the first line therapy of an Ophthalmological anti-infective agent.

On December 6, 2010, a Pre-NDA meeting with the FDA was held to discuss the requirements for filing the NDA submission as a 505(b)(2) submission.
Acyclovir ophthalmic ointment, 3% was granted Orphan drug Designation on December 13, 2010.

This is a 505(b)(2) application. Zovirax (acyclovir) Ointment 5% (NDA 18-604) is claimed as the listed drug. In this application, acyclovir has been formulated for topical ophthalmic use for a new indication, i.e., treatment of acute herpetic keratitis (dendritic ulcers). The literature provided in the application describes the use of acyclovir ophthalmic ointment, 3% for this proposed ocular indication.

The application references both a listed drug (Zovirax Ointment) and published literature. Zovirax (acyclovir) Ointment 5% (NDA 18-604) is a listed drug since it was approved in 1982 and has not been withdrawn. Clinical safety and efficacy studies which supported the approval of Zovirax are not relevant to the evaluation of Avaclyr. The applicant has therefore provided literature in the form of adequate and well controlled studies which demonstrate the safety and efficacy of acyclovir ophthalmic ointment 3%.

There is no listed drug which is or has been approved that includes acyclovir in an ophthalmic dosage form.

The studies published in the literature are applicable to the proposed drug product because they were conducted with a drug product which contains, to the extent that can be determined, the same active and inactive ingredients. The proposed drug product includes acyclovir uniformly distributed throughout the drug product (as documented in the Chemistry/Manufacturing Review). No absorption or transport of the active ingredient is necessary for the drug product to reach the infected cells since the disease being treated affects only the outermost layer of the cornea. The drug product will be placed in direct contact with the site where the disease occurs (on the corneal epithelium). There is no known interaction between the active ingredient and the base ingredient of the formulation. The drug substance has been shown in vitro to be incorporated into cells infected with herpes simplex virus when the drug is placed in direct contact with the cells.

### 3. Product Quality

The CMC review dated 3/13/14 recommends approval. In an email dated 3/12/14, CMC stated their issues have been resolved and they are writing a second review recommending approval. The finished drug product specifications in this review are the updated, finalized specifications.

**DRUG SUBSTANCE**

The drug substance information for Acyclovir is referenced through Drug Master File (DMF) and a letter of authorization was provided in the NDA on January 25, 2012. The DMF holder is Acyclovir, USP is purchased from

Reference ID: 3471030
Avacyr (acyclovir ophthalmic ointment) 3%  

DRUG PRODUCT  
The drug product was developed on behalf of Fera Pharmaceuticals. Zovirax ophthalmic ointment is not a US-approved drug but was approved in UK and many other countries for more than 30 years but is now discontinued.  

Product development of the acyclovir formula and dosage form was undertaken by on behalf of Fera Pharmaceuticals. The drug product was Zovirax is not approved in the United States as an ophthalmic dosage form; however it is approved in other dosage forms such as tablets, capsules, suspension, cream, ointment, and injectable.  

It was determined through the product labeling of Zovirax Ophthalmic Ointment, the UK brand (Zovirax UK), that the formulation consists solely of acyclovir and white petrolatum. The Fera formulation was

<table>
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<th>Ingredient</th>
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<th>Amount w/w (%)</th>
<th>Function</th>
<th>ID limit</th>
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<tbody>
<tr>
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<td>3%</td>
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<tr>
<td>white petrolatum, USP</td>
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<td></td>
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<tr>
<td>Total</td>
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Table 3.2.P.1-1 Qualitative/Quantitative Composition of the Formulation Acyclovir Ophthalmic Ointment, 3%
## Acyclovir Ophthalmic Ointment, 3%, Formula No AO357

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<thead>
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<th>Test</th>
<th>Analytical Method</th>
<th>Acceptance Criteria</th>
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<tbody>
<tr>
<td><strong>Description</strong></td>
<td>TMQC-203</td>
<td>Soft white ointment without visible discoloration, phase change or particulate matter</td>
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<tr>
<td>ID</td>
<td>TMQC-203</td>
<td>Retention time of major peak is same for std and sample</td>
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<td>ID: IR</td>
<td>USP &lt;197K&gt;</td>
<td>The IR absorption spectrum of the preparation of the test preparation exhibits maxima only at the same wavelengths as that of a similar preparation of the reference standard.</td>
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<td>Individual unknown</td>
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<td>Complies with USP &lt;71&gt;</td>
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<tr>
<td>Center</td>
<td></td>
<td>% label claim</td>
</tr>
<tr>
<td>Near crimp</td>
<td></td>
<td>% label claim</td>
</tr>
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</table>

**CONTAINER CLOSURE SYSTEM**

The container/closure system that will be used for the acyclovir ophthalmic ointment, 3% commercial product is a 3.5 g pre-printed tin tube with a black low density polyethylene cap. The tubes are purchased to use in production.

**INSPECTIONS:**

The Office of Compliance has made an “Overall Acceptable” recommendation for the manufacturing sites.
FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

<table>
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<th>NDA 202408/000</th>
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**Sponsor:** FERA PHARMS
**Brand Name:** ACYCLOVIR OPHTHALMIC OINTMENT, 3.0%
**Generic Name:** ACYCLOVIR OPHTHALMIC OINTMENT, 3.0%

**ACYCLOVIR OPHTHALMIC OINTMENT, 3.0%**

**Product Number:**
- Dosage Form: OINTMENT
- Ingredient: ACYCLOVIR
- Strengths: 3%

**FDA Contacts:**
- S. FAGAY: Prod Qual Reviewer
- N. SWEENEY: Med Rev
- N. BHANDARI: Product Quality RM
- L. ALMOZA: Regulatory Project Mgr
- B. SHANMUGAM: Team Leader

**FEDRA Contacts:**

**Establishment:**

**CFN:**

**FEI:**

**AADA:**

**DMF No:**
- FINISHED DOSAGE MANUFACTURER
- FINISHED DOSAGE OTHER TESTER
- FINISHED DOSAGE PACKAGER

**Profile:** STERILE OINTMENT

**OAI Status:** NONE

**Last Milestone:** OAI RECOMMENDATION

**Milestone Date:** 20-NOV-2013

**Decision:** ACCEPTABLE

**Reason:** DISTRICT RECOMMENDATION

---

Reference ID: 3471030
**FDA CDER EES ESTABLISHMENT EVALUATION REQUEST SUMMARY REPORT**

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<td>Responsibilities:</td>
<td>DRUG SUBSTANCE</td>
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<tr>
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<td>DISTRICT RECOMMENDATION</td>
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4. Nonclinical Pharmacology/Toxicology

From the original Pharmacology/Toxicology Review finalized 2/24/14:

All nonclinical data were derived from the referenced drug or published literature reports.

The literature referenced by the applicant supports previous findings detailed in the labeling for the listed acyclovir drug products. Systemic exposure following topical ocular administration is minimal, particularly when compared to the approved intravenous dose. Systemic toxicity following topical ophthalmic administration was not observed. In neonatal rats administered acyclovir subcutaneously, lower body weight gain, injection site reactions and findings related to renal pathology including increased BUN and cellular debris in the collecting ducts and Loop of Henle were observed in animals treated in rats treated with 80 mg/kg/day. Intravenous acyclovir is approved in neonates at a dose of 10 mg/kg infused at a constant rate over 1 hour, every 8 hours for 10 days.

From the package insert:

Acyclovir was not shown to be carcinogenic in mouse and rat bioassays at oral doses up to 450mg/kg (1000-2000 times the recommended human ophthalmic dose [RHOD], on a mg/m² basis).

Acyclovir was tested in 16 in vitro and in vivo genetic toxicity assays. Acyclovir was found to be negative in the Ames test, positive in vitro mouse lymphoma assay (TK locus), and positive in vitro and in vivo assays for chromosomal effects.

In reproduction studies acyclovir did not impair fertility or reproduction at oral doses up to 450 mg/kg/day in mice (1000 times the RHOD), or at subcutaneous doses of 25 mg/kg/day in rats (125 times the RHOD). At higher doses in rats and rabbits (50 mg/kg/day, subcutaneous), implantation efficacy was decreased.

5. Clinical Pharmacology/Biopharmaceutics

Although the Clinical Pharmacology review cites multiple listed products, the applicant’s only currently listed product is N018604 for Zovirax (acyclovir) Ointment 0.5%.

From the original Clinical Pharmacology Review finalized 2/19/14:

No new clinical pharmacology studies were conducted for this NDA. Acyclovir ophthalmic ointment 3.0% (30 mg/g) is a sterile drug product.
6. Sterility Assurance

From the original Product Quality Micro Review dated 1/23/14:

The Acyclovir, USP drug substance is manufactured by Altana Inc. Pharmaceutical Group, and each incoming drug substance lot is tested and microbiological control of the drug substance includes microbial quality acceptance criteria that comply with those specified for pharmaceutical use. Drug substance validation methods and results comply.

The container/closure system that will be used for the commercial drug product is a 3.5 g pre-printed tin tube with a black low density polyethylene cap. The tubes are purchased to use in production. Testing and release of the tin tubes is conducted by Altana Inc. Pharmaceutical Group, and reported in Validation Study # V-N-0000-16.12, dated October 20, 2003.
The drug product is for topical, ophthalmic multi-dose administration and does not contain a preservative. The drug product is sterile.

7. Clinical/Statistical - Efficacy

A total of 5 published clinical studies were presented and the original results re-evaluated to demonstrate the safety and efficacy of Acyclovir Ophthalmic Ointment 3% for the treatment of acute herpetic keratitis (dendritic ulcers) in patients with herpes simplex virus. The control in these trials was idoxuridine ophthalmic solution (IDU). IDU was the subject of several approved new drug applications for the treatment of herpes simplex keratitis. The new drug applications for IDU were supported by adequate and well controlled studies which demonstrated the superiority of IDU over its vehicle.

From the original Medical Officer Review finalized 2/18/2014:

The dosage regimen, patient demographics and study objectives and endpoints were consistent across the 5 studies. One or more of the following efficacy endpoints in the original publications included:

- Time to ulcer healing
- Ulcer healing rate at Day 7
- Ulcer healing rate at the end of the study

Since the healing rate at Day 7 is considered to be an important regulatory endpoint for approval of drugs for the proposed indication and not all of the original publications provided an analysis at this time point then all studies were reanalyzed to confirm the Day 7 healing rate.

<table>
<thead>
<tr>
<th>Study</th>
<th>Type of Study</th>
<th>Objective(s) of the Study</th>
<th>Study Design and Type of Control</th>
<th>Dosage Regimen; Concomitant Medications</th>
<th>Number of Subjects</th>
<th>Duration of Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colin 1981</td>
<td>Superficial herpetic keratitis: A comparative treatment in a doubleblind trial using acyclovir and idoxuridine</td>
<td>To evaluate the activity of acyclovir in human herpetic keratitis and to compare its effectiveness to that of idoxuridine</td>
<td>Comparative, multicenter, randomized, doublemasked comparison of acyclovir 3% vs. idoxuridine 0.5%</td>
<td>Acyclovir ophthalmic ointment 3% Idoxuridine ophthalmic ointment 0.5% 5 times daily for 7 days or until ulcer healing Atropine 1% twice daily</td>
<td>N=52 ACV=25 IDU=27</td>
<td>7 days or until ulcer healing</td>
</tr>
<tr>
<td>Collum 1980</td>
<td>A randomized doubleblind trial of acyclovir and idoxuridine in dendritic corneal ulceration</td>
<td>To compare the time to ulcer healing and the proportion of patients with healed ulcers between the two treatment groups.</td>
<td>Comparative, multicenter, randomized, doublemasked comparison of acyclovir 3% vs. idoxuridine 0.5%</td>
<td>Acyclovir ophthalmic ointment 3% Idoxuridine ophthalmic ointment 0.5% 5 times daily for at least 4 days or until ulcer healing</td>
<td>N=60 ACV=30 IDU=30</td>
<td>At least 4 days or until ulcer healing</td>
</tr>
</tbody>
</table>
### Analysis of Primary Endpoint(s)

The primary efficacy endpoint used in the review of this NDA is cure rate (healed ulcers) at Day 7.

**Acyclovir vs IDU – Day 7 Ulcer Healing Rates**

<table>
<thead>
<tr>
<th>First Author</th>
<th>Year</th>
<th>Control</th>
<th>Acyclovir Cures n/N (%)</th>
<th>IDU Cures n/N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colin</td>
<td>1981</td>
<td>IDU</td>
<td>19/25 (76)</td>
<td>11/27 (41)</td>
</tr>
<tr>
<td>Collum</td>
<td>1980</td>
<td>IDU</td>
<td>29/30 (97)</td>
<td>6/30 (20)</td>
</tr>
<tr>
<td>Coster</td>
<td>1980</td>
<td>IDU</td>
<td>27/28 (96)</td>
<td>22/26 (85)</td>
</tr>
</tbody>
</table>
Acyclovir 3% is superior to IDU for the treatment of dendritic ulcers in the Day 7 ulcer healing rates in all of the studies.

**Analysis of Secondary Endpoints(s)**
Time to ulcer cure was used as a supportive efficacy endpoint.

### Acyclovir vs IDU – Time to Ulcer Healing

<table>
<thead>
<tr>
<th>First Author</th>
<th>Year</th>
<th>Control</th>
<th>Acyclovir (days)</th>
<th>IDU (days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colin</td>
<td>1981</td>
<td>IDU</td>
<td>7.5</td>
<td>9</td>
</tr>
<tr>
<td>Collum</td>
<td>1980</td>
<td>IDU</td>
<td>Data not reported</td>
<td>8.7</td>
</tr>
<tr>
<td>Coster</td>
<td>1980</td>
<td>IDU</td>
<td>Data not reported</td>
<td>Data not reported</td>
</tr>
<tr>
<td>Klauber</td>
<td>1982</td>
<td>IDU</td>
<td>50% in 5-6 days Epithelial and stromal</td>
<td>50% in 10-12 days Epithelial and stromal</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>50% in 3-4 days Epithelial only</td>
<td>50% in 7 days Epithelial only</td>
</tr>
<tr>
<td>McCulley</td>
<td>1982</td>
<td>IDU</td>
<td>6.4 Dendritic only</td>
<td>6.6 Dendritic only</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>5.9 Dendritic and geographic</td>
<td>7.2 Dendritic and geographic</td>
</tr>
</tbody>
</table>

The time to ulcer healing provides additional evidence that Acyclovir 3% is effective in treating dendritic ulcers.

### Summary Efficacy Statement
The literature describing adequate and well-controlled clinical trials demonstrate that acyclovir ophthalmic ointment 3% is superior to IDU for the treatment of dendritic ulcers in the Day 7 ulcer healing rates.

8. **Safety**

From the original Medical Officer Review finalized 2/18/14:

The major sources of clinical data utilized include:

Two single center randomized, double-masked clinical trials – Klauber et al 1982 and Coster et al 1980 (Note: Coster study did not report adverse events and is not included in the safety data base)

Worldwide marketing experience

The patient exposure and safety assessments were adequate.

274 patients were included in the 5 clinical studies. Since no adverse events were reported in Coster et al 1980, the overall safety assessment is based on 214 patients exposed to either ACV 3% (n=103) and or IDU 0.5% (n=111).

Both ACV and IDU were dosed 5 times daily initially for 7 days. At the point of ulcer healing treatment was either withdrawn or reduced to 3 times daily for a further treatment period. Hence treatment durations varied considerably between patients and studies ranging from 2 to 17 days.

### Common Adverse Events

#### Adverse Events for Acyclovir Ophthalmic Ointment 3%

**Studies Pooled: Colin, Collum, Klauber and McCulley**

**Safety Population ***

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<tbody>
<tr>
<td></td>
<td>ACV 3%</td>
<td>IDU 0.5%</td>
<td>ACV 3%</td>
<td>IDU 0.5%</td>
<td>ACV 3%</td>
</tr>
<tr>
<td></td>
<td>n = 25</td>
<td>n = 27</td>
<td>n = 30</td>
<td>n = 30</td>
<td>n = 18</td>
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<tr>
<td>Punctate keratitis</td>
<td>2 (8%)</td>
<td>2 (7.4%)</td>
<td>0</td>
<td>6 (20%)</td>
<td>2 (11.1%)</td>
</tr>
<tr>
<td>Eye pain (stinging)</td>
<td>0</td>
<td>0</td>
<td>8 (26.7%)</td>
<td>1 (3.3%)</td>
<td>0</td>
</tr>
<tr>
<td>Follicular conjunctivitis</td>
<td>2 (8%)</td>
<td>2 (7.4%)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Lacrimation increased</td>
<td>0</td>
<td>0</td>
<td>2 (6.7%)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Palpebral allergy</td>
<td>1 (4%)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Punctal occlusion</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Glossodynia</td>
<td>0</td>
<td>0</td>
<td>1 (3.3%)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Eye irritation (Uveitis)</td>
<td>0</td>
<td>0</td>
<td>1 (3.3%)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Lid edema</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

* Since no adverse events were reported in Coster 1980 the overall safety assessment is based on 214 patients exposed to either ACV 3% (n=103) and or IDU 0.5% (n=111).

* One subject developed hypersensitivity to scopolamine

Source: Fera Section 2.7.4 Table 2

Overall, Acyclovir Ophthalmic Ointment 3% was well tolerated with a safety profile in these clinical studies (qualitatively and quantitatively) similar to that previously reported from products approved and marketed outside of the United States for the last 3 decades. Based on this evidence, as well as
the assessment of excellent systemic and local tolerance Acyclovir Ophthalmic Ointment 3% has an excellent safety and tolerability profile.

Overall for Acyclovir 3%, AEs reported with a frequency greater than 1% include punctuate keratitis, eye pain (burning and stinging on instillation) and follicular conjunctivitis. Those AEs occurring at a rate greater than 5% include punctuate keratitis and eye pain (burning and stinging on instillation).

Safety Summary Statement
The submitted studies in this NDA support a favorable safety profile for acyclovir in the treatment of acute herpes simplex keratitis (dendritic ulcer).

The most common adverse events (>1%) were punctuate keratitis, and eye pain (burning, stinging), follicular conjunctivitis, and increased lacrimation.

9. Advisory Committee Meeting
No Advisory Committee Meeting was held. There were no new issues raised in the review of the application which were thought to benefit from an Advisory Committee Meeting.

10. Pediatrics
This drug product has been designated an orphan drug and hence, is exempt from the pediatric assessment requirement under 21 CFR 314.55(d). Safety and efficacy in pediatric patients below the age of 2 years have not been established.

11. Other Relevant Regulatory Issues

BIOSTATISTICS
Per the original Biostatistics review finalized 10/30/13:

The applicant has provided publications for five studies comparing ACV to IDU as evidence for the efficacy of ACV in the treatment of dendritic ulcers.

All five studies are double-blind, randomized trials conducted in the early 1980’s and designed to compare ACV to IDU. IDU 0.5% was the comparator in four of the five studies; Study 004 used IDU 1%. All trials used ACV 3%. One study (006) was conducted in the US; with 64 patients, it was the largest study. Three of the five studies were multicenter trials.
The healing rates at Day 7 are considered the primary endpoint. The presentation of results differed across the studies but a Day 7 healing rate could be computed from the data provided with either the data provided explicitly or interpolated from graphs of healing rates. End of study data was always provided but the definition of end of study varied across studies. This reviewer did not consider summarizing time to healing since schedules for following patients during the trial varied considerably. In some studies, patients were seen on specific follow-up days while in others patients were seen twice a week or every other day. Also length of follow-up varied as can be seen from Table 3.1.

The results for all 5 studies are provided in Table 3.2. As stated earlier, Study 002 included results for dendritic and geographic ulcers combined; so this reviewer is presenting the results for that study for completion but not including this study in the overall statistical assessment of efficacy of acyclovir for the treatment of dendritic ulcers. Healing rates were ascertained from the publications and treatment differences with 95% confidence intervals were computed by the reviewer.

Studies 003, 004 and 005 showed higher healing rates at Day 7 for ACV than IDU; the treatment difference was statistically significant in one study (Study 003, p<0.0001, Fisher’s exact test). The US study (006) showed Day 7 healing rates for both ACV and IDU that were 20-30% lower than what was seen in the other 3 studies. Also the US study showed slightly higher rates for IDU than ACV; 4% higher on Day 7 and 7% higher on Day 14. One difference between the report for the US study and the other 3 studies is that the other three study reports all mention that an anticholinergic was given with the randomized treatment. There may also be patient population differences that could explain the difference in rates between the US study and the other studies but there is insufficient information to assess this hypothesis.

<table>
<thead>
<tr>
<th>Reference</th>
<th>FP-ACV-002</th>
<th>FP-ACV-003</th>
<th>FP-ACV-004</th>
<th>FP-ACV-005</th>
<th>FP-ACV-006</th>
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<tbody>
<tr>
<td>Healing rates¹ Day 7 ACV</td>
<td>19/25 (76%)</td>
<td>29/30 (97%)</td>
<td>27/28 (96%)</td>
<td>8/10 (80%)</td>
<td>16/26 (62%)</td>
</tr>
<tr>
<td>IDU</td>
<td>11/27 (41%)</td>
<td>6/30 (20%)</td>
<td>22/26 (85%)²</td>
<td>5/10 (50%)</td>
<td>17/26 (65%)</td>
</tr>
<tr>
<td>Risk Difference³ ACV-IDU (95%CI)</td>
<td>+35% (+8%, +60%)</td>
<td>+77% (+57%, +88%)</td>
<td>+12% (-5%, +32%)</td>
<td>+30% (-15%, +67%)</td>
<td>-3.8% (-30%, +23%)</td>
</tr>
<tr>
<td>End of study ACV</td>
<td>23/25 (92%)</td>
<td>30/30 (100%)</td>
<td>28/28 (100%)</td>
<td>10/10 (100%)</td>
<td>22/26 (85%)</td>
</tr>
<tr>
<td>IDU</td>
<td>22/27 (81%)</td>
<td>22/30 (73%)</td>
<td>26/26 (100%)</td>
<td>10/10 (100%)</td>
<td>24/26 (92%)</td>
</tr>
</tbody>
</table>
The healing rates were extracted from the literature and study reports. When 7 day results were not available, the applicant interpolated the 7 day results from a graph of time to healing found in the publication; this reviewer checked the interpolation.

2 The high rate of 85% for IDU in this study is for a dosage of 1% for IDU compared to 0.5% in the rest of the studies.

3 Risk differences were computed by this reviewer and are based on an exact test to compare proportions. Positive risk differences favor ACV.

**DMEPA**
The proposed proprietary name, Avacyl, was found acceptable from both a promotional and safety perspective, and Fera Pharmaceuticals, Inc. was informed in a letter dated 9/6/13.

DMEPA provided formal labeling comments for the original package insert and carton and container labeling in a review dated 10/24/13.

**OFFICE OF PRESCRIPTION DRUG PROMOTION (OPDP)**
OPDP completed a review of the substantially complete labeling on 2/25/14. A number of the suggested revisions could not be made because this application is a literature-based, 505(b)(2) application. A teleconference was held between this reviewer and the OPDP reviewer on 2/26/14 to discuss.

**FINANCIAL DISCLOSURE**
This is a 505(b)(2) application. There are no covered clinical studies in this application.

**OSI**
An Office of Scientific Investigations (OSI) audit was not requested.

### 12. Labeling

NDA 202408 for Avacyl (acyclovir opthalmic ointment) 3%, is recommended for approval for the treatment of acute herpetic keratitis (dendritic ulcers) with the revised package insert and suggested revisions to carton and container labeling found in this CDTL review.

### 13. Recommendations/Risk Benefit Assessment

**RECOMMENDED REGULATORY ACTION:**
NDA 202408 for Avacyl (acyclovir opthalmic ointment) 3%, is recommended for approval for the treatment of acute herpetic keratitis (dendritic ulcers) with the revised package insert and suggested revisions to carton and container labeling found in this CDTL review (see Appendix).

**RISK BENEFIT ASSESSMENT:**
There is adequate information in the literature to demonstrate that the active ingredient, acyclovir, a synthetic purine nucleoside analogue antiviral agent, inhibits replication of herpes viruses both in vitro and in vivo. Sensitive human viruses include herpes simplex virus (HSV, types 1 and 2) and varicella-zoster virus (VRZ).
Acyclovir (ACV) is the active ingredient that has been approved and marketed in the US under the trade name Zovirax with various strengths and formulations since 1982. However, no ophthalmic ointment formulation of acyclovir has been approved in the United States. Acyclovir ophthalmic ointment 3% (Zovirax) has been marketed in Europe and many countries around the world for several decades.

The submitted studies in this NDA support a favorable risk benefit profile regarding the safety and efficacy of acyclovir in the treatment of acute herpes simplex keratitis (dendritic ulcer).

The most common adverse events (>1%) were punctuate keratitis, and eye pain (burning, stinging), follicular conjunctivitis, and increased lacrimation.

Clinical, Biostatistics, Pharmacology/Toxicology, Product Quality and Clinical Pharmacology have recommended approval for this application.

**RECOMMENDATION FOR POSTMARKETING RISK MANAGEMENT ACTIVITIES:**

**CLINICAL**

There are no risk management activities recommended beyond the routine monitoring and reporting of all adverse events. There are no recommended Postmarketing Requirements or Phase 4 Commitments.

**Appendix**

NDA 202408 for Avaclyr (acyclovir ophthalmic ointment) 3%, is recommended for approval for the treatment of treatment of acute herpetic keratitis (dendritic ulcers) with the revised package insert and with the suggested revisions to carton and container labeling found here.

5 Pages of Draft Labeling have been Withheld in Full as B4 (CCI/TS) immediately following this page.

Reference ID: 3471030
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

WILLIAM M BOYD
03/18/2014

WILEY A CHAMBERS
03/18/2014
Deputy Division Director Review of NDA 202-408

<table>
<thead>
<tr>
<th>Date</th>
<th>March 15, 2014</th>
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<td>From</td>
<td>Wiley A. Chambers, M.D.</td>
</tr>
<tr>
<td>NDA #</td>
<td>NDA 202-408</td>
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<tr>
<td>Applicant</td>
<td>Fera Pharmaceuticals, Inc.</td>
</tr>
<tr>
<td>Date of Submission</td>
<td>May 31, 2013</td>
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<td>Proprietary Name / Established (USAN) names</td>
<td>Avacyl (acyclovir ophthalmic ointment) 3%</td>
</tr>
<tr>
<td>Dosage forms / Strength</td>
<td>Topical ophthalmic ointment</td>
</tr>
<tr>
<td>Indication(s)</td>
<td>Treatment of acute herpetic keratitis (dendritic ulcers)</td>
</tr>
<tr>
<td>Recommendation</td>
<td>Recommended for Approval</td>
</tr>
</tbody>
</table>

1. Introduction

Acyclovir is a synthetic nucleoside analog active against herpes viruses. The drug substance is a white crystalline powder with the molecular formula of \( \text{C}_8\text{H}_{11}\text{N}_5\text{O}_3 \) and a molecular weight of 225.2. The maximum solubility in water at \( 37°C \) is 1.41 mg/mL. The pKa's of acyclovir are 2.52 and 9.35.

The chemical name of acyclovir is 2-amino-1,9-dihydro-9-[(2-hydroxyethoxy)methyl]6H-purin-6-one, it has the following chemical structure:

![Chemical Structure of Acyclovir](image)

Avacyl is a sterile ointment for topical administration. Each gram of ointment contains 30 mg of acyclovir in a white petrolatum base.

2. Background

Acyclovir ophthalmic ointment 3% was developed in the mid-1980s by Burroughs-Wellcome under IND 13,923. At the same time, Burroughs-Wellcome developed IND Viroptic (trifluridine ophthalmic solution). Burroughs submitted an NDA for Viroptic in the United States, but never submitted an NDA for acyclovir ophthalmic ointment. Burroughs did submit a marketing application in Europe. Following various corporate mergers, GalaxoSmithKline now markets acyclovir ophthalmic ointment in Europe. Based on meetings with the firm, GlaxoSmithKline does not have access to the original studies conducted with the product, although several have been published. Acyclovir ophthalmic ointment has been marketed in Europe and several countries around the world for over three decades.

There is no evidence that any formulation of acyclovir ophthalmic ointment other than the one proposed for marketing in this application (acyclovir USP mixed with white petrolatum, USP) has been used in any clinical trial or marketed. The manufacturing synthesis of the drug substance, acyclovir, has changed multiple times and it does not appear that any product is currently (or has been for years) manufactured the same way it was manufactured for the clinical trials.
Acyclovir ophthalmic ointment, 3% was granted Orphan drug Designation on December 13, 2010.

The present application was submitted as a 505(b)(2) application. Zovirax (acyclovir) Ointment 0.5% (NDA 18-604) was cited as the listed drug. Zovirax (acyclovir) Ointment 5% has a different formulation, a different indication, a different site of use, and a different concentration. It does not include the same active ingredient. Zovirax is indicated in the management of initial genital herpes and in limited non-life-threatening mucocutaneous Herpes simplex virus infections in immunocompromised patients. Zovirax is not approved in the United States as an ophthalmic dosage form; however, it is approved in other dosage forms such as tablets, capsules, suspension, cream, ointment, and injectable.

Zovirax ointment with its different formulation is intended for use on the skin, but not the eye. In this application, acyclovir has been formulated for topical ophthalmic use for a new indication, i.e., treatment of acute herpetic keratitis (dendritic ulcers). The application references studies in the literature to support the safety and efficacy of acyclovir ophthalmic ointment, 3% for this proposed ocular indication.

3. Product Quality

The CMC review recommends approval. The drug substance information for Acyclovir is referenced through Drug Master File (DMF) and a letter of authorization was provided in the NDA on January 25, 2012. The DMF holder is Acyclovir, USP is purchased from Microbiological control of the drug substance includes The container/closure system that will be used for the commercial drug product is a 3.5 g pre-printed tin tube with a black low density polyethylene cap. The tubes are purchased.
Validation of drug product container/closure (C/C) integrity was demonstrated via microbial challenge by Altha Inc. Pharmaceutical Group, and reported in Validation Study # V-N-0000-16.12, dated October 20, 2003.

Product development of the acyclovir formula and dosage form was undertaken by ___ on behalf of Fera Pharmaceuticals. The drug product is required to list all active and inactive ingredients.

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Amount/gm</th>
<th>Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acyclovir, USP</td>
<td>30 mg</td>
<td>Active</td>
</tr>
<tr>
<td>White petrolatum, USP</td>
<td></td>
<td>Base</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Test</th>
<th>Analytical Method</th>
<th>Acceptance Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Description</td>
<td>TMQC-203</td>
<td>Soft white ointment without visible discoloration, phase change or particulate matter.</td>
</tr>
<tr>
<td>ID</td>
<td>TMQC-203</td>
<td>Retention time of major peak is same for std and sample.</td>
</tr>
<tr>
<td>ID, IR</td>
<td>USP 197K</td>
<td>The IR absorption spectrum of the preparation of the test preparation exhibits maxima only at the same wavelengths as that of a similar preparation of the reference standard.</td>
</tr>
<tr>
<td>Assay (30 mg/g)</td>
<td>TMQC-203</td>
<td>NMT, NMT, NMT, NMT, NMT, NMT, NMT.</td>
</tr>
<tr>
<td>Related Substances and Impurities</td>
<td>TMQC-203</td>
<td>NMT.</td>
</tr>
<tr>
<td>Total known and unknown</td>
<td></td>
<td>NMT.</td>
</tr>
<tr>
<td>Water Content USP 921</td>
<td>TMQC-203</td>
<td>NMT.</td>
</tr>
<tr>
<td>Minimum Fill</td>
<td>TMQC-203</td>
<td>NMT.</td>
</tr>
<tr>
<td>Metal Particles USP 751</td>
<td></td>
<td>NMT.</td>
</tr>
<tr>
<td>Leak Test USP 771</td>
<td>TMQC-203</td>
<td>No leakage in tubes.</td>
</tr>
<tr>
<td>Sterility USP 711</td>
<td></td>
<td>NMT.</td>
</tr>
<tr>
<td>Particle size Less than 0.5</td>
<td>TMQC-203</td>
<td>NMT.</td>
</tr>
<tr>
<td>Kinematic viscosity</td>
<td></td>
<td>NMT.</td>
</tr>
<tr>
<td>Residual Solvents USP 467</td>
<td>TMQC-203</td>
<td>NMT.</td>
</tr>
<tr>
<td>Homogeneity Assay (30 mg/g)</td>
<td>TMQC-203</td>
<td>NMT.</td>
</tr>
</tbody>
</table>
INSPECTIONS:
The Office of Compliance has made an “Overall Acceptable” recommendation for the manufacturing sites.

4. 505(b)(2) Bridging

The present application was submitted as a 505(b)(2) application. The application references both a listed drug (Zovirax Ointment) and published literature. Zovirax (acyclovir) Ointment 0.5% (NDA 18-604) is a listed drug since it was approved in 1982 and has not been withdrawn. The clinical safety and efficacy studies which supported the approval of Zovirax are not relevant to the evaluation of Avaclyr. The applicant has therefore provided literature in the form of adequate and well controlled studies which demonstrate the safety and efficacy of acyclovir ophthalmic ointment 3%.

There is no listed drug which is or has been approved that includes acyclovir in an ophthalmic dosage form.

The studies published in the literature are applicable to the proposed drug product because they were conducted with a drug product which contains, to the extent that can be determined, the same active and inactive ingredients. The proposed drug product includes acyclovir uniformly distributed throughout the drug product (as documented in the Chemistry/Manufacturing Review). No absorption or transport of the active ingredient is necessary for the drug product to reach the infected cells since the disease being treated affects only the outermost layer of the cornea. The drug product will be placed in direct contact with the site where the disease occurs (on the corneal epithelium). There is no known interaction between the active ingredient and the base ingredient of the formulation. The drug substance has been shown in vitro to be incorporated into cells infected with herpes simplex virus when the drug is placed in direct contact with the cells.

5. Nonclinical Pharmacology/Toxicology

All nonclinical data were derived from the referenced drug or published literature reports. The published literature is applicable because it includes the same active ingredient. While the relevant literature is not limited to studies with the current formulation, the regulations permit reference to nonclinical studies conducted with different dosage forms and different drug products including different concentrations. The literature referenced by the applicant supports previous findings detailed in the labeling for the listed acyclovir drug products. Systemic exposure following topical ocular administration is minimal, particularly when compared to the approved intravenous dose. Systemic toxicity following topical ophthalmic administration was not observed. In neonatal rats administered acyclovir subcutaneously, lower body weight gain, injection site reactions and findings related to renal pathology including increased BUN and cellular debris in the collecting ducts and Loop of Henle were observed in animals treated in rats treated with 80 mg/kg/day. Intravenous acyclovir is approved in neonates at a dose of 10 mg/kg infused at a constant rate over 1 hour, every 8 hours for 10 days.
6. Clinical Pharmacology/Biopharmaceutics
No new clinical pharmacology studies were conducted for this NDA.

7. Clinical/Statistical - Efficacy
A total of 5 published clinical studies were presented. The control in these trials was idoxuridine ophthalmic solution (IDU). IDU was the subject of several approved new drug applications for the treatment of herpes simplex keratitis. The new drug applications for IDU were supported by adequate and well controlled studies which demonstrated the superiority of IDU over its vehicle.

The original results of the acyclovir ophthalmic ointment studies demonstrated the safety and efficacy of Acyclovir Ophthalmic Ointment 3% for the treatment of acute herpetic keratitis (dendritic ulcers) in patients with herpes simplex virus. The dosage regimen, patient demographics and study objectives and endpoints were consistent across the 5 studies. One or more of the following efficacy endpoints in the original publications included:
• Time to ulcer healing
• Ulcer healing rate at Day 7
• Ulcer healing rate at the end of the study

Since the healing rate at Day 7 is considered to be an important endpoint for the proposed indication and not all of the original publications provided an analysis at this time point, all studies were reanalyzed to confirm the Day 7 healing rate.

**Analysis of Primary Endpoint(s)**
The primary efficacy endpoint used in the review of this NDA is cure rate (healed ulcers) at Day 7.

<table>
<thead>
<tr>
<th>First Author</th>
<th>Year</th>
<th>Control</th>
<th>Acyclovir Cures n/N (%)</th>
<th>IDU Cures n/N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colin</td>
<td>1981</td>
<td>IDU</td>
<td>19/25 (76)</td>
<td>11/27 (41)</td>
</tr>
<tr>
<td>Collum</td>
<td>1980</td>
<td>IDU</td>
<td>29/30 (97)</td>
<td>6/30 (20)</td>
</tr>
<tr>
<td>Coster</td>
<td>1980</td>
<td>IDU</td>
<td>27/28 (96)</td>
<td>22/26 (85)</td>
</tr>
<tr>
<td>Klauber</td>
<td>1982</td>
<td>IDU</td>
<td>8/10 (80)</td>
<td>5/10 (50)</td>
</tr>
<tr>
<td>McCulley</td>
<td>1982</td>
<td>IDU</td>
<td>16/26 (62)</td>
<td>17/26 (65)</td>
</tr>
<tr>
<td>Average (95% CI)</td>
<td>IDU</td>
<td>99/119 (83) (76% - 90%)</td>
<td>60/119 (50) (41% - 59%)</td>
<td></td>
</tr>
</tbody>
</table>

Source: Fera Section 2.5 Table 1

Acyclovir 3% is superior to IDU for the treatment of dendritic ulcers in the Day 7 ulcer healing rates in all of the studies.
Results for five double-blind, randomized studies of acyclovir versus idoxuridine; Study 002 results are for dendritic and geographic ulcers while results for Studies 003, 004, 005 and 006 are for dendritic ulcers only

<table>
<thead>
<tr>
<th>Reference</th>
<th>FP-ACV-002</th>
<th>FP-ACV-003</th>
<th>FP-ACV-004</th>
<th>FP-ACV-005</th>
<th>FP-ACV-006</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colin, 1981</td>
<td>19/25 (76%)</td>
<td>29/30 (97%)</td>
<td>27/28 (96%)</td>
<td>8/10 (80%)</td>
<td>16/26 (62%)</td>
</tr>
<tr>
<td>Collum, 1980</td>
<td>11/27 (41%)</td>
<td>6/30 (20%)</td>
<td>22/26 (85%)</td>
<td>5/10 (50%)</td>
<td>17/26 (65%)</td>
</tr>
<tr>
<td>Coster, 1980</td>
<td>+35% (+8%, +60%)</td>
<td>+77% (+57%, +88%)</td>
<td>+12% (-5%, +32%)</td>
<td>+30% (-15%, +67%)</td>
<td>-3.8% (-30%, +23%)</td>
</tr>
<tr>
<td>Klauber, 1982</td>
<td>23/25 (92%)</td>
<td>30/30 (100%)</td>
<td>28/28 (100%)</td>
<td>10/10 (100%)</td>
<td>22/26 (85%)</td>
</tr>
<tr>
<td>McCulley, 1982</td>
<td>22/27 (81%)</td>
<td>22/30 (73%)</td>
<td>26/26 (100%)</td>
<td>10/10 (100%)</td>
<td>24/26 (92%)</td>
</tr>
</tbody>
</table>

1The healing rates were extracted from the literature and study reports. When 7 day results were not available, the applicant interpolated the 7 day results from a graph of time to healing found in the publication; this reviewer checked the interpolation.

2The high rate of 85% for IDU in this study is for a dosage of 1% for IDU compared to 0.5% in the rest of the studies.

3Risk differences were computed by the statistical reviewer and are based on an exact test to compare proportions. Positive risk differences favor ACV.

**Analysis of Secondary Endpoints(s)**
Time to ulcer cure was used as a supportive efficacy endpoint.

<table>
<thead>
<tr>
<th>First Author</th>
<th>Year</th>
<th>Control</th>
<th>Acyclovir (days)</th>
<th>IDU (days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colin</td>
<td>1981</td>
<td>IDU</td>
<td>7.5</td>
<td>9</td>
</tr>
<tr>
<td>Collum</td>
<td>1980</td>
<td>IDU</td>
<td>4.4</td>
<td>8.7</td>
</tr>
<tr>
<td>Coster</td>
<td>1980</td>
<td>IDU</td>
<td>Data not reported</td>
<td>Data not reported</td>
</tr>
<tr>
<td>Klauber</td>
<td>1982</td>
<td>IDU</td>
<td>50% in 5-6 days</td>
<td>50% in 10-12 days</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Epithelial and stromal</td>
<td>Epithelial and stromal</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>50% in 3-4 days</td>
<td>50% in 7 days</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Epithelial only</td>
<td>Epithelial only</td>
</tr>
<tr>
<td>McCulley</td>
<td>1982</td>
<td>IDU</td>
<td>6.4 Dendritic only</td>
<td>6.6 Dendritic only</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>5.9 Dendritic and geographic</td>
<td>7.2 Dendritic and geographic</td>
</tr>
</tbody>
</table>

Source: Fera Section 2.7.3 Table 3

The literature describing adequate and well-controlled clinical trials demonstrate that acyclovir ophthalmic ointment 3% is superior to IDU for the treatment of dendritic ulcers in the Day 7 ulcer healing rates. The time to ulcer healing provides additional evidence that Acyclovir 3% is effective in treating dendritic ulcers.
8. Safety
The major sources of clinical data utilized included:

- Two single center randomized, double-masked clinical trials – Klauber et al 1982 and Coster et al 1980 (Note: Coster study did not report adverse events and is not included in the safety data base)
- Worldwide marketing experience

274 patients were included in the 5 clinical studies. Since no adverse events were reported in Coster et al 1980, the overall safety assessment is based on 214 patients exposed to either ACV 3% (n=103) and or IDU 0.5% (n=111).

Both ACV and IDU were dosed 5 times daily initially for 7 days. At the point of ulcer healing treatment was either withdrawn or reduced to 3 times daily for a further treatment period. Hence treatment durations varied considerably between patients and studies ranging from 2 to 17 days.

Acyclovir 3%, AEs reported with a frequency greater than 1% include punctuate keratitis, eye pain (burning and stinging on instillation) and follicular conjunctivitis. Those AEs occurring at a rate greater than 5% include punctuate keratitis and eye pain (burning and stinging on instillation).

9. Advisory Committee Meeting
No Advisory Committee Meeting was held. There were no new issues raised in the review of the application which were thought to benefit from an Advisory Committee Meeting.

10. Pediatrics
This drug product has been designated an orphan drug and hence, is exempt from the pediatric assessment requirement under 21 CFR 314.55(d). Safety and efficacy in pediatric patients below the age of 2 years have not been established.

11. Other Relevant Regulatory Issues

DMEPA
The proposed proprietary name, Avaclyr, was found acceptable from both a promotional and safety perspective, and Fera Pharmaceuticals, Inc. was informed in a letter dated 9/6/13.

FINANCIAL DISCLOSURE
There are no covered clinical studies in this application.

OSI
An Office of Scientific Investigations (OSI) audit was not requested.
12. **Labeling**

The proposed labeling for NDA 202408 for Avaclyr (acyclovir ophthalmic ointment) 3%, has been revised. The revised package insert with suggested revisions to carton and container labeling can be found in the Cross Discipline Team Leader review (CDTL) and at the end of this review.

13. **Recommendations/Risk Benefit Assessment**

NDA 202408 for Avaclyr (acyclovir ophthalmic ointment) 3%, is recommended for approval for the treatment of acute herpetic keratitis (dendritic ulcers) with the revised package insert and revisions to carton and container labeling found at the end of this review.

There are no risk management activities recommended beyond the routine monitoring and reporting of all adverse events. There are no recommended Postmarketing Requirements or Phase 4 Commitments.
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

WILEY A CHAMBERS
03/18/2014
CLINICAL REVIEW

Application Type NDA 202-408
Submission Number 000
Submission Code Original

Letter Date May 31, 2013
Stamp Date May 31, 2013
PDUFA Goal Date March 31, 2014

Reviewer Name Martin P Nevitt, M.D., M.P.H.
Review Completion Date March 1, 2014

Established Name acyclovir ophthalmic ointment 3%
(Proposed) Trade Name Avacylr
Therapeutic Class antiviral
Applicant Fera Pharmaceuticals, Inc.

Priority Designation S

Formulation Active ingredient: acyclovir (a synthetic nucleoside analogue), 2-amino-1,9 dihydro-9-[(2-hydroxyethoxy)methyl]6H-purin-6-one

Dosing Regimen 1 cm ribbon in the lower cul-de-sac of the affected eye 5 times per day (approximately every 3
hours while awake) until the corneal ulcer heals, and then 3 times per day for 7 days.

(Proposed) Indication: treatment of acute herpetic keratitis (dendritic ulcers)

Intended Population: Patients with acute herpetic keratitis
Clinical Review
Martin P Nevitt, M.D., M.P.H.
NDA 202-408 000
Avaclyr (acyclovir ophthalmic ointment) 3%

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

It is recommended that NDA 202-408 be approved with the labeling revisions found in this review.

The application supports the safety and effectiveness of acyclovir ophthalmic ointment 3% for the treatment of acute herpetic keratitis (dendritic ulcers).

1.2 Risk Benefit Assessment

There is adequate information in the literature to demonstrate that the active ingredient, acyclovir, a synthetic purine nucleoside analogue antiviral agent, inhibits replication of herpes viruses both in vitro and in vivo. Sensitive human viruses include herpes simplex virus (HSV, types 1 and 2) and varicella-zoster virus (VRZ).

Acyclovir (ACV) is the active ingredient that has been approved and marketed in the US under the trade name Zovirax with various strengths and formulations since 1981. However, no ophthalmic ointment formulation of acyclovir has been approved in the US.

Acyclovir Ophthalmic Ointment 3% (Zovirax) has been marketed in Europe and many countries around the world for several decades. Acyclovir Ophthalmic Ointment 3% is included on the WHO List of Essentials Medicines as the first line therapy of an Ophthalmological anti-infective agent.

The submitted studies in this NDA support a favorable risk benefit profile regarding the safety and efficacy of acyclovir in the treatment of acute herpes simplex keratitis (dendritic ulcer).

The most common adverse events (>1%) were punctuate keratitis, and eye pain (burning, stinging), follicular conjunctivitis, and increased lacrimation.

1.3 Recommendations for Postmarketing Risk Management Activities

There are no recommended Phase 4 clinical study commitments.

1.4 Recommendations for other Post Marketing Study Commitments

There are no optional or recommended Phase 4 requests.
2 Introduction and Regulatory Background

2.1 Product Information

Acyclovir is a synthetic nucleoside analog active against herpes viruses. The drug substance is a white crystalline powder with the molecular formula of C\textsubscript{8}H\textsubscript{11}N\textsubscript{5}O\textsubscript{3} and a molecular weight of 225. The maximum solubility in water at 37°C is 2.5 mg/mL. The pka’s of acyclovir are 2.27 and 9.25.

The chemical name of acyclovir is 2-amino-1,9-dihydro-9-[(2-hydroxyethoxy)methyl]6H-purin-6-one, it has the following chemical structure:

\[
\text{\includegraphics[width=0.5\textwidth]{acyclovir.png}}
\]

AVACLYR is a sterile ointment for topical administration only. Each gram of ointment contains 30 mg of acyclovir in a white petrolatum base.

2.2 Currently Available Treatments for Proposed Indications

Trifluridine ophthalmic solution 1% (NDA 18-299) is approved and marketed for the treatment of primary keratoconjunctivitis and recurrent epithelial keratitis due to herpes simplex virus, types 1 and 2.

Ganciclovir ophthalmic gel 0.15% (NDA 22-211) is approved and marketed for the treatment of acute herpetic keratitis (dendritic ulcers).

2.3 Availability of Proposed Active Ingredient in the United States

Acyclovir is a synthetic purine nucleoside analogue with \textit{in vitro} and \textit{in vivo} inhibitory activity against herpes simplex virus types 1 and 2 (HSV-1 and HSV-2) and varicella-zoster virus (VZV).

Acyclovir has been approved by the FDA for the following indications and dosage forms:

<table>
<thead>
<tr>
<th>NDA #</th>
<th>Active Ingredient</th>
<th>Dosage Form</th>
<th>Route of Administration</th>
<th>Strength</th>
<th>Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>N018604</td>
<td>acyclovir</td>
<td>ointment</td>
<td>topical</td>
<td>5%</td>
<td>Genital herpes</td>
</tr>
<tr>
<td>N021478</td>
<td>acyclovir</td>
<td>cream</td>
<td>topical</td>
<td>5%</td>
<td>Herpes labialis (lip cold sore)</td>
</tr>
<tr>
<td>N018828</td>
<td>acyclovir</td>
<td>capsule</td>
<td>oral</td>
<td>200 mg</td>
<td>Acute treatment of herpes zoster (shingles)</td>
</tr>
<tr>
<td>N019909</td>
<td>acyclovir</td>
<td>suspension</td>
<td>oral</td>
<td>200 mg/ml</td>
<td></td>
</tr>
<tr>
<td>N020089</td>
<td>acyclovir</td>
<td>tablet</td>
<td>oral</td>
<td>400 and 800 mg</td>
<td></td>
</tr>
</tbody>
</table>
2.4 Important Safety Issues With Consideration to Related Drugs

AVACLYR is contraindicated for patients who develop a sensitivity to acyclovir or valacyclovir. Patients should not wear contact lenses during the course of therapy while taking AVACLYR.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

On December 6, 2010 a Pre-NDA meeting with the FDA was held to discuss the requirements for filing the NDA submission as a 505(b)(2) submission.

Acyclovir ophthalmic ointment, 3% was granted Orphan drug Designation on December 13, 2010.

2.6 Other Relevant Background Information

Acyclovir has been shown to be active against HSV and HZV in human clinical studies.

Acyclovir Ophthalmic Ointment 3% (Zovirax) has been marketed in Europe and many countries around the world for several decades. Acyclovir Ophthalmic Ointment 3% is included on the WHO List of Essentials Medicines as the first line therapy of an Ophthalmological anti-infective agent.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

There is no evidence that the submitted studies were not conducted in accordance with acceptable clinical ethical standards.

3.2 Compliance with Good Clinical Practices

The clinical studies included in this application conformed to Good Clinical Practices.

3.3 Financial Disclosures

All clinical studies included in this application were conducted in Europe and the US between 1980 and 1982.
4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

See Section 2.1 this review.

4.2 Clinical Microbiology

Not applicable to this review.

4.3 Preclinical Pharmacology/Toxicology

The prescribing information for Acyclovir Ophthalmic Ointment 3% (Zovirax) approved in countries outside of the US contains the following preclinical safety information:

- A range of mutagenicity tests in vitro and in vivo indicate that acyclovir does not pose a genetic risk.
- Acyclovir was not found to be carcinogenic in long term studies in the rat and the mouse.
- Largely reversible adverse effects on spermatogenesis in association with overall toxicity in rats and dogs have been reported only at doses of acyclovir greatly in excess of those employed therapeutically. Studies in mice did not reveal any effect of orally administered acyclovir on fertility.
- Systemic administration of acyclovir did not produce embryotoxicity or teratogenic effects in rats, rabbits or mice.
- Fetal abnormalities were observed, but only following high subcutaneous doses such that maternal toxicity was produced. The clinical relevance of these findings is uncertain.

Since systemic exposure following topical ocular administration is low these nonclinical findings are not considered to be a safety concern for Acyclovir Ophthalmic Ointment 3%. Nevertheless it is recommended that:

- Use during pregnancy should only occur if the potential benefit justifies the potential risk to the fetus.
- Caution should be used in nursing mothers since acyclovir is known to pass into breast milk at low concentrations.
4.4 Clinical Pharmacology

4.4.1 Mechanism of Action

Acyclovir is a synthetic purine nucleoside analogue with *in vitro* and *in vivo* inhibitory activity against herpes simplex virus types 1 and 2 (HSV-1 and HSV-2) and varicella-zoster virus (VZV).

The inhibitory activity of acyclovir is highly selective due to its affinity for the enzyme thymidine kinase (TK) encoded by HSV and VZV. This viral enzyme converts acyclovir into acyclovir monophosphate, a nucleotide analogue. The monophosphate is further converted into diphosphate by cellular guanylate kinase and into triphosphate by a number of cellular enzymes.

*In vitro*, acyclovir triphosphate stops replication of herpes viral DNA. This is accomplished in three ways:
1) Competitive inhibition of viral DNA polymerase
2) Incorporation into and termination of the growing viral DNA chain
3) Inactivation of the viral DNA polymerase.

The greater antiviral activity of acyclovir against HSV compared to VZV is due to its more efficient phosphorylation by the viral TK.

The quantitative relationship between the *in vitro* susceptibility of herpes virus to antivirals and the clinical response to therapy has not been established in humans, and virus sensitivity testing has not been standardized. Sensitivity testing results, expressed as the concentration of drug required to inhibit by 50% the growth of virus in cell culture (IC50), vary greatly depending upon a number of factors. Using plaque-reduction assays, the IC50 against herpes simplex virus isolates ranges from 0.02 to 13.5 mcg/mL for HSV-1 and from 0.01 to 9.9 mcg/mL for HSV-2. The IC50 for acyclovir against most laboratory strains and clinical isolates of VZV ranges from 0.12 to 10.8 mcg/mL. Acyclovir also demonstrates activity against the Oka vaccine strain of VZV with a mean IC50 of 1.35 mcg/mL (Zovirax® oral PI).

Resistance of HSV and VZV to acyclovir can result from qualitative and quantitative changes in the viral TK and/or DNA polymerase. Clinical isolates of HSV and VZV with reduced susceptibility to acyclovir have been recovered from immune compromised patients, especially with advanced HIV infection. While most of the acyclovir resistant mutants isolated thus far from such patients have been found to be TK deficient mutants, other mutants involving the viral TK gene (TK partial and TK altered) and DNA polymerase have been isolated. TK negative mutants may cause severe disease in infants and immune compromised adults. The possibility of viral resistance to acyclovir should be considered in patients who show poor response during therapy (Zovirax® oral PI).
3.2. Pharmacokinetics

4.4.2 Pharmacokinetics

No formal comparative bioavailability studies have been conducted with Acyclovir Ophthalmic Ointment, 3%. The drug product is a simple formulation consisting solely of acyclovir 30 mg/g in a white petrolatum base. The finished product was formulated to match the listed drug Zovirax in both active and inactive ingredients. Zovirax is not currently approved in the United States for Ophthalmic use, but is approved and marketed in over 30 (+) countries outside the United States.

5 Sources of Clinical Data

5.1 Tables of Clinical Studies

A total of 5 clinical published clinical studies are presented and the original results re-evaluated to demonstrate the safety and efficacy of Acyclovir Ophthalmic Ointment 3% for the treatment of acute herpetic keratitis (dendritic ulcers) in patients with herpes simplex virus. The dosage regimen, patient demographics and study objectives and endpoints were consistent across the 5 studies. One or more of the following efficacy endpoints in the original publications included:

- Time to ulcer healing
- Ulcer healing rate at Day 7
- Ulcer healing rate at the end of the study

Since the healing rate at Day 7 is considered to be an important regulatory endpoint for approval of drugs for the proposed indication and not all of the original publications provided an analysis at this time point then all studies were reanalyzed to confirm the Day 7 healing rate.

<table>
<thead>
<tr>
<th>Study</th>
<th>Type of Study</th>
<th>Objective(s) of the Study</th>
<th>Study Design and Type of Control</th>
<th>Dosage Regimen; Concomitant Medications</th>
<th>Number of Subjects</th>
<th>Duration of Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colin 1981</td>
<td>Superficial herpetic keratitis: A comparative treatment in a doubleblind trial using acyclovir and idoxuridine</td>
<td>To evaluate the activity of acyclovir in human herpetic keratitis and to compare its effectiveness to that of idoxuridine</td>
<td>Comparative, multicenter, randomized, doublemasked comparison of acyclovir 3% vs. idoxuridine 0.5%</td>
<td>Acyclovir ophthalmic ointment 3% Idoxuridine ophthalmic ointment 0.5% 5 times daily for 7 days or until ulcer healing Atropine 1% twice daily</td>
<td>N=52 ACV=25 IDU=27</td>
<td>7 days or until ulcer healing</td>
</tr>
<tr>
<td>Collum 1980</td>
<td>A randomized doubleblind trial of acyclovir and idoxuridine in dendritic</td>
<td>To compare the time to ulcer healing and the proportion of patients with</td>
<td>Comparative, multicenter, randomized, doublemasked comparison of</td>
<td>Acyclovir ophthalmic ointment 3% Idoxuridine ophthalmic</td>
<td>N=60 ACV=30 IDU=30</td>
<td>At least 4 days or until ulcer healing</td>
</tr>
</tbody>
</table>
### Table

<table>
<thead>
<tr>
<th>Study</th>
<th>Design Description</th>
<th>Treatment 1</th>
<th>Treatment 2</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coster 1980</td>
<td>A comparison of acyclovir and idoxuridine as treatment for ulcerative keratitis</td>
<td>Acyclovir ophthalmic ointment 3% vs. idoxuridine ophthalmic ointment 0.5%</td>
<td>Homatropine 1% twice daily</td>
<td>N=60 ACV=30 IDU=30</td>
</tr>
<tr>
<td></td>
<td>To compare the effects of acyclovir and idoxuridine ophthalmic ointments on the rate of healing of herpetic corneal ulcers.</td>
<td>Comparative, single center, randomized, double-masked comparison of acyclovir 3% vs. idoxuridine 1.0%</td>
<td>Acyclovir ophthalmic ointment 3% Idoxuridine ophthalmic ointment 1.0% 5 times daily until ulcer healing then 3 times daily for 3 days Atropine 1% once daily</td>
<td></td>
</tr>
<tr>
<td>Klauber 1982</td>
<td>Ayclovir and idoxuridine treatment of herpes simplex keratitis – a double blind clinical study</td>
<td>To compare acyclovir to idoxuridine for the ulcer cure rate and time to ulcer healing of herpes simplex keratitis</td>
<td>Comparative, single center, randomized, double-masked comparison of acyclovir 3% vs. idoxuridine 0.5%</td>
<td>N=38 ACV=18 IDU=20</td>
</tr>
<tr>
<td></td>
<td>Acyclovir ophthalmic ointment 3% vs. idoxuridine ophthalmic ointment 0.5%</td>
<td>Acyclovir ophthalmic ointment 3% Idoxuridine ophthalmic ointment 0.5% 5 times daily until ulcer improvement then 3 times daily until healed Scopolamine 0.2% twice daily</td>
<td></td>
<td></td>
</tr>
<tr>
<td>McCulley 1982</td>
<td>A double masked multicenter clinical trial of acyclovir vs. idoxuridine for treatment of epithelial herpes simplex keratitis</td>
<td>To evaluate the healing time patterns between patients with herpes simplex keratitis treated with acyclovir compared to patients treated with idoxuridine.</td>
<td>Comparative, multicenter, randomized, double-masked comparison of acyclovir 3% vs. idoxuridine 0.5%</td>
<td>N=64 ACV=30 IDU=34</td>
</tr>
<tr>
<td></td>
<td>Acyclovir ophthalmic ointment 3% Idoxuridine ophthalmic ointment 0.5% 5 times daily for 14 days</td>
<td>Acyclovir ophthalmic ointment 3% Idoxuridine ophthalmic ointment 0.5% 5 times daily for 14 days</td>
<td>None</td>
<td></td>
</tr>
</tbody>
</table>

### 5.2 Review Strategy

The May 31, 2013, submission was submitted electronically. All subsequent amendments were submitted electronically. All study reports and literature were reviewed. The included clinical study reports, post-marketing safety reports, literature review, and package inserts for the reference active ingredient acyclovir formed the basis for the review of efficacy and safety for acyclovir ophthalmic ointment 3% for the proposed indication.

A literature search conducted by this reviewer failed to identify any literature references which were contrary to the information provided or referenced by the applicant in this application for this indication.
5.3 Discussion of Individual Studies

This 505(b)(2) application relies on the five clinical studies listed in Section 5.1 that were conducted in Europe and the US between 1980 and 1982.

A. Study objectives

The principal objective of the clinical studies was to evaluate the therapeutic efficacy and safety of Acyclovir Ophthalmic Ointment, 3% on dendritic and in some cases geographic corneal ulcers in subjects with acute herpetic keratitis relative to Idoxuridine (IDU) ophthalmic ointment 0.5% or 1.0% with time to healing of the ulceration as the primary endpoint. An additional retrospective analysis of the data from these 5 studies was also conducted to evaluate healing rates at Day 7. An additional objective in McCulley 1982 study was to evaluate the incidence of development of involvement of deeper ocular structures during the 21-day observation period.

B. Study Design

All 5 clinical studies were randomized, double masked, comparator controlled studies. Three studies were multicenter (Colin 1981, Collum 1980, and McCulley 1982) and two were single center (Coster 1980, Klauber 1982). The therapeutic efficacy and safety of Acyclovir Ophthalmic Ointment 3% was evaluated in comparison to Idoxuridine ophthalmic ointment 0.5% in all studies except Coster 1980 which used Idoxuridine ophthalmic ointment 1.0% as the comparator. Both Acyclovir Ophthalmic Ointment and Idoxuridine were dosed 5 times daily initially for 7 days. At the point of ulcer healing treatment was either withdrawn or reduced to 3 times daily for a further treatment period. Hence treatment durations varied considerably between patients and studies ranging from 2 to 17 days.

All patients also received atropine 1% in study Colin 1981 (twice daily) and study Coster 1980 (once daily), Homatropine 1% in study Collum 1980 (twice daily) and Scopolamine 0.2% in study Klauber 1982 (twice daily).

C. Major Eligibility Criteria

The primary diagnosis for all subjects in the clinical trials was dendritic or geographic herpetic keratitis for all studies except Collum 1980 which included only patients with dendritic ulcers.

C. Treatment Groups

- Acyclovir 3% ophthalmic ointment
- Idoxuridine 0.5% ophthalmic ointment (except Coster 1980 – Idoxuridine 1% ophthalmic ointment 1%)

D. Duration of Treatment

- Overall treatment varied from 2 days to 17 days
In general, treatment was applied 5 times daily for 7 days or up to point of ulcer improvement or healing and then reduced to 3 times daily.

**E. Main Efficacy Outcomes**

- Time to ulcer healing
- Ulcer healing rate at Day 7

**G. Sample Size**

A total of 274 subjects were enrolled, 133 were treated with ACV and 141 treated with IDU (111 with 0.5% and 30 with 1.0%).

**H. Study Visits**

Subjects in all the studies were examined at a minimum of twice a week.

**I. Statistical Analysis**

The analyses presented in this application are largely based on the analyses presented in the original publications that had used standard statistical methodologies. The applicant’s analyses of these publications included 1) a re-evaluation of the data relevant to Day 7 healing rate and 2) confirmation of the author’s conclusions presented in each publication. Since Day 7 ulcer healing rate is an important clinical endpoint, the results in the original publication for Day 7 were either confirmed when there was an existing Day 7 clinical endpoint, or extrapolated/calculated *de novo* when it was not part of the original analysis.

**6 Review of Efficacy**

**Efficacy Summary**

**6.1 Indication**

The proposed indication is for the treatment of acute herpetic keratitis (dendritic ulcers).

**6.1.1 Methods**

The major sources of clinical data utilized in this review include:

- Two single center randomized, double-masked clinical trials – Coster 1980 and Klauber 1982
6.1.2 Demographics

### Demographics (Age, Sex)

<table>
<thead>
<tr>
<th>Study</th>
<th>Age (yrs)</th>
<th>Sex</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colin Study 1981</td>
<td>N</td>
<td></td>
<td>Acyclovir 3%</td>
</tr>
<tr>
<td></td>
<td>Mean</td>
<td></td>
<td>49.9</td>
</tr>
<tr>
<td>Sex</td>
<td>n (%)</td>
<td></td>
<td>14 (56.0)</td>
</tr>
<tr>
<td>Male</td>
<td></td>
<td></td>
<td>11 (44.0)</td>
</tr>
<tr>
<td>Female</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Collum Study 1980</td>
<td>N</td>
<td></td>
<td>30</td>
</tr>
<tr>
<td></td>
<td>Mean</td>
<td></td>
<td>39</td>
</tr>
<tr>
<td>Sex</td>
<td>n (%)</td>
<td></td>
<td>19 (64.0)</td>
</tr>
<tr>
<td>Male</td>
<td></td>
<td></td>
<td>11 (36.0)</td>
</tr>
<tr>
<td>Female</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Klauber 1982</td>
<td>N</td>
<td></td>
<td>18</td>
</tr>
<tr>
<td></td>
<td>Mean</td>
<td></td>
<td>51</td>
</tr>
<tr>
<td>Sex</td>
<td>n (%)</td>
<td></td>
<td>13 (72.0)</td>
</tr>
<tr>
<td>Male</td>
<td></td>
<td></td>
<td>5 (28.0)</td>
</tr>
<tr>
<td>Female</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>McCulley 1982</td>
<td>N</td>
<td></td>
<td>30</td>
</tr>
<tr>
<td></td>
<td>Mean</td>
<td></td>
<td>48.8</td>
</tr>
<tr>
<td>Sex</td>
<td>n (%)</td>
<td></td>
<td>20 (67.0)</td>
</tr>
<tr>
<td>Male</td>
<td></td>
<td></td>
<td>10 (33.0)</td>
</tr>
<tr>
<td>Female</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Coster 1980</td>
<td>N</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Mean</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td>n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Source: Fera Section 2.7.4 Table 1 and Section 2.7 page 9 Demographic and Other Characteristics

* There is a discrepancy in gender reported as a total of 27 subjects were in study

### Combined Studies - Demographics (Age, Sex)

<table>
<thead>
<tr>
<th></th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Acyclovir 3%</td>
</tr>
<tr>
<td>Age (yrs) N</td>
<td>103*</td>
</tr>
<tr>
<td>Mean range</td>
<td>39 - 51</td>
</tr>
<tr>
<td>Age range</td>
<td>4 - 84</td>
</tr>
<tr>
<td>Sex N</td>
<td>214</td>
</tr>
<tr>
<td>Male n (%)</td>
<td>127 (59%)</td>
</tr>
<tr>
<td>Female n (%)</td>
<td>87 (41%)</td>
</tr>
</tbody>
</table>

Source: Fera Section 2.7.4 Table 1 and Section 2.7 page 9 Demographic and Other Characteristics

* Gender and age not reported in an additional 30 Acyclovir group

** Gender and age not reported in 30 Idoxuridine 1% group
6.1.3 Patient Disposition

No patients were withdrawn due to adverse events and no deaths were reported during the clinical studies.

6.1.4 Analysis of Primary Endpoint(s)

The primary efficacy endpoint used in the review of this NDA is cure rate (healed ulcers) at Day 7. Additionally, time to ulcer cure was used as a supportive efficacy endpoint.

6.1.4.1 Efficacy Findings

<table>
<thead>
<tr>
<th>Acyclovir vs IDU – Day 7 Ulcer Healing Rates</th>
</tr>
</thead>
<tbody>
<tr>
<td>First Author</td>
</tr>
<tr>
<td>---------------</td>
</tr>
<tr>
<td>Colin</td>
</tr>
<tr>
<td>Collum</td>
</tr>
<tr>
<td>Coster</td>
</tr>
<tr>
<td>Klauber</td>
</tr>
<tr>
<td>McCulley</td>
</tr>
<tr>
<td>Average</td>
</tr>
</tbody>
</table>

Source: Fera Section 2.5 Table 1

**Reviewer’s Comments:** *Acyclovir 3% is superior to IDU for the treatment of dendritic ulcers.*

<table>
<thead>
<tr>
<th>Acyclovir vs IDU – Time to Ulcer Healing</th>
</tr>
</thead>
<tbody>
<tr>
<td>First Author</td>
</tr>
<tr>
<td>---------------</td>
</tr>
<tr>
<td>Colin</td>
</tr>
<tr>
<td>Collum</td>
</tr>
<tr>
<td>Coster</td>
</tr>
<tr>
<td>Klauber</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>McCulley</td>
</tr>
<tr>
<td></td>
</tr>
</tbody>
</table>

Source: Fera Section 2.7.3 Table 3
**Reviewer’s Comments:** The time to ulcer healing provides additional evidence that Acyclovir 3% is effective in treating dendritic ulcers.

6.1.5 Analysis of Secondary Endpoints(s)

There were no secondary endpoints evaluated.

6.1.6 Other Endpoints

No other efficacy endpoints were evaluated.

6.1.7 Subpopulations

No subgroup analyses were conducted.

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

The optimal frequency of administration was based on the results of the clinical studies. Both Acyclovir Ophthalmic Ointment and Idoxuridine were dosed 5 times daily initially for 7 days. At the point of ulcer healing treatment was either withdrawn or reduced to 3 times daily for a further treatment period. Hence treatment durations varied considerably between patients and studies ranging from 2 to 17 days.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

There is no persistence of efficacy or tolerability issue.

6.1.10 Additional Efficacy Issues/Analyses

There are no additional efficacy issues/analyses.

7 Review of Safety

Safety Summary

7.1 Methods

7.1.1 Clinical Studies Used to Evaluate Safety

The major sources of clinical data utilized in this review include:

Two single center randomized, double-masked clinical trials – Klauber 1982 and Coster 1980 (Note: Coster study did not report adverse events and is not included in the safety data base)

Worldwide marketing experience

7.1.2 Adequacy of Data

The patient exposure and safety assessments were adequate.

274 patients were included in the 5 clinical studies. Since no adverse events were reported in Coster 1980 the overall safety assessment is based on 214 patients exposed to either ACV 3% (n=103) and or IDU 0.5% (n=111).

7.1.3 Pooling Data Across Studies to Estimate and Compare Incidence

Individual study data and pooled data are presented because of the small number of adverse events reported.

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

274 patients were included in the 5 clinical studies. Both ACV and IDU were dosed 5 times daily initially for 7 days. At the point of ulcer healing treatment was either withdrawn or reduced to 3 times daily for a further treatment period. Hence treatment durations varied considerably between patients and studies ranging from 2 to 17 days.

7.2.2 Explorations for Dose Response

Dose ranging was not performed in these clinical studies.

7.2.3 Special Animal and/or In Vitro Testing

No special animal and in vitro testing is necessary.

7.2.4 Routine Clinical Testing

The clinical testing performed in the studies was adequate for evaluation of the new drug product.
7.2.5 Metabolic, Clearance, and Interaction Workup

No systemic adverse events were reported in any of the clinical studies.

Immediate hypersensitivity reactions (including angioedema and urticaria) are the only systemic adverse events reported in prescribing information from countries where Acyclovir eye ointment is approved.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

The prescribing information for Acyclovir Ophthalmic Ointment 3% (Zovirax) approved in countries outside of the US contains the following safety information (contraindications, warnings, precautions and adverse events):

• Contraindicated in patients with a known hypersensitivity to acyclovir or valacyclovir.
• Avoid wearing contact lenses when using Acyclovir Eye Ointment
• Caution when driving or using machines as eye ointments can temporarily affect visual acuity.
• Adverse reactions:
  - Superficial punctuate keratopathy (≥ 10%)
  - Transient mild stinging of the eye on instillation (< 10%)
  - Blepharitis (< 0.1%)
  - Immediate hypersensitivity reactions including angioedema and urticaria (< 0.01%)

7.3 Major Safety Results

7.3.1 Deaths

No deaths were reported for subjects treated with acyclovir 3%.

7.3.2 Nonfatal Serious Adverse Events

No nonfatal serious adverse events were reported for subjects treated with acyclovir 3%.

7.3.3 Dropouts and/or Discontinuations

No withdrawals due to adverse events were reported in any of the clinical studies.

7.3.4 Significant Adverse Events

There were no serious adverse events reported in any of the clinical studies.
7.3.5 Submission Specific Primary Safety Concerns

There are additional no specific safety issues related to this drug product were identified in these clinical studies. Refer to Section 7.2.6 for potential adverse events for this drug.

7.4 Supportive Safety Results
7.4.1 Common Adverse Events

**Adverse Events for Acyclovir Ophthalmic Ointment 3%**

**Studies Pooled: Colin, Collum, Klauber and McCulley**

**Safety Population**

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ACV 3% n = 25</td>
<td>IDU 0.5% n = 27</td>
<td>ACV 3% n = 30</td>
<td>IDU 0.5% n = 30</td>
<td>ACV 3% n = 18</td>
</tr>
<tr>
<td>Punctate keratitis</td>
<td>2 (8%)</td>
<td>0</td>
<td>6 (20%)</td>
<td>2 (11.1%)</td>
<td>3 (10%)</td>
</tr>
<tr>
<td>Eye pain (stinging)</td>
<td>0</td>
<td>0</td>
<td>8 (26.7%)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Follicular conjunctivitis</td>
<td>2 (8%)</td>
<td>2 (7.4%)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Lacerimation increased</td>
<td>0</td>
<td>0</td>
<td>2 (6.7%)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Palpebral allergy</td>
<td>1 (4%)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Punctal occlusion</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Glossodynia</td>
<td>0</td>
<td>0</td>
<td>1 (3.3%)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Eye irritation (Uveitis)</td>
<td>0</td>
<td>0</td>
<td>1 (3.3%)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Lid edema</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

* Since no adverse events were reported in Coster 1980 the overall safety assessment is based on 214 patients exposed to either ACV 3% (n=103) and or IDU 0.5% (n=111).

*One subject developed hypersensitivity to scopolamine

Source: Fera Section 2.7.4 Table 2

Overall, Acyclovir Ophthalmic Ointment 3% was well tolerated with a safety profile in these clinical studies (qualitatively and quantitatively) similar to that previously reported from products approved and marketed outside of the United States for the last 3 decades. Based on this evidence, as well as the assessment of excellent systemic and local tolerance Acyclovir Ophthalmic Ointment 3% has an excellent safety and tolerability profile.

**Reviewer’s Comments:** Overall for Acyclovir 3%, AEs reported with a frequency greater than 1% include punctate keratitis, eye pain (burning and stinging on instillation) and follicular conjunctivitis. Those AEs occurring at a rate greater than 5% include punctuate keratitis and eye pain (burning and stinging on instillation).

7.4.2 Laboratory Findings

Clinical laboratory data was not reported in the published study reports.

7.4.3 Vital Signs

Clinical laboratory data was not reported in the published study reports.
7.4.4 Electrocardiograms (ECGs)
No ECG was collected in the studies performed.

7.4.5 Special Safety Studies
No special safety studies were performed.

7.4.6 Immunogenicity
Immunogenicity studies were not performed.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events
No dose dependency for adverse events was identified.

7.5.2 Time Dependency for Adverse Events
No time dependency for adverse events was identified.

7.5.3 Drug-Demographic Interactions
No studies were performed specifically to analyze responses to the drug in different demographic subsets.

7.5.4 Drug-Disease Interactions
There is no evidence of drug-disease interactions.

7.5.5 Drug-Drug Interactions
No formal drug interaction studies were performed with topical ophthalmic ganciclovir.

7.6 Additional Safety Explorations

7.6.1 Human Carcinogenicity
No human carcinogenicity studies were conducted.
7.6.2 Human Reproduction and Pregnancy Data

No studies in humans on the effects of topical ophthalmic acyclovir on reproduction or pregnancy were conducted.

7.6.3 Pediatrics and Effect on Growth

This drug product has been designated an orphan drug and hence, is exempt from the pediatric assessment requirement under 21 CFR 314.55(d). No studies of the effect on growth have been performed.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

No overdose experience is available. There is no drug abuse potential, no withdrawal effect, and no rebound effect with this drug product.

7.7 Additional Submissions

There were no additional submissions.

8 Postmarketing Experience

Acyclovir Ophthalmic Ointment 3% (Zovirax®) has been marketed in Europe and many countries around the world for several decades and is included on the WHO List of Essentials Medicines as an ophthalmological anti-infective agent (WHO 2010). Acyclovir is the active ingredient in several products approved in the United States under the trade name Zovirax with various strengths and formulations marketed since 1981. However, no ophthalmic ointment formulation of acyclovir has been approved in the US.

The prescribing information for Acyclovir Ophthalmic Ointment 3% (Zovirax) approved in countries outside of the US contains the following safety information (contraindications, warnings, precautions and adverse events):

• Contraindicated in patients with a known hypersensitivity to acyclovir or valacyclovir.
• Avoid wearing contact lenses when using Acyclovir Eye Ointment
• Caution when driving or using machines as eye ointments can temporarily affect visual acuity.
• Adverse reactions:
  - Superficial punctuate keratopathy (≥ 10%)
  - Transient mild stinging of the eye on instillation (< 10%)
  - Blepharitis (< 0.1%)
  - Immediate hypersensitivity reactions including angioedema and urticaria (< 0.01%)
9 Appendices

9.1 Literature Review/References

A literature search conducted by this reviewer failed to identify any literature references which were contrary to the information provided or referenced by Fera in this application for this indication.

9.2 Advisory Committee Meeting

No Advisory Committee was necessary or convened for this drug product.

9.3 Labeling Recommendations

NDA 202-408, Avacylr (acyclovir ophthalmic ointment) 3% is recommended for approval for the treatment of acute herpetic keratitis (dendritic ulcers) with the labeling changes made to the originally submitted label on May 31, 2013 found here at the end of this Medical Officer review.

6 Pages of Draft Labeling have been Withheld in Full as B4 (CCI/TS) immediately following this page
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MARTIN P NEVITT
02/18/2014

WILLIAM M BOYD
02/18/2014