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*APPLICATION NUMBER:*

**202408Orig1s000**

**OFFICE DIRECTOR MEMO**

**Memo to File****Date: March 28, 2019****From:** Peter P. Stein, M.D. Director, Office of New Drugs, CDER/FDA**Topic:** Approval of NDA 202408**Applicant:** Fera Pharmaceuticals, Inc.**Proprietary Name:** Avaclyr (acyclovir ophthalmic ointment) 3%**Indication:** Treatment of acute herpetic keratitis (dendritic ulcers)

This memo documents my support for proceeding with the approval of NDA 202408, Avaclyr (acyclovir ophthalmic ointment) 3%. This document supersedes the original memo to file, dated November 26, 2018. This document reflects my current thinking regarding the scientific bridge between the proposed product under NDA 202408 and the published literature relied upon by NDA 202408, and, in particular, the scientific aspect of the bridge between the proposed product and the product(s) used in the published literature.<sup>1</sup> This document also reflects my current thinking on Dr. Chambers' appeal of the prior Complete Response (CR) letters issued for NDA 202408 and OND's prior position on the scientific bridge between the proposed product and the product(s) used in the relied-upon published studies.

**Background**

NDA 202408 is a 505(b)(2) application referencing two data sources for approval: an FDA-approved listed drug (i.e., Zovirax topical ointment (5%) under NDA 18604) and the literature reports of clinical studies evaluating the use of acyclovir 3% ophthalmic ointment in the treatment of acute herpetic keratitis.

The listed drug relied upon (Zovirax 5% ointment, NDA 18604) was intended to provide support for the preclinical toxicology of the Fera NDA product. In the Pharmacology/Toxicology review (filed 5-13-2013), Avaclyr was considered to have acceptable preclinical safety based upon the Agency's findings for the safety and effectiveness for the listed drug as reflected in the approved labeling. I will not further comment on the acceptability of this aspect of the application.

The Fera NDA also referenced literature describing five clinical trials published from 1980-1982 that evaluated acyclovir ophthalmic ointment 3% product(s) in the treatment of acute herpetic keratitis. Although the specific products studied were not identified in all of the relevant

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<sup>1</sup> The focus of this memo is on a specific aspect of the scientific bridge (i.e., the scientific bridge between the proposed product and the product(s) used in the published literature relied upon for approval.). As noted elsewhere in this memo, the relevant published studies were discussed in reviews by the medical officer, team leader, and deputy division director (Dr. Chambers), and all three concluded that the referenced studies provided substantial evidence of effectiveness and evidence of safety for the acyclovir ophthalmic ointment 3% in the treatment of acute herpetic keratitis under NDA 202408. Given the consensus of these experts on the conclusions from the clinical trials described in the referenced literature, I will consider it a settled matter that if a scientific bridge from the Fera NDA product to the drug product(s) used in these trials is established, then the conclusions from the FDA ophthalmology experts on the referenced studies providing substantial evidence of effectiveness and evidence of safety are applicable to NDA 202408.

literature, each article described the drug product studied as acyclovir ophthalmic ointment 3%. The drug product(s) used in the referenced clinical studies was not approved in the U.S., as an NDA was not submitted by Burroughs-Wellcome or any other manufacturer. The product from Burroughs-Wellcome was submitted to EU health agencies and approved by several EU countries as Zovirax ophthalmic ointment 3%, indicated for the treatment of herpetic keratitis. This 505(b)(2) application does not propose to rely on the EU health agencies' prior finding of safety and/or effectiveness for the acyclovir ophthalmic ointment 3%. Rather, as noted above, the application relies upon literature reports of clinical studies evaluating the use of acyclovir 3% ophthalmic ointment in the treatment of acute herpetic keratitis. As such, a scientific bridge must be established between the proposed product under NDA 202408 and the product(s) described in the published literature in order to scientifically justify FDA's reliance on the clinical results from the published literature describing the clinical trials.

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As Dr. Chambers pointed out in his prior review, the Fera NDA product is a simple mixture of the same ingredients used in the referenced clinical trials described in the literature (including two ingredients, petrolatum and acyclovir 3%) (b) (4).<sup>2</sup> His review further notes that the NDA product would be applied directly to the target tissue (the corneal epithelium) and, therefore would deliver drug in a manner comparable to that of the drug product(s) in the referenced studies. He considered these factors sufficient to establish a scientific bridge between the Fera NDA product and the drug product(s) used in the clinical trials described in the literature, and therefore determined that this NDA was approvable. I will return to this point later in this document.

Based on prior consultation with experts in the Office of Generic Drugs (OGD) and Office of Pharmaceutical Quality (OPQ), the Division Director for the Division of Transplant and Ophthalmology Products (Dr. Albrecht) previously concluded that a scientific bridge between

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<sup>2</sup> As noted above, the relevant published clinical trials that evaluated acyclovir ophthalmic ointment 3% are described in several contemporaneous published articles as studying acyclovir 3% and a petrolatum base and do not identify any other ingredients as being included in the ointment. *See, e.g.,* W. Tucker, R. Johnston et al., Preclinical Toxicology Studies with Acyclovir: Ophthalmic and Cutaneous Tests, *Fundamental and Applied Toxicology*, 3:569-572, 1983; J. Lass, R. Langston et al., Antiviral medications and corneal wound healing, *Antiviral Research*, 4:143-157, 1984; D. Grant, Acyclovir (Zovirax<sup>R</sup>) ophthalmic ointment: a review of clinical tolerance, *Current Eye Research*, 6:1, 231-235 (1987). Although there are different types of petrolatum, including different USP monographs for petrolatum and white petrolatum, there is no reason to believe that differences between types of petrolatum would be clinically relevant.

the proposed product under NDA 202408 and the product(s) used in the relied-upon published literature required demonstration of similarity of the proposed NDA product to an FDA-approved reference product. It was recognized that there was no US-approved reference product to support such a comparison. Since the currently-marketed EU product (Zovirax 3% ophthalmic ointment) was considered likely to be similar to the product(s) studied in the published literature describing the clinical trials, it was thought that this currently-marketed EU product could serve as the reference for comparison for purposes of establishing a bridge between Fera's proposed product and the drug product(s) used in the published trials. A CR letter was issued (May 31, 2014) by the Division Director (Dr. Albrecht) including the requirement that the applicant demonstrate similarity of the Fera NDA to the currently-marketed EU product on a number of parameters including viscosity, specific gravity, pH, melting temperature, particle size, and drug release rates using *in vitro* release testing (IVRT); in addition, the applicant was to provide information (b) (4) between their product and the EU product.

The applicant resubmitted an NDA (December 24, 2015) providing chemical and physical comparison of 3 lots of the NDA product to 3 lots of the currently-marketed EU product; the results contained in the resubmission showed that drug concentration, melting temperature, impurity profile, viscosity, and API particle size distribution were all similar to the currently-marketed EU product. (b) (4)

However, the applicant's efforts to develop the IVRT methodology to evaluate release rates were unsuccessful, and based upon this, a second CR was issued on June 24, 2016. In the Division Director Review for this second CR letter, it was noted that "*the testing results for viscosity, specific gravity, pH, melting temperature and particle size were considered acceptable. This addressed the Petrolatum, Viscosity...portion of the Quality and Performance Tests, and the Acyclovir Particle Size items from the CR letter. However, Fera was not able to adequately address the Quality and Performance/In-Vitro Release Testing and Acyclovir Polymorphism items and OPQ/OGD concluded that a scientific bridge has not been established*".

Dr. Chambers disagreed with this decision, questioning the regulatory basis and scientific need for a comparison between the Fera NDA product and the EU product in support of a scientific bridge, and appealed to Dr. Edward Cox, the Office Director who supported the CR decision. Dr. Chambers subsequently appealed the decision by Dr. Cox, and my review addresses this appeal.

### Scientific Considerations

In his review of NDA 202408, Dr. Chambers noted that "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 outmost layers of the cornea. The drug product will be placed in direct contact with the site where the disease occurs." (Deputy Division Director Review, June 21, 2016). Thus, release rate of drug from the ointment to tear fluid, and concentration in the tear fluid which bathes the target cells, are primarily relevant for determining efficacy. According to the Clinical Pharmacology review (May 31, 2013), the 1 cm ribbon of acyclovir 3% ointment is

approximately 21 mg of drug product, with 630 µg of acyclovir (30 µg/g x 21 mg). The IC<sub>50</sub>s for HSV-1 range from 0.02-13.5 µg/mL for HSV-1 and 0.01-9.9 µg/mL for HSV-2 (Consult from DAVP). Although the extent of release of drug into the cul-de-sac cannot be readily quantitated, even if only a small percentage of drug is released, given tear volume (typically 7 µL), acyclovir concentrations would markedly exceed these IC<sub>50</sub> values. This suggests that modest differences (for example, up to several-fold) in acyclovir ointment drug release rates are highly unlikely to lead to differences in clinical performance.

Another consideration is the effect of patient-related factors on drug exposure. These patient-related factors include dose administered, frequency of blinking (and rubbing), and the rate of tearing. The proposed dose to be administered is a 1 cm ribbon three times per day to the cul-de-sac. The actual amount that would be delivered based upon self-administration of a “1 cm ribbon” of an ophthalmic ointment would be variable (as patients will not measure the length of the ribbon upon self-administration). Further, blinking can lead to approximately a two-fold difference in tear fluid ophthalmic drug concentrations (R Hardberger, C Hanna, et al. Arch Ophthalmology 93:42-45, 1975), and the rate of tearing can also affect drug exposure. These factors (administered dose, tearing rate, and blinking frequency) are likely to lead to at least a several-fold difference in drug exposure within and between patients when applying acyclovir ointment.

Based upon acyclovir exposure at the site of disease (the corneal surface) that will have a substantial margin above needed concentrations for effectiveness (i.e., IC<sub>50</sub>), and given the expected large variability of exposure based upon patient-related factors, it would seem unlikely that even several-fold differences in release rates between the Fera NDA product and the product(s) used in the clinical trials described in the referenced literature would lead to a clinically relevant difference in treatment response. I would conclude that differences of up to this magnitude in release rates between the Fera NDA product and the drug product(s) used in the clinical studies would not preclude a scientific bridge, and that the high degree of similarity between products recommended previously by OGD and OPQ is not necessary. I will discuss the support for the conclusion that any differences in release rate between the Fera NDA product and the clinical trial drug product(s) are likely in this range (i.e., several-fold) or smaller.

As noted, both the NDA product and the product(s) described in the literature are a simple mixture of two ingredients, the API, acyclovir, and petrolatum. Ophthalmic ointments have been reported to release drug as the ointment warms and then melts in the cul-de-sac of the eye. Work supported by OGD has provided insight into how chemical and physical characteristics can affect the rate of acyclovir ointment drug release. I will briefly summarize some of these studies, and then comment on their relevance to the issues at hand.

Al-Ghabeish et. al. (M. Al-Ghabeish, X Xu, et al. Int'l J of Pharmaceutics 495:783-791, 2015) examined three different acyclovir formulations: acyclovir in a water-soluble solution, an ointment with mineral oil and petrolatum, and an ointment with petrolatum, mineral oil and lanolin alcohol. These three formulations had different *in vitro* release characteristics, but with only *modest* differences between the two ointments and *marked* differences of the ointments compared to the aqueous solution. This study showed that differences in drug loading had a

relatively large effect on drug release rates of approximately 4-fold going from 2% to 6% acyclovir drug loading. Bao et al (Q. Bao, R. Jog, J. Shen, et al. International J. of Pharmaceutics 523: 310-319, 2017) compared ointments produced using different methods for mixing the petrolatum and drug, including simple mixing and various heat melting approaches. In vitro release rates varied by a factor of approximately 2- to 3-fold across ointments made using these different mixing methods, likely related to differences in viscosity. Finally, Xu and colleagues (X Xu, M Al-Ghabeish, et al. International J. of Pharmaceutics 493: 412-425, 2015) examined in vitro release rates, and in vitro transcorneal permeation rates, based upon different ointment characteristics including drug loading, API particle size, inclusion of mineral oil, and mixing temperature. The largest factor affecting release rate was drug loading (loading varying from 2-6%), with smaller effects of API particle size, mixing temperature, and the presence of mineral oil. Notably, none of these differences affected the transcorneal permeation rate. Considering the 4-fold difference seen in the Al-Ghabeish study across differences in drug loading from 2% to 6%, the differences in release rates based upon other factors would be quantitatively much smaller. I note that antiviral ointments approved at the time that Acyclovir 3% ointment was developed had the same two ingredients (the antiviral agent in a petrolatum base [J. Bartlett et al (1989) Ophthalmic drug facts. St. Louis, Missouri: J.B. Lippincott Company]).

These studies suggest that differences in the characteristics of ophthalmic ointments may result in differences in the vitro release rates to a varying extent, with differences in drug loading and in the formulation (aqueous vs ointment, and the presence of other ingredients) having the largest effect, and other differences having a more modest effect. Since the Fera NDA product and the product(s) described in the literature are simple mixtures of acyclovir 3% (same drug loading) and petrolatum, the differences in release rates would be limited (several-fold or less). Based upon the direct application of the ointment to the target tissue, the MIC for acyclovir substantially above the needed exposure, and the marked variability that is expected based upon factors related to drug administration, any differences in release rates between the Fera NDA product and the clinical trial drug product(s) are highly unlikely to be therapeutically relevant.

#### Prior OND Position on Scientific Bridge

As discussed above, the Director's summary (by Dr. Albrecht) and the appeal response to Dr. Chambers (by Dr. Cox) stated that comparable in vitro release rates (IVRT) between the Fera NDA product and the EU Zovirax 3% ointment must be demonstrated. As I outlined above, I disagree that demonstrating a high degree of comparability in release rates between the Fera NDA product and the EU product is needed to support a scientific bridge. First, FDA has made no conclusions regarding the safety and efficacy of the EU Zovirax ophthalmic product, and therefore bridging the Fera NDA product to that product does not support the Fera 505(b)(2) NDA application. It is important to point out that over the decades since the EU Zovirax product was registered, manufacturing and ingredient supply changes have inevitably occurred. Hence, there is no assurance that the EU product and the clinical trial drug product(s) would, at present, have a high degree of comparability in release rate using IVRT. The chemical and physical similarity between the Fera NDA product and the EU Zovirax, discussed above, is not surprising

since both are simple mixtures of 3% acyclovir and petrolatum, manufactured using standard processes for producing ophthalmic ointments. This provides a useful example supporting the general conclusion that simple ophthalmic ointments with the same drug loading and formulation are similar in chemical and physical characteristics. However, I disagree with the reviews by Drs. Albrecht and Cox that such a comparison is necessary or appropriate. Rather, as discussed above, I have concluded that a scientific bridge can be supported from the Fera NDA product to the product(s) used in the clinical trials described in the literature since both are simple ophthalmic ointments with the same acyclovir drug loading and the same two ingredients. The similarity of the EU product and the Fera NDA product just illustrates that such simple ointments with the same ingredients would be expected to share chemical and physical properties and would have similar therapeutic performance.

Based upon the showing that both the Fera NDA product and the drug product(s) used in the clinical trials in herpes keratitis were simple mixtures of acyclovir 3% and petrolatum and taking into consideration the variability in dosing for ophthalmic ointments, patient-related factors, and the needed drug concentrations for efficacy of acyclovir, conclusions from the published literature about the clinical trials of the acyclovir ointment drug product in the treatment of acute herpetic keratitis are applicable to the NDA 202408 drug product. As a result of my conclusion that there is an adequate scientific bridge between the Fera NDA product and the drug product(s) used in the published literature on the clinical trials, I note that the deficiencies related to the scientific bridge previously communicated to Fera in the May 31, 2014 and June 24, 2016 CR letters are no longer applicable to NDA 202408 and that there remain no outstanding deficiencies at this time preventing approval of the NDA. I also note that following a conversation with Dr. Chambers, Fera submitted an amendment to their NDA on November 27, 2018, submitting a safety update.

I concur with Dr. Chambers that this NDA is approvable.

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