

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**203791Orig1s000**

**PHARMACOLOGY REVIEW(S)**

**DEPARTMENT OF HEALTH AND HUMAN SERVICES  
PUBLIC HEALTH SERVICE  
FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH**

**PHARMACOLOGY/TOXICOLOGY NDA LABELING REVIEW AMENDMENT**

Application number: 203791  
Supporting document/s: 19, 20  
Applicant's letter date: 2/12/13 – SDN 19, 3/7/13 – SDN 20  
CDER stamp date: 2/12/13 – SDN 19, 3/7/13 – SDN 20  
Product: Acyclovir Lauriad™ 50 mg mucoadhesive  
Buccal Tablets (ABT 50 mg)  
Indication: Local treatment of orofacial herpes and  
(b) (4)  
Applicant: BioAlliance Pharma  
Review Division: Division of Anti-Viral Products  
Reviewer: Janice Lansita, PhD, DABT  
Supervisor/Team Leader: Hanan Ghantous, PhD, DABT  
Division Director: Debra Birnkrant, MD  
Project Manager: Sohail Mosaddegh, Pharm.D.

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**AMENDED REVIEW – Labeling and Clarification**

The sponsor submitted revised labeling on 2/12/13 (SDN 19). This review amends the previously finalized nonclinical pharmacology/toxicology NDA review (12/6/12) to 1) include an evaluation of the sponsor's proposed labeling from 2/12/13 and 2) clarify safety margins that were referenced in Section 9 Reproductive and Developmental Toxicology of the pharmacology/toxicology NDA review to reflect consistency with the proposed labeling.

**LABELING REVIEW**

The relevant nonclinical sections of the sponsor's proposed labeling, Section 8.1 Pregnancy and Section 13 Nonclinical Toxicology, are included below. The Division's edits and comments were sent to the sponsor on 2/26/13. The sponsor accepted all of the nonclinical labeling changes to Sections 8.1 and 13 in the revised labeling submitted by the sponsor on 3/7/13 (SDN 20). An additional change sent to the sponsor on 3/18/13 was to remove the subheader, "Teratogenic Effects" since the teratogenicity data was moved to the new "Animal Data" section and the clinical data section did not describe any positive teratogenic findings.

**SPONSOR'S PROPOSED LABELING (2/12/13):****8     *Use in Specific Populations*****8.1   *Pregnancy***

(b) (4)

**13    *Nonclinical Toxicology***

(b) (4)

(b) (4)

**PROPOSED REVISIONS FROM THE DIVISION SENT TO THE SPONSOR:**

(b) (4)

The revisions below were sent to the sponsor on 2/26/13. The sponsor agreed with the changes in revised labeling submitted on 3/7/13. The edit to remove the subsection title, "Teratogenic Effects" was sent to the sponsor on 3/18/13 and incorporated by the sponsor on 3/18/13.

**8.1 Pregnancy****Pregnancy Category B**

*No studies with SITAVIG have been performed in pregnant women. Systemic exposure of acyclovir following buccal administration of SITAVIG is minimal. SITAVIG should be used during pregnancy only if the potential benefit outweighs the potential risk to the fetus.*

*There are no adequate and well-controlled studies of systemic acyclovir in pregnant women. A prospective epidemiologic registry of acyclovir use during pregnancy between 1984 and 1999 followed 749 pregnancies in women exposed to systemic acyclovir during the first trimester of pregnancy resulting in 756 outcomes. The occurrence rate of birth defects approximated that found in the general population.*

*However, the size of the registry was insufficient to evaluate the risk for less common defects or to permit reliable or definitive conclusions regarding the safety of acyclovir in pregnant women and their developing fetuses.*

#### Animal Data

*Animal reproduction studies have not been conducted with SITAVIG. Acyclovir was not teratogenic in the mouse, rabbit or rat at exposures greatly in excess of human exposure.*

### **13 Nonclinical Toxicology**

#### **13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility**

*Systemic exposure following buccal administration of acyclovir is minimal. Results from previous studies of carcinogenesis, mutagenesis and fertility for acyclovir are not included in the full prescribing information for SITAVIG due to the minimal exposure that results from buccal administration. Information on these studies following systemic exposure is available in the full prescribing information for acyclovir products approved for oral and parenteral administration.*

#### **CLARIFICATION TO SECTION 9 REPRODUCTIVE AND DEVELOPMENTAL TOXICOLOGY OF PREVIOUSLY FINALIZED NDA REVIEW (12/6/12):**

In Section 9 Reproductive and Developmental Toxicology, of the previously finalized Pharmacology/Toxicology NDA Review, the USPI for ZOVIRAX IV injection was referenced to describe the nonclinical reproductive toxicity findings. The safety margins for the teratology studies are misleadingly low for the IV route of administration and do not reflect the minimal exposures anticipated following buccal administration of acyclovir. The nonclinical safety margins for the teratology studies described in the labeling for ZOVIRAX IV are only 1 to 9 times human exposure levels whereas the safety margins described in labeling for ZOVIRAX oral (capsule, tablet, and suspension) are 9 to 106 times human exposure levels. By extension, the safety margins should be even higher for the buccal route since minimal acyclovir is absorbed systemically. The labeling for ZOVIRAX cream states that "Acyclovir was not teratogenic in the mouse, rabbit, or rat at exposures greatly in excess of human exposure." This same language is appropriately used in the proposed labeling for SITAVIG Section 8.1 Pregnancy, subsection Animal Data, since buccal administration of a single 50 mg tablet of acyclovir is not anticipated to result in significant systemic exposures. In conclusion, although the ZOVIRAX IV labeling was previously referenced in the pharmacology/toxicology NDA review to describe the nonclinical reproductive toxicity findings, the safety margins for the IV route do not apply to the buccal route of administration for acyclovir. Therefore, the sponsor's proposed labeling to describe the acyclovir teratology studies is appropriate.

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/s/  
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JANICE A LANSITA  
03/20/2013

HANAN N GHANTOUS  
03/20/2013

**DEPARTMENT OF HEALTH AND HUMAN SERVICES  
PUBLIC HEALTH SERVICE  
FOOD AND DRUG ADMINISTRATION  
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**PHARMACOLOGY/TOXICOLOGY NDA LABELING REVIEW AND EVALUATION**

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*Template Version: December 7, 2009*

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# 1 Executive Summary

## 1.1 Introduction

The sponsor, BioAlliance Pharma submitted NDA 203791 in accordance with Section 505(b)(2) for Acyclovir Lauriad™ for the treatment of orofacial herpes and (b) (4). Acyclovir is an inhibitor of herpes simplex virus (HSV) type 1 and type 2. HSV thymidine kinase converts acyclovir to acyclovir monophosphate which is then converted to a triphosphate by cellular enzymes which has high affinity for the viral DNA polymerase. Acyclovir has been approved in the US since 1982 and used for the treatment of cold sores. Approved formulations in the US include an oral capsule (200 mg), oral tablets (400 and 800 mg), an oral suspension (200 mg/5mL), 5% topical cream, 5% ointment and a solution for injection. Acyclovir Lauriad™ buccal tablet (ABT) was developed to provide a new delivery system (rapid and prolonged drug release) and new route of administration to the buccal cavity with a single dose application. The sponsor conducted two clinical trials to support the approval of ABT, a pharmacokinetic trial (BA2004/21/01) in 12 subjects and a Phase 3 clinical trial (BA2005/21/02) in 775 immunocompetent patients at risk of developing recurrences of labial herpes. The sponsor concluded from these trials that the 50 mg dose provided an optimal buccal dose with low plasma levels and high local concentrations.

## 1.2 Brief Discussion of Nonclinical Findings

To support the nonclinical package, the sponsor relied on the historical experience with acyclovir as well as the published literature on the oral and systemic toxicity of acyclovir. In addition the sponsor conducted a local tolerance study of 50 mg ABT on the jugal mucosa of the hamster. Nonclinical literature publications describe studies on the acute, subchronic, chronic, mutagenicity, carcinogenicity, and reproductive toxicity of acyclovir. These studies were performed using systemic dose routes which would likely over-predict the potential toxicity of acyclovir Lauriad™ since systemic plasma exposure following buccal administration is likely to be minimal based on the clinical pharmacokinetic (PK) data of acyclovir Lauriad™.

The sponsor performed a hamster single-dose local tolerance study with 50 mg acyclovir Lauriad™. No significant local test article related findings were seen following local administration of 50 mg acyclovir Lauriad™ to the jugal mucosa of the hamster. A flaw of the study is that no local or systemic pharmacokinetic or toxicokinetic analyses were performed. Therefore, the extrapolation of the nonclinical data to the clinical data is limited. However, in considering the extensive historical clinical experience with acyclovir and the low proposed clinical dose of 50 mg, this is not an approval issue in this reviewer's opinion.

The single dose of 50 mg used in the hamster is the same as the proposed clinical dose. No test article-related findings were seen in the local tolerance study in hamsters. The 50 mg dose was also well-tolerated in patients. Therefore the proposed clinical dose of 50 mg acyclovir Lauriad™ in humans is safe and reasonable from a nonclinical perspective. In conclusion, there are no nonclinical issues that would preclude the approval of 50 mg acyclovir Lauriad™ buccal tablet.

### **1.3 Recommendations**

None.

#### **1.3.1 Approvability**

From a pharmacology/toxicology perspective, there are no identified safety issues that would preclude the approval of this product. However, a complete response action will be taken by the Clinical and Statistical Review Teams because ABT did not demonstrate adequate clinical efficacy.

#### **1.3.2 Additional Non Clinical Recommendations**

None.

#### **1.3.3 Labeling**

The relevant nonclinical sections of the labeling, Section 8.1 Pregnancy and Section 13 Nonclinical Toxicology are included below. No changes or edits to the sponsor's proposed labeling were requested by this reviewer during this review cycle.

**The sponsor's proposed labeling is presented below:**

#### **8 Use in Specific Populations**

##### **8.1 Pregnancy**

(b) (4)



**13 Nonclinical Toxicology**

(b) (4)

**2 Drug Information****2.1 Drug**

SITAVIG (acyclovir) Lauriad™ 50 mg mucoadhesive Buccal Tablets (ABT 50 mg)

**2.1.1 CAS Registry Number (Optional)**

59277-89-3

**2.1.2 Generic Name**

Acyclovir

**2.1.3 Code Name**

Acyclovir

**2.1.4 Chemical Name**

I: 2-amino-1,9-dihydro -9 -(2-hydroxyethoxymethyl)-6H-purin-6-one

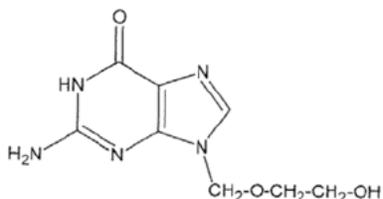
II: 9-(2-hydroxyethoxymethyl)guanine

III: acycloguanosine

**2.1.5 Molecular Formula/Molecular Weight**

C<sub>8</sub>H<sub>11</sub>N<sub>5</sub>O<sub>3</sub> /225.2

**2.1.6 Structure**



### 2.1.7 Pharmacologic class

Synthetic purine nucleoside analogue of guanine active against herpes viruses

### 2.2 Relevant IND/s, NDA/s, and DMF/s

IND 77,812 Acyclovir Lauriad™ 50 mg buccal tablets (BioAlliance Pharma)

NDA 22-404 Oravig® (BioAlliance Pharma)

DMF (b) (4) Aciclovir

### 2.3 Clinical Formulation

#### 2.3.1 Drug Formulation

The composition of ABT 50 mg was provided by the sponsor in the table below.

Table 1 Composition of Acyclovir Lauriad™ 50 mg ABT				
Component	Reference to Quality Standard	Function	Quantity per Tablet	
			mg	% w/w
Active Ingredient:				
Acyclovir	Current USP	Drug Substance	50.00	(b) (4)
Excipients:				
Microcrystalline cellulose	Current NF	(b) (4)	(b) (4)	(b) (4)
Povidone	Current USP	(b) (4)	(b) (4)	(b) (4)
Sodium Lauryl sulfate <sup>a</sup>	Current NF	(b) (4)	(b) (4)	(b) (4)
Hypromellose <sup>(b) (4)</sup>	Current USP	(b) (4)	(b) (4)	(b) (4)
Milk Protein Concentrate <sup>b</sup>	In-house standard	(b) (4)	(b) (4)	(b) (4)
Magnesium stearate	Current NF	(b) (4)	(b) (4)	(b) (4)
Colloidal Silicon Dioxide	Current NF	(b) (4)	(b) (4)	(b) (4)
Total			100.00	(b) (4)
a = Sodium laurylsulfate is synonymous with sodium lauril sulfate (SLS) and sodium monododecyl sulfate (SDS). b = Milk Protein Concentrate is a non-compendial non-novel excipient that has been approved by FDA for use in Oravig® tablets (b) (4)				

### 2.3.2 Comments on Novel Excipients

None, there are no novel excipients in the drug product.

### Comments on Impurities/Degradants of Concern

A potential process related genotoxic impurity, (b) (4) was identified. The sponsor was requested to control the potential genotoxic process-related impurity down to levels consistent with the FDA draft Guidance for Industry "Genotoxic and Carcinogenic Impurities in Drug Substances and Products: Recommended Approaches." The agency submitted a DMF Deficiency letter (DMF- (b) (4)) on July 11, 2012 that requested, "...the level of (b) (4) should be controlled to no more than (b) (4) ug/day. In this case, for a 50 mg daily dose, it means no more than 0. (b) (4)%. If the level of the impurity cannot be controlled at this level, it should be further qualified in the Ames assay; the need for additional qualification studies will depend on the outcome of the Ames assay."

### 2.4 Proposed Clinical Population and Dosing Regimen

The proposed indication is the treatment of labial and facial herpes and (b) (4) following a single 50 mg administration of acyclovir Lauriad™ mucoadhesive buccal tablets (ABT) to the oral cavity.

### 2.5 Regulatory Background

Acyclovir has been approved in the US since 1982 and used for the treatment of cold sores. Acyclovir Lauriad™ buccal tablet (ABT) was developed to provide a new delivery system (rapid and prolonged drug release) and new route of administration to the buccal cavity with a single dose application.

## 3 Studies Submitted

The sponsor submitted a local tolerance study in the hamster and referenced the literature to support the nonclinical package.

### 3.1 Studies Reviewed

7-day local tolerance study in the hamster by oral route according to the cheek pouch technique, Study No. 20100225THP

### 3.2 Studies Not Reviewed

None.

### 3.3 Previous Reviews Referenced

None.

## **4 Pharmacology**

### **4.1 Primary Pharmacology**

The primary in vitro and in vivo virology studies were reviewed by the Clinical Virology reviewer, LALJI MISHRA, Ph.D.

### **4.2 Safety Pharmacology**

The sponsor did not identify safety pharmacology studies with acyclovir in the literature. Since limited systemic exposure is anticipated following a single buccal administration as evidenced by the clinical data, additional safety pharmacology studies were not required. In addition, extensive systemic clinical data are available and the safety profile of acyclovir is well-defined following systemic exposures. Therefore, the lack of nonclinical safety pharmacology data was not considered to be a deficiency.

## **5 Pharmacokinetics/ADME/Toxicokinetics**

The sponsor submitted an extensive literature review of the nonclinical systemic PK/ADME of acyclovir across species including mouse, rat, dog and nonhuman primate. The systemic PK/ADME nonclinical data are not included in this review since minimal systemic exposure is anticipated following buccal administration. The sponsor developed the buccal dose formulation in order to improve upon the poor oral bioavailability of acyclovir. No local or systemic pharmacokinetic or toxicokinetic analyses were performed in the hamster single-dose local tolerance study with 50 mg acyclovir Lauriad™. The clinical PK following buccal administration of ABT was characterized in the clinical PK study, BA2004/21/01. Acyclovir concentrations in the saliva, labial mucosa and plasma were measured. This study confirmed that minimal plasma levels resulted following buccal administration of ABT. For further details, see Clinical Pharmacology review.

## **6 General Toxicology**

Acute, subchronic and chronic repeat-dose toxicology studies were conducted across species and are reported in the published literature. Since minimal systemic exposure following buccal administration of acyclovir is anticipated, the results of these toxicology studies are not directly relevant to ABT and are not discussed in detail in this review.

The sponsor conducted a 7-day local tolerance study in hamsters with ABT at 50 mg in order to evaluate buccal irritation. A review of the study is below.

Study title: 7-day local tolerance study in hamster by the oral route using the cheek pouch method

Study no.: 20100225THP  
 Study report location: BioAlliance Pharma  
 49 boulevard du General Martial Valin  
 75015 Paris, France  
 Conducting laboratory and location: (b) (4)  
 Date of study initiation: 10/12/2010  
 GLP compliance: Yes  
 QA statement: Yes  
 Drug, lot #, and % purity: Acyclovir Lauriad™ 50 mg mucoadhesive buccal tablet., Batch Number: DEV 7504, Purity: 99.6%

## Key Study Findings

No test article related findings were observed. The only macroscopic finding reported was the presence of an undissolved whole acyclovir Lauriad™ tablet in 1 male hamster seen on Day 7. Significant microscopic changes were seen in the male that had an undissolved tablet after 7 days. In this male, local to the tablet the cheek pouch showed greater hyperkeratosis (moderate), an increased epithelial depth (minimal acanthosis) and a minimal (<25 leucocytes per high power field) increase in acute inflammatory cells. There were no signs of erosion, congestion or edema. Similar findings were not seen in other treated animals and appear to be the result of the physical contact of the tablet with the cheek pouch for a prolonged duration.

## Methods

Doses: Two dose groups - Control (Group1) and 50 mg Acyclovir (Group 2)

Group 1: Absolute control (left pouch), no treatment  
 Group 1: Control (right pouch) with sodium chloride solution 0.9%.  
 Group 2: Absolute control (left pouch), no treatment  
 Group 2: 50 mg Acyclovir (right pouch)

Frequency of dosing: Single dose  
 Route of administration: Oral, cheek pouch  
 Dose volume: NA  
 Formulation/Vehicle: Isotonic solution of sodium chloride (i.e. 0.9% NaCl)  
 Species/Strain: Hamster/Syrian  
 Number/Sex/Group: 5/sex/group

Age: 30-42 days  
Weight: Males: 92.3 g to 104.1 g at the start of the study  
(between 30 to 42 days).  
Females: 89.7 g to 104.6 g at the start of the  
study (between 30 to 42 days).  
Satellite groups: None.  
Unique study design: None.  
Deviation from study protocol: Minimal deviations occurred that did not impact  
the study.

## **Observations and Results**

### **Mortality**

No mortality was observed.

### **Clinical Signs**

No clinical signs related to treatment were observed.

### **Body Weights**

Body weights were measured on Day 1, Day 4, and Day 7 and at necropsy. Although a statistically significant difference in female body weight was seen on Day 7 in treated animals, this difference was attributed to two individual animals whose body weights were already lower than the overall group mean on Day -1.

### **Feed Consumption**

Food and water consumption were estimated daily, although there were a few animals with variations (increase in one male and a decrease in one female that was attributed to the animal being found outside of the cage) there were no clear test article related effects on food consumption.

### **Ophthalmoscopy**

Not evaluated.

### **ECG**

Not evaluated.

### **Hematology**

Not evaluated.

## Clinical Chemistry

Not evaluated.

## Urinalysis

Not evaluated.

## Gross Pathology

Cheek pouches were examined macroscopically for signs of inflammation, necrosis, or other local reactions. The only macroscopic finding reported was the presence of an undissolved whole acyclovir Lauriad™ tablet in 1 male hamster seen on Day 7.

## Organ Weights

Not evaluated.

## Histopathology

Adequate Battery: Yes, only the cheek pouches were evaluated which is appropriate for this local tolerance study.

Peer Review: None.

Histological Findings: Evaluation of the epithelium, leukocyte infiltration, edema, vascular congestion, hyperkeratosis and acanthosis were performed on the cheek pouches. There were no significant effects of acyclovir Lauriad™ mucoadhesive buccal tablet on the hamster cheek pouch. The reviewing pathologist determined there was "slightly variable depth of keratin overlying the squamous epithelium of the hamster pouches"; the change was not directly attributed to treatment. There was also a slight increase in hyperkeratosis in the depth of the pouches compared to the mouths of the pouches. Significant microscopic changes were seen in the 1 male that had an undissolved tablet after 7 days. In this male, local to the tablet the cheek pouch showed greater hyperkeratosis (moderate), an increased epithelial depth (minimal acanthosis) and a minimal (<25 leucocytes per high power field) increase in acute inflammatory cells. There were no signs of erosion, congestion or edema. Similar findings were not seen in other treated animals and appear to be the result of the physical contact of the tablet with the cheek pouch for a prolonged duration. A summary of the histological scores, grades and irritation index is provided in Table 1 below.

**Table 1 Hamster Cheek Pouch Histological Scores, Grades, and Irritation Index**

	Groupe 1 : Absolute control	Groupe 1 : Control	Groupe 2 : Absolute control	Groupe 2 : Test item
Score obtained in oral tissue :				
Epithelium	0	0	0	0
Hyperkeratosis	7 (10)	9 (10)	11 (10)	9 (10)
Acanthosis	0	0	0	1 (10)
Leucocyte infiltration	0	0	0	1 (10)
Vascular congestion	0	0	0	0
Oedema	0	0	0	0
Total Score	7	9	11	11
Calculated grades	0,7	0,9	1,1	1,1
Irritation index	NA	0	NA	0
Description of response	NA	None	NA	None

Group 1: Absolute control (left pouch), pouch without any treatment

Group 1: Control (right pouch) pouch with sodium chloride solution 0.9%

Group 2: Absolute control (left pouch), pouch without any treatment

Group 2: Test item (right pouch)

( ): number of signs observed

Calculated grades: grades were added and the sum was divided by the number of observation

Irritation index: the control group average was subtracted from the test group

NA: not applicable

Hyperkeratosis was slightly higher in the Group 2 absolute control (treatment group, left pouch, untreated cheek pouch) compared with the Group 1 absolute control (control group, left pouch, untreated cheek pouch) with a calculated score of 11 vs. 7. The overall calculated grades were only slightly higher in the Group 2 treated animals compared with the Group 1 control animals: treated cheek pouches - 0.9 in controls vs. 1.1 in treated animals; absolute control cheek pouches - 0.7 in controls vs. 1.1 in the treated absolute control cheek pouches.

## Special Evaluation

None.

## Toxicokinetics

Not evaluated.

## Stability and Homogeneity

A stability statement was provided indicating the drug product was stable for the duration of the study. The drug product is a tablet therefore, homogeneity analyses were not performed.

## 6.1 Single-Dose Toxicity

Acute studies in rats and mice have been reported in the literature following single doses of acyclovir by intravenous, oral and intraperitoneal dose routes. The lowest LD<sub>50</sub> following IV dosing was >600 mg/kg in rats and >405 mg/kg in mice. No deaths were observed at the maximum feasible doses used (Tucker, 1982).

## 6.2 Repeat-Dose Toxicity

Repeat dose toxicity studies of acyclovir ranged in duration from 21 days to 12 months as reported in the literature. However these studies were performed by parenteral routes and not the buccal route. The systemic exposure of acyclovir following buccal administration is expected to be significantly lower based on the clinical data, therefore, the relevance of the systemic acyclovir toxicity data to ABT is limited and likely over-predicts the potential toxicity of ABT following a single buccal administration.

## 7 Genetic Toxicology

Acyclovir has been evaluated in both *in vitro* and *in vivo* genotoxicity assays. The genotoxicity literature indicates that acyclovir does not cause mutagenicity but does appear to cause clastogenicity (Clive et al. 1983). The genotoxicity results are summarized in the product labeling for ZOVIRAX, the reference listed drug.

## 8 Carcinogenicity

Acyclovir was not carcinogenic in rats and mice at doses up to 450 mg/kg/day (Tucker 1982; Tucker et al. 1983b). The carcinogenicity results are summarized in the product labeling of ZOVIRAX, the reference listed drug.

## 9 Reproductive and Developmental Toxicology

Reproductive toxicity studies in mice, rats and rabbits were reported in the literature with the key findings reported in the product labeling for ZOVIRAX, the reference listed drug.

The labeling indicates findings of a reduction of implantation efficacy, decreases in corpora lutea, total implantation sites and numbers of live fetuses. Additionally, testicular atrophy and aspermatogenesis were seen in rats and dogs.

Sections of the ZOVIRAX US Package Insert that include information on reproductive toxicity including fertility and pregnancy are as follows:

Acyclovir did not impair fertility or reproduction in mice (450 mg/kg/day, p.o.) or in rats (25 mg/kg/day, s.c.). In the mouse study, plasma levels were the same as human levels, while in the rat study, they were 1 to 2 times human levels. At higher doses (50 mg/kg/day, s.c.) in rats and rabbits (1 to 2 and 1 to 3 times human levels, respectively) implantation efficacy, but not litter size, was

decreased. In a rat peri- and post-natal study at 50 mg/kg/day, s.c., there was a statistically significant decrease in group mean numbers of corpora lutea, total implantation sites, and live fetuses.

No testicular abnormalities were seen in dogs given 50 mg/kg/day, IV for 1 month (1 to 3 times human levels) or in dogs given 60 mg/kg/day orally for 1 year (the same as human levels). **Testicular atrophy and aspermatogenesis were observed in rats and dogs at higher dose levels.**

**Pregnancy: Teratogenic Effects:** Pregnancy Category B. Acyclovir administered during organogenesis was not teratogenic in the mouse (450 mg/kg/day, p.o.), rabbit (50 mg/kg/day, s.c. and IV), or rat (50 mg/kg/day, s.c.). These exposures resulted in plasma levels the same as, 4 and 9, and 1 and 2 times, respectively, human levels.

There are no adequate and well-controlled studies in pregnant women. A prospective epidemiologic registry of acyclovir use during pregnancy was established in 1984 and completed in April 1999. There were 749 pregnancies followed in women exposed to systemic acyclovir during the first trimester of pregnancy resulting in 756 outcomes. The occurrence rate of birth defects approximates that found in the general population. However, the small size of the registry is insufficient to evaluate the risk for less common defects or to permit reliable or definitive conclusions regarding the safety of acyclovir in pregnant women and their developing fetuses. Acyclovir should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

## 10 Integrated Summary and Safety Evaluation

The sponsor, BioAlliance Pharma submitted NDA 203791 in accordance with Section 505(b)(2) for Acyclovir Lauriad<sup>TM</sup> for the treatment of orofacial herpes and (b) (4). Acyclovir is an inhibitor of herpes simplex virus (HSV) type 1 and type 2. HSV thymidine kinase converts acyclovir to acyclovir monophosphate which is then converted to a triphosphate by cellular enzymes which has a high affinity for the viral DNA polymerase. Acyclovir has been approved in the US since 1982 and used for the treatment of cold sores. Approved formulations in the US include an oral capsule (200 mg), oral tablets (400 and 800 mg), an oral suspension (200 mg/5 mL), 5% topical cream, 5% ointment and a solution for injection. Acyclovir Lauriad<sup>TM</sup> tablet (ABT) was developed to provide a new delivery system (rapid and prolonged drug release) and new route of administration to the buccal cavity with a single dose application. The sponsor conducted two clinical trials to support the approval of ABT, a pharmacokinetic trial (BA2004/21/01) in 12 subjects and a Phase 3 clinical trial (BA2005/21/02) in 775 immunocompetent patients at risk of developing recurrences of labial herpes.

The sponsor relied on the historical experience with acyclovir as well as the literature on the oral and systemic toxicity of acyclovir to support the nonclinical package. In addition the sponsor conducted a local tolerance study of 50 mg ABT on the jugal mucosa of the

hamster. Nonclinical literature reports describe the acute, subchronic, chronic, mutagenicity, carcinogenicity, and reproductive toxicity of acyclovir. The in vivo toxicology studies were generally performed by systemic dose routes which would likely over-predict the potential toxicity of acyclovir Lauriad™ since systemic plasma exposure following buccal administration is likely to be minimal based on the clinical pharmacokinetic (PK) data of acyclovir Lauriad™.

In summary, the nonclinical data from the literature indicate that acyclovir is mainly eliminated by the kidney, rapidly distributes to all tissues; but mainly to the liver, kidney and intestine. Renal toxicity has been observed in the toxicology studies at high doses. The renal toxicity was characterized as a secondary toxicity since acyclovir precipitates out of urine resulting in obstructive nephropathy in the rat and impairment of renal function in the dog (Tucker, 1983).

In genotoxicity assays, acyclovir caused clastogenicity but not mutagenicity. No effect on tumor incidence was observed in lifetime oral gavage carcinogenicity bioassays in rats (110-122 weeks duration) and mice (110-126 weeks duration) at doses of 50, 150, and 450 mg/kg/day.

Reproductive toxicity studies in mice, rats and rabbits were reported in the literature with the key findings summarized in the product labeling for ZOVIRAX, the reference listed drug. The labeling indicates findings of a reduction of implantation efficacy, decreases in corpora lutea, total implantation sites and numbers of live fetuses. Additionally, testicular atrophy and aspermatogenesis were seen in rats and dogs.

The sponsor conducted a single-dose local tolerance study in the hamster with 50 mg of acyclovir Lauriad™ administered to the jugal mucosa of the hamster. There were no significant local test article related findings identified in the study. A flaw of the study is that no pharmacokinetic or toxicokinetic analyses were performed. Therefore, the extrapolation of the nonclinical data to the clinical data is limited. However, in considering the extensive historical clinical experience with acyclovir and the low proposed clinical dose of 50 mg, this is not an approval issue in this reviewer's opinion.

The single dose of 50 mg used in the hamster is the same as the proposed clinical dose. No findings were seen in the local tolerance study in hamsters. The 50 mg dose was also well-tolerated in patients. Therefore the proposed clinical dose of 50 mg of acyclovir Lauriad™ in humans is safe and reasonable from a nonclinical perspective.

## 11 References:

1. Tucker WE Jr. Preclinical toxicology profile of acyclovir: an overview. *Am J Med.* 1982 Jul 20;73(1A):27-30.
2. Zovirax® US Package Insert, 2002.
3. Tucker WE Jr, Macklin AW, Szot RJ, Johnston RE, Elion GB, de Miranda P, Szczech GM. Preclinical toxicology studies with acyclovir: acute and subchronic tests. *Fundam Appl Toxicol.* 1983 Nov-Dec;3(6):573-8.
4. Clive D, Turner NT, Hozier J, Batson AG, Tucker WE Jr. Preclinical toxicology studies with acyclovir: genetic toxicity tests. *Fundam Appl Toxicol.* 1983 Nov-Dec;3(6):587-602.
5. Tucker WE Jr, Krasny HC, de Miranda P, Goldenthal EI, Elion GB, Hajian G, Szczech GM. Preclinical toxicology studies with acyclovir: carcinogenicity bioassays and chronic toxicity tests. *Fundam Appl Toxicol.* 1983 Nov-Dec;3(6):579-86.

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/s/  
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JANICE A LANSITA  
12/05/2012

HANAN N GHANTOUS  
12/06/2012  
I concur with Dr. lansita's conclusion.

## PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR NDA/BLA or Supplement

**NDA Number: 203791**

**Applicant: Bioalliance Pharma**

**Stamp Date: March 12, 2012**

**Drug Name: Sitavig (Acyclovir NDA Type: 505(b)(2)  
Buccal Tablet)**

On **initial** overview of the NDA/BLA application for filing:

	<b>Content Parameter</b>	<b>Yes</b>	<b>No</b>	<b>Comment</b>
1	Is the pharmacology/toxicology section organized in accord with current regulations and guidelines for format and content in a manner to allow substantive review to begin?	X		
2	Is the pharmacology/toxicology section indexed and paginated in a manner allowing substantive review to begin?	X		
3	Is the pharmacology/toxicology section legible so that substantive review can begin?	X		
4	Are all required (*) and requested IND studies (in accord with 505 b1 and b2 including referenced literature) completed and submitted (carcinogenicity, mutagenicity, teratogenicity, effects on fertility, juvenile studies, acute and repeat dose adult animal studies, animal ADME studies, safety pharmacology, etc)?	X		Nonclinical studies were referenced from: the literature, Zovirax labeling, and the Zovirax Product Monograph.
5	If the formulation to be marketed is different from the formulation used in the toxicology studies, have studies by the appropriate route been conducted with appropriate formulations? (For other than the oral route, some studies may be by routes different from the clinical route intentionally and by desire of the FDA).	X		A 7-day local cheek pouch study in hamsters with the clinical drug product was performed.
6	Does the route of administration used in the animal studies appear to be the same as the intended human exposure route? If not, has the applicant <u>submitted</u> a rationale to justify the alternative route?	X		
7	Has the applicant <u>submitted</u> a statement(s) that all of the pivotal pharm/tox studies have been performed in accordance with the GLP regulations (21 CFR 58) <u>or</u> an explanation for any significant deviations?	X		One study was submitted, the 7-day hamster cheek pouch study; this study was conducted under GLPs.
8	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?			Not applicable - special nonclinical toxicology studies were not requested.

File name: 5\_Pharmacology\_Toxicology Filing Checklist for NDA\_BLA or Supplement  
010908

## PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	Comment
9	Are the proposed labeling sections relative to pharmacology/toxicology appropriate (including human dose multiples expressed in either mg/m2 or comparative serum/plasma levels) and in accordance with 201.57?	X		The sponsor chose not to include the data on carcinogenesis, mutagenesis and fertility for acyclovir “due to the minimal exposure that results from buccal administration.” The nonclinical labeling further references the “...full prescribing information for acyclovir products approved for oral and parenteral administration. (b) (4) ”
10	Have any impurity – etc. issues been addressed? (New toxicity studies may not be needed.)	X		DMF (b) (4) is referenced for the complete listing of DS impurities. CMC is currently investigating these and any additional impurities.  DP impurities include (b) (4) unknown impurities at low levels of (b) (4)%, slightly above the limit of quantification (0.05%).  Known Impurities include (b) (4), the (b) (4) of the drug substance and a likely degradation product.  (b) (4) include (b) (4) at < (u) (4) ppm, (u) (4) times lower than the limit fixed by the ICH (e.g. according to the (b) (4) (u) (4) the Permitted Daily Exposure for (b) (4) is (b) (4) mg/day (corresponding to (b) (4) ppm)).”
11	Has the applicant addressed any abuse potential issues in the submission?			Not applicable - to date, acyclovir has not been associated with abuse potential.
12	If this NDA/BLA is to support a Rx to OTC switch, have all relevant studies been submitted?			Not applicable.

**IS THE PHARMACOLOGY/TOXICOLOGY SECTION OF THE APPLICATION FILEABLE? Yes**

If the NDA/BLA is not fileable from the pharmacology/toxicology perspective, state the reasons and provide comments to be sent to the Applicant - **No issues.**

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter- **No issues.**

Janice Lansita, PhD, DABT

4/23/12

Reviewing Pharmacologist

Date

Hanan Ghantous, PhD, DABT

4/23/12

Team Leader/Supervisor

Date

File name: 5\_Pharmacology\_Toxicology Filing Checklist for NDA\_BLA or Supplement 010908

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/s/  
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JANICE A LANSITA  
04/24/2012

HANAN N GHANTOUS  
04/24/2012