CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

202408Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

OFFICE OF CLINICAL PHARMACOLOGY REVIEW

NDA	202,408
Submission Date(s)	May 31, 2013
Brand Name	Avaclyr®
Generic Name	Acyclovir ophthalmic ointment 3.0%
Primary Reviewer	Yoriko Harigaya, Pharm.D.
Team Leader	Philip Colangelo, Pharm.D., Ph.D.
OCP Division	Division of Clinical Pharmacology 4
OND Division	Division of Transplant and Ophthalmology Products
Applicant	FERA Pharmaceuticals, LLC
Relevant IND(s)	N/A
Submission Type	Original 505(b)(2); Standard Review
Formulation; Strength(s)	Acyclovir ophthalmic ointment 3.0%
Proposed Indication	Treatment of acute herpetic keratitis (dendritic ulcers) in patients with herpes simplex (HSV-1 and HSV-2) virus.
Proposed Dosage Regimen	Apply a 1 cm ribbon in the lower cul-de-sac of the affected eye 5 times per day until healed then 3 times per day for 7 days.

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1. EXECUTIVE SUMMARY

FERA Pharmaceuticals, LLC., submitted a 505(b)(2) NDA 202408 for acyclovir ophthalmic ointment 3.0% for the treatment of acute herpetic keratitis (dendritic ulcers) in patients with herpes simplex (HSV-1 and HSV-2) virus. Acyclovir is a synthetic purine nucleoside analogue anti-viral agent, and its metabolite, acyclovir triphosphate, inhibits replication of herpes viral DNA. Acyclovir has been approved and marketed in the U.S. with various strengths and formulations since 1981. Acyclovir ophthalmic ointment 3% (Zovirax®) has been approved in Europe in October 1996 and in many other countries. However, no ophthalmic ointment formulation of acyclovir has been approved in the U.S. The currently marketed product, Zovirax® eye ointment 3.0% in Europe, is indicated for the treatment of herpes simplex keratitis and administered as follows: a 1 cm ribbon of ointment should be placed inside the lower conjunctival sac five times a day at approximately four hourly intervals, omitting the night time application. Treatment should continue for at least 3 days after healing is complete.

Acyclovir ophthalmic ointment 3.0% was (b) (4) The proposed dosage regimen is as follows: apply a 1 cm ribbon in the lower cul-de-sac of the affected eye 5 times per day until healed then 3 times per day for 7 days. This 505(b)(2) NDA 202408 relies on the previous finding of safety and efficacy for the currently approved acyclovir NDAs as follows:

Application No. (Applicant)	Active Ingredient	Dosage Form	Route of Administration	Strength
N018604	acyclovir	ointment	topical	5%
N021478	acyclovir	cream	topical	5%
N018828	acyclovir	capsule	oral	200 mg
N019909	acyclovir	suspension	oral	200 mg/mL
N020089	acyclovir	tablet	oral	400 mg and 800 mg
N018603	acyclovir	injectable	intravenous	500 mg and 1000 mg base

The applicant also presents published clinical data from 5 clinical studies evaluating the safety and efficacy of acyclovir ophthalmic ointment 3% for the treatment of acute herpetic keratitis compared to idoxuridine ophthalmic ointment 0.5% and 1%. The applicant has not conducted any additional clinical evaluations to support this NDA, and no new clinical pharmacology data was presented in this submission.

1.1 Recommendation

From a Clinical Pharmacology perspective, the 505(b)(2) NDA submission for Acyclovir ophthalmic ointment 3.0% is acceptable, and the reviewer recommends approval of this product.

1.2 Labeling Recommendations

Please refer to Section 2 for detailed labeling recommendations.

1.3 Phase 4 Requirements

No Phase 4 study recommendation.

1.4 Summary of Important Clinical Pharmacology Findings

No new clinical pharmacology studies were conducted for this NDA.

Acyclovir ophthalmic ointment 3.0% (30 mg/g) is a sterile drug produc (b) (4)

The labeling of Zovirax® eye ointment 3% approved in Europe includes the following clinical pharmacology study result. The applicant does not have access to the original data of this study.

Zovirax® eye ointment 3%[1]

- Acyclovir is rapidly absorbed from the ophthalmic ointment through the corneal epithelium and superficial ocular tissues, achieving antiviral concentrations in the aqueous humor. It has not been possible by existing methods to detect acyclovir in the blood after topical application to the eye. However, trace quantities are detectable in the urine. These levels are not therapeutically significant.

1. *Zovirax Eye Ointment 3% labeling in UK. GlaxoSmithKline UK. November 2012.*

Upon review of the above labeling information of Zovirax® eye ointment 3%, no further clinical pharmacology studies to support this NDA are necessary based on the result that systemic exposure to acyclovir would be negligible following topical ocular administration of the currently proposed acyclovir ophthalmic ointment 3.0%, given the fact that acyclovir was not a new molecular entity, and there was prior pharmacokinetic (PK) knowledge for this compound via other routes of administration (e.g., oral and intravenous injection).

In the 5 published clinical studies submitted in this NDA evaluating the safety and efficacy of acyclovir ophthalmic ointment 3% for the treatment of acute herpetic keratitis compared to idoxuridine ophthalmic ointment 0.5% and 1%, no systemic adverse events were observed. Punctate keratitis (n=7/103: 6.8%) and ocular pain (n=9/103: 8.7%) were the most frequently observed local adverse events. Based on the post marketing information of Zovirax® eye ointment 3.0%, immediate hypersensitivity reactions including angioedema and urticaria is the only systemic adverse event reported.

A 1 cm ribbon of acyclovir ophthalmic ointment 3.0% (30 mg/g) is approximately 21 mg which contains 630 mcg of acyclovir (=30 mcg/mg x 21 mg). The currently approved labeling of Zovirax® ointment 5.0% indicates that using plaque-reduction assays, the IC_{50} 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. Based on the above information and considering a total volume of aqueous humor in anterior and posterior chamber is approximately 0.3

mL, acyclovir will reach therapeutic level in the cornea and aqueous humor following topical ocular administration.

2. LABELING RECOMMENDATIONS

Clinical Pharmacology recommended changes to the proposed labeling are given below as underline and ~~strikethrough~~.

(b) (4)

[redacted]

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

3. OCP FILING AND REVIEW FORM

Office of Clinical Pharmacology

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA/BLA Number	**202,408**	**Brand Name**	**Avaclyr**
OCP Division (I, II, III, IV, V)	**IV**	**Generic Name**	**Acyclovir ophthalmic ointment 3.0%**
Medical Division	**DTOP**	**Drug Class**	**Antiviral**
OCP Reviewer	**Yoriko Harigaya, Pharm.D.**	**Indication(s)**	**Treatment of acute herpetic keratitis (dendritic ulcers)**
OCP Team Leader	**Philip M. Colangelo, Pharm.D., Ph.D.**	**Dosage Form**	**Ophthalmic ointment**
Pharmacometrics Reviewer	**N/A**	**Dosing Regimen**	(b) (4)
Date of Submission	**May 31, 2013**	**Route of Administration**	**Topical administration to the eye**
Estimated Due Date of OCP Review	**February 24, 2014**	**Sponsor**	**FERA Pharmaceuticals LLC**
Medical Division Due Date	**N/A**	**Priority Classification**	**Standard**
PDUFA Due Date	**March 31, 2014**		

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.				
Tabular Listing of All Human Studies				
HPK Summary				
Labeling				
Reference Bioanalytical and Analytical Methods				
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:				
multiple dose:				
Patients-				
single dose:				
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				

Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD -				
Phase 2:				
Phase 3:	**X**	**5**		
PK/PD -				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies				
Bio-waiver request based on BCS				
BCS class				
Dissolution study to evaluate alcohol induced dose-dumping				
III. Other CPB Studies				
Genotype/phenotype studies				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies		**5**		

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/s/

YORIKO HARIGAYA
02/18/2014

PHILIP M COLANGELO
02/19/2014