

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

203791Orig1s000

OTHER REVIEW(S)

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for *each* PMR/PMC in the Action Package.

NDA/BLA # 203791
Product Name: Sitavig, acyclovir 50 mg mucoadhesive buccal tablet (ABT)

PMR/PMC Description: Deferred pediatric study under PREA to evaluate the safety of SITAVIG in pediatric patients greater than 6 years to less than 18 years of age with recurrent herpes labialis and to assess duration of HSV episode in the treated population. At least 100 treated subjects, distributed across the age range, must be evaluated.

PMR/PMC Schedule Milestones: Final Protocol Submission: 01/31/2014
Study/Trial Completion: 06/31/2017
Final Report Submission: 12/31/2018
Other: _____

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

The adult application is ready for approval.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

Sitavig 50 mg has not been studied in any patients less than 18 years of age. Bioalliance received a deferral in Europe for patients ages 10 and greater and will perform a PK study there. Bioalliance proposed

(b) (4)

After review of other applications including XERESE cream, it seems reasonable to request that the Applicant follow a similar pediatric plan for Sitavig 50 mg; and should be studied for both activity and safety in children greater than 6 years to less than 18 years. A deferral will be granted for this age group and a waiver for patients six years of age and younger. After discussion with the PeRC committee, a partial waiver will be issued for pediatric patients 6 years of age and younger primarily for the following reason: Evidence suggests that product would be unsafe in pediatric subpopulations 6 years of age and younger. Sitavig is a mucoadhesive buccal tablet applied or placed on the gum until the drug completely dissolves. This type of application may be unsafe in young children due to potential choking hazards.

In addition,

- Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in this/these pediatric subpopulation(s) AND is not likely to be used in a substantial number of pediatric patients in this/these pediatric subpopulation(s).
- The nature of the mucoadhesive tablet use requires the need for its accurate application in the oral cavity- i.e. the timing of the application needs to be within the first hour of onset of prodromal symptoms. Young children may not be able to identify prodromal symptoms to know when to apply the medication.

3. If the study/clinical trial is a PMR, check the applicable regulation.

If not a PMR, skip to 4.

- **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

(b) (4)
pediatric subjects greater than 6 years to less than 18 years of age with recurrent herpes labialis.
(b) (4)

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
- Pharmacokinetic studies or clinical trials
- Drug interaction or bioavailability studies or clinical trials
- Dosing trials

Continuation of Question 4

- Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

- Meta-analysis or pooled analysis of previous studies/clinical trials
- Immunogenicity as a marker of safety
- Other (provide explanation)

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
- Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
- Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
- Dose-response study or clinical trial performed for effectiveness
- Nonclinical study, not safety-related (specify)

Other

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

If so, does the clinical trial meet the following criteria?

- There is a significant question about the public health risks of an approved drug
- There is not enough existing information to assess these risks
- Information cannot be gained through a different kind of investigation
- The trial will be appropriately designed to answer question about a drug's efficacy and safety, and
- The trial will emphasize risk minimization for participants as the protocol is developed

PMR/PMC Development Coordinator:

- This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

(Signature line for BLAs)

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/s/

SOHAIL MOSADDEGH
04/12/2013

505(b)(2) ASSESSMENT

Application Information		
NDA # 203791	NDA Supplement #: S- 000	Efficacy Supplement Type SE-
Proprietary Name: Sitavig Established/Proper Name: acyclovir Dosage Form: Buccal tablet Strengths: 50 mg		
Applicant: Bioalliance Pharma		
Date of Receipt: 03/12/12		
PDUFA Goal Date: 04/12/13 (major amendment)	Action Goal Date (if different): 04/12/2013	
Proposed Indication(s): SITAVIG is indicated in immunocompetent adults for the treatment of recurrent orofacial herpes simplex virus infections.		

GENERAL INFORMATION

- 1) Is this application for a recombinant or biologically-derived product and/or protein or peptide product *OR* is the applicant relying on a recombinant or biologically-derived product and/or protein or peptide product to support approval of the proposed product?

YES NO

If "YES" contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

**INFORMATION PROVIDED VIA RELIANCE
(LISTED DRUG OR LITERATURE)**

- 2) List the information essential to the approval of the proposed drug that is provided by reliance on our previous finding of safety and efficacy for a listed drug or by reliance on published literature. *(If not clearly identified by the applicant, this information can usually be derived from annotated labeling.)*

Source of information* (e.g., published literature, name of referenced product)	Information provided (e.g., pharmacokinetic data, or specific sections of labeling)
Published literature	Pharm/tox, PK
Zovirax capsule (NDA 18828)	Contraindications, pregnancy, overdose, non-clinical toxicology, Warning and precautions, nursing mothers. Microbiology

*each source of information should be listed on separate rows

- 3) 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)

The active ingredient in ABT-50 (Sitavig) is acyclovir. Acyclovir oral tablets are not approved for a herpes labialis indication but acyclovir cream is approved for the treatment of herpes labialis. Therefore a bridge to an approved formulation of acyclovir (cream) for the herpes labialis indication is appropriate. However because acyclovir cream and ABT 50 are both topical products (or topical delivery systems in the case of ABT 50), a bioequivalence study between acyclovir cream and ABT 50 is not adequate to support efficacy and safety. BA/BE studies are not used to link different topical formulations with respect to supporting efficacy and safety. Clinical trial data are generally required. In this case, given the active ingredient is known to be efficacious against herpes and topical delivery of acyclovir is known to be clinically efficacious for the treatment of herpes labialis, a single new clinical trial of the new formulation (ABT-50) was deemed to be sufficient to support clinical labeling. Therefore, the Division of Antiviral Products is relying on our past findings in the review of the clinical trials of acyclovir cream to support the use of a single new clinical trial evaluating ABT 50.

In addition a bioavailability study conducted by the applicant showed that acyclovir buccal tablet 50 mg (ABT 50) yielded local (salivary) acyclovir concentrations greater than concentrations needed to suppress HSV-1 based on in vitro studies. This study provided proof of concept that the mucoadhesive acyclovir tablet delivers substantial concentrations of acyclovir topically to the orofacial region that needed to be confirmed with a clinical trial and therefore provides a bridge to acyclovir cream.

RELIANCE ON PUBLISHED LITERATURE

- 4) (a) Regardless of whether the applicant has explicitly stated a reliance on published literature to support their application, is reliance on published literature necessary to support the approval of the proposed drug product (i.e., the application *cannot* be approved without the published literature)?

YES NO

If "NO," proceed to question #5.

- (b) Does any of the published literature necessary to support approval identify a specific (e.g., brand name) *listed* drug product?

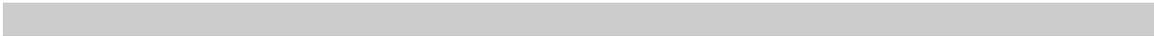
YES NO

If "NO," proceed to question #5.

If "YES", list the listed drug(s) identified by name and answer question #4(c).

- (c) Are the drug product(s) listed in (b) identified by the applicant as the listed drug(s)?

YES NO



RELIANCE ON LISTED DRUG(S)

Reliance on published literature which identifies a specific approved (listed) drug constitutes reliance on that listed drug. Please answer questions #5-9 accordingly.

- 5) Regardless of whether the applicant has explicitly referenced the listed drug(s), does the application **rely** on the finding of safety and effectiveness for one or more listed drugs (approved drugs) to support the approval of the proposed drug product (i.e., the application cannot be approved without this reliance)?

YES NO

If "NO," proceed to question #10.

- 6) Name of listed drug(s) relied upon, and the NDA/ANDA #(s). Please indicate if the applicant explicitly identified the product as being relied upon (see note below):

Name of Drug	NDA/ANDA #	Did applicant specify reliance on the product? (Y/N)
Zovirax capsule	18828	yes

Applicants should specify reliance on the 356h, in the cover letter, and/or with their patent certification/statement. If you believe there is reliance on a listed product that has not been explicitly identified as such by the applicant, please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

- 7) If this is a (b)(2) supplement to an original (b)(2) application, does the supplement rely upon the same listed drug(s) as the original (b)(2) application?

N/A YES NO

If this application is a (b)(2) supplement to an original (b)(1) application or not a supplemental application, answer "N/A".

If "NO", please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

- 8) Were any of the listed drug(s) relied upon for this application:

- a) Approved in a 505(b)(2) application?

YES NO

If "YES", please list which drug(s).

Name of drug(s) approved in a 505(b)(2) application:

- b) Approved by the DESI process?

YES NO

If "YES", please list which drug(s).

Name of drug(s) approved via the DESI process:

- c) Described in a monograph?

YES NO

If "YES", please list which drug(s).

Name of drug(s) described in a monograph:

d) Discontinued from marketing?

YES NO

If "YES", please list which drug(s) and answer question d) i. below.

If "NO", proceed to question #9.

Name of drug(s) discontinued from marketing:

i) Were the products discontinued for reasons related to safety or effectiveness?

YES NO

(Information regarding whether a drug has been discontinued from marketing for reasons of safety or effectiveness may be available in the Orange Book. Refer to section 1.11 for an explanation, and section 6.1 for the list of discontinued drugs. If a determination of the reason for discontinuation has not been published in the Federal Register (and noted in the Orange Book), you will need to research the archive file and/or consult with the review team. Do not rely solely on any statements made by the sponsor.)

9) Describe the change from the listed drug(s) relied upon to support this (b)(2) application (for example, "This application provides for a new indication, otitis media" or "This application provides for a change in dosage form, from capsule to solution").

This application provides new dosage form (buccal tablet), new route of administration (tablet placed on the upper gum), and new indications ((b) (4))

The purpose of the following two questions is to determine if there is an approved drug product that is equivalent or very similar to the product proposed for approval that should be referenced as a listed drug in the pending application.

The assessment of pharmaceutical equivalence for a recombinant or biologically-derived product and/or protein or peptide product is complex. If you answered YES to question #1, proceed to question #12; if you answered NO to question #1, proceed to question #10 below.

10) (a) Is there a pharmaceutical equivalent(s) to the product proposed in the 505(b)(2) application that is already approved (via an NDA or ANDA)?

*(Pharmaceutical equivalents are drug products in identical dosage forms that: (1) contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; (2) do not necessarily contain the same inactive ingredients; **and** (3) meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates. (21 CFR 320.1(c)).*

Note that for proposed combinations of one or more previously approved drugs, a pharmaceutical equivalent must also be a combination of the same drugs.

YES NO

If "NO" to (a) proceed to question #11.

If "YES" to (a), answer (b) and (c) then proceed to question #12.

(b) Is the pharmaceutical equivalent approved for the same indication for which the 505(b)(2) application is seeking approval?
YES NO

(c) Is the listed drug(s) referenced by the application a pharmaceutical equivalent?
YES NO

If "YES" to (c) and there are no additional pharmaceutical equivalents listed, proceed to question #12.

If "NO" or if there are additional pharmaceutical equivalents that are not referenced by the application, list the NDA pharmaceutical equivalent(s); you do not have to individually list all of the products approved as ANDAs, but please note below if approved approved generics are listed in the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

Pharmaceutical equivalent(s):

11) (a) Is there a pharmaceutical alternative(s) already approved (via an NDA or ANDA)?

(Pharmaceutical alternatives are drug products that contain the identical therapeutic moiety, or its precursor, but not necessarily in the same amount or dosage form or as the same salt or ester. Each such drug product individually meets either the identical or its own respective compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times and/or dissolution rates. (21 CFR 320.1(d)) Different dosage forms and strengths within a product line by a single manufacturer are thus pharmaceutical alternatives, as are extended-release products when compared with immediate- or standard-release formulations of the same active ingredient.)

Note that for proposed combinations of one or more previously approved drugs, a pharmaceutical alternative must also be a combination of the same drugs.

YES NO
If "NO", proceed to question #12.

(b) Is the pharmaceutical alternative approved for the same indication for which the 505(b)(2) application is seeking approval? See comment
YES NO

(c) Is the approved pharmaceutical alternative(s) referenced as the listed drug(s)?
YES NO

If "YES" and there are no additional pharmaceutical alternatives listed, proceed to question #12.

If "NO" or if there are additional pharmaceutical alternatives that are not referenced by the application, list the NDA pharmaceutical alternative(s); you do not have to individually list all of the products approved as ANDAs, but please note below if approved generics are listed in

the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

Pharmaceutical alternative(s):

Zovirax ointment (NDA 18604), Zovirax oral suspension (NDA 19909), Zovirax tablets (NDA 200089), generic capsules, generic oral suspensions, and generic tablets

PATENT CERTIFICATION/STATEMENTS

12) List the patent numbers of all unexpired patents listed in the Orange Book for the listed drug(s) for which our finding of safety and effectiveness is relied upon to support approval of the (b)(2) product.

Listed drug/Patent number(s):

No patents listed *proceed to question #14*

13) Did the applicant address (with an appropriate certification or statement) all of the unexpired patents listed in the Orange Book for the listed drug(s) relied upon to support approval of the (b)(2) product?

YES NO

If "NO", list which patents (and which listed drugs) were not addressed by the applicant.

Listed drug/Patent number(s): same as #12 above

14) Which of the following patent certifications does the application contain? (*Check all that apply and identify the patents to which each type of certification was made, as appropriate.*)

- No patent certifications are required (e.g., because application is based solely on published literature that does not cite a specific innovator product)
- 21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA. (Paragraph I certification)
- 21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired. (Paragraph II certification)
- 21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire. (Paragraph III certification)

Patent number(s):

Expiry date(s):

- 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted. (Paragraph IV certification). *If Paragraph IV certification was submitted, proceed to question #15.*
- 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the NDA holder/patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above). *If the applicant has a licensing agreement with the NDA holder/patent owner, proceed to question #15.*
- 21 CFR 314.50(i)(1)(ii): No relevant patents.
- 21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent as described in the corresponding use code in the Orange Book. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications. (Section viii statement)

Patent number(s):
Method(s) of Use/Code(s):

15) Complete the following checklist **ONLY** for applications containing Paragraph IV certification and/or applications in which the applicant and patent holder have a licensing agreement:

- (a) Patent number(s):
- (b) Did the applicant submit a signed certification stating that the NDA holder and patent owner(s) were notified that this b(2) application was filed [21 CFR 314.52(b)]?
YES NO

If "NO", please contact the applicant and request the signed certification.

- (c) Did the applicant submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)]? This is generally provided in the form of a registered mail receipt.
YES NO

If "NO", please contact the applicant and request the documentation.

- (d) What is/are the date(s) on the registered mail receipt(s) (i.e., the date(s) the NDA holder and patent owner(s) received notification):

Date(s):

- (e) Has the applicant been sued for patent infringement within 45-days of receipt of the notification listed above?

Note that you may need to call the applicant (after 45 days of receipt of the notification) to verify this information **UNLESS** the applicant provided a written statement from the notified patent owner(s) that it consents to an immediate effective date of approval.

YES NO Patent owner(s) consent(s) to an immediate effective date of approval

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/s/

SOHAIL MOSADDEGH
04/12/2013

**FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion**

*****Pre-decisional Agency Information*****

Memorandum

Date: March 13, 2013

To: Sohail Mosaddegh, PharmD, Regulatory Project Manager
Division of Antiviral Products (DAVP)

From: Jessica Fox, PharmD, Regulatory Review Officer
Kemi Asante, PharmD, Regulatory Review Officer

Subject: NDA 203791
SITAVIG (acyclovir) buccal tablets

As requested in DAVP's consult dated March 12, 2013, OPDP reviewed the proposed substantially complete versions of the SITAVIG prescribing information (PI), patient labeling (PPI), instructions for use, and carton and container labeling.

OPDP's comments are provided below in the proposed PI sent via email by DAVP on February 26, 2013.

OPDP reviewed the proposed PPI and instructions for use, sent via email by the Division of Medical Policy Programs on March 8, 2013, and has no comments at this time.

OPDP reviewed the carton and container labeling, dated March 12, 2012, accessed via the EDR location: <\\CDSESUB1\EVSPROD\NDA203791\0000>. OPDP makes reference to the correspondence sent from DAVP to the sponsor on March 8, 2013, regarding comments on the carton and container labeling. This correspondence addresses OPDP's concerns with the carton and container labeling, and OPDP has no additional comments at this time.

Thank you for your consult. If you have any questions on the PI or carton and container labeling, please contact Jessica Fox at 6-5329 or at Jessica.Fox@fda.hhs.gov. If you have any questions on the PPI or instructions for use, please contact Kemi Asante at 6-7425 or at Kemi.Asante@fda.hhs.gov.

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/s/

JESSICA M FOX
03/13/2013

OLUWASEUN A ASANTE
03/13/2013

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy Initiatives
Division of Medical Policy Programs**

PATIENT LABELING REVIEW

Date: March 8, 2013

To: Debra B. Birnkrant, MD
Director
Division of Antiviral Products (DAVP)

Through: LaShawn Griffiths, MSHS-PH, BSN, RN
Associate Director for Patient Labeling
Division of Medical Policy Programs (DMPP)
Barbara Fuller, RN, MSN, CWOCN
Team Leader, Patient Labeling
Division of Medical Policy Programs (DMPP)

From: Karen Dowdy, RN, BSN
Patient Labeling Reviewer
Division of Medical Policy Programs (DMPP)

Subject: DMPP Review of Patient Labeling: Patient Package Insert
(PPI) and Instructions for Use (IFU)

Drug Name (established name): SITAVIG (acyclovir)

Dosage Form and Route: buccal tablet

Application Type/Number: NDA 203-791

Applicant: BioAlliance Pharma

1 INTRODUCTION

On March 12, 2012, BioAlliance Pharma submitted for the Agency's review an original New Drug Application (NDA) 203-791 for SITAVIG (acyclovir) buccal tablets. On January 4, 2013, BioAlliance Pharma submitted a major amendment to this application. Since the receipt of the major amendment was within three months of the Application goal date, the PDUFA clock has been extended by three months to provide a full review of the submission. The proposed indication for SITAVIG (acyclovir) buccal tablets is for the treatment of recurrent herpes labialis (cold sores) in immunocompetent adults.

On February 7, 2013, the Division of Antiviral Products (DAVP) requested that the Division of Medical Policy Programs (DMPP) review the Applicant's proposed Patient Package Insert (PPI) and Instructions for Use (IFU) for SITAVIG (acyclovir) buccal tablets.

This review is written in response to a request by DAVP for DMPP to review the Applicant's proposed Patient Package Insert (PPI) and Instructions for Use (IFU) for SITAVIG (acyclovir) buccal tablets.

A separate review by the Division of Medication Error, Prevention, and Analysis (DMEPA) was completed on November 9, 2012.

2 MATERIAL REVIEWED

- Draft SITAVIG (acyclovir) buccal tablets Patient Package Insert (PPI) received on February 12, 2013, revised by the Review Division throughout the review cycle, and received by DMPP on February 26, 2013.
- Draft SITAVIG (acyclovir) buccal tablets Instructions for Use (IFU) received on February 12, 2013, and received by DMPP on February 26, 2013.
- Draft SITAVIG (acyclovir) buccal tablets Prescribing Information (PI) received on February 12, 2013, revised by the Review Division throughout the review cycle, and received by DMPP on February 26, 2013.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level. In our review of the PPI and IFU the target reading level is at or below an 8th grade level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APFont to make medical information more accessible for patients with vision loss. We have reformatted the PPI and IFU documents using the Verdana font, size 10.

In our review of the PPI and IFU we have:

- simplified wording and clarified concepts where possible
- ensured that the PPI and IFU are consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the PPI and IFU meet the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The PPI and IFU are acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP on the correspondence.
- Our review of the PPI and IFU is appended to this memorandum. Consult DMPP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the PPI or IFU.

Please let us know if you have any questions.

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/s/

KAREN M DOWDY
03/08/2013

BARBARA A FULLER
03/08/2013

LASHAWN M GRIFFITHS
03/08/2013

M E M O R A N D U M

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

CLINICAL INSPECTION SUMMARY

DATE: December 5, 2012

TO: Sohail Mosaddegh, Pharm.D., Regulatory Health Project Manager
Regina Alivisatos, M.D., Medical Officer
Division of Antiviral Drug Products

FROM: Antoine El-Hage, Ph.D.
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

THROUGH: Susan Leibenhaut, M.D.
Acting Team Leader
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

Susan D. Thompson, M.D.
Acting Branch Chief
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections

NDA: 203-791

APPLICANT: BioAlliance Pharma.

DRUG: Sitavig Buccal Tablet, 50 mg (Lauriad[®])

NME: No

THERAPEUTIC CLASSIFICATION: Standard review
INDICATION: Treatment (b) (4) of recurrent orofacial herpes
CONSULTATION REQUEST DATE: May 11, 2012
DIVISION ACTION GOAL DATE: January 12, 2013
PDUFA DATE: January 12, 2013

I. BACKGROUND:

BioAlliance Pharma submitted this application for the use of Acyclovir Lauriad 50 mg muco-adhesive buccal tablet in the treatment of herpes labialis in immunocompetent patients. One clinical trial Study BA 2005/21/02 was submitted in support of the application.

Investigational Drug

Herpes labialis, also known as cold sores or fever blisters, is the most common recurrent infection caused by HSV-1 with a considerable number of the world's population seropositive for HSV-1. It is unpleasant and induces considerable discomfort to patients. Approximately one third of patients with HSV-1 infection will experience recurrent episodes of herpes labialis.

Current topical treatments, such as creams or ointments, are available to target the labial infection site. Generally, the recommended five daily applications raise issues of patient treatment compliance, and the efficacy was only apparent when the therapy was initiated early. Herpes labialis is a cutaneo-mucosal infection; therefore, the goal of the applicant was to develop a novel and potent drug delivery system allowing local/regional diffusion and high level of concentrations of acyclovir in the mucosa, epidermis, and dermis, i.e. the infection and expression site of the disease. A drug delivery system should result in better treatment compliance. A once daily application within the first hour of the prodromal symptoms combined with an early and sustained release of acyclovir should also make it possible to exert a "continuous antiviral pressure" against HSV-1.

Lauriad technology is a new proprietary delivery system belonging to BioAlliance Pharma that allows a rapid and prolonged release of the active substance in the buccal cavity and at the infection site. The technology represented by the muco-adhesive buccal tablet appears suitable for cutaneous and mucosal delivery of acyclovir with early and sustained release and improved drug diffusion to herpes expression and infection site(s) in the epidermis and dermis.

Compared with conventional local medications, muco-adhesive buccal tablet represents an attractive alternative for local drug delivery for topical medication with poor penetration, increasing the residence time of drugs, improving contact between drug and target site, and maintaining efficacious drug levels at the application/action site for a prolonged time.

The mechanism of tablet adhesion implies: 1) a good contact between tablet and mucosa, obtained in exerting a slight pressure on the tablet at the surface of the mucosa and leading to a good wetting, 2) swelling of the bioadhesive polymer, leading to the interpenetration of the polymer and the mucous chains, and 3) the creation of interfacial bond between the interpenetrated chains and mucous. The applicant claims the technology of bioadhesive tablet was based on the choice of the right bioadhesive polymer.

Using acyclovir as the active ingredient, acyclovir Lauriad was designed for once daily application to the upper gum, and to increase local regional diffusion of acyclovir reaching a local concentration above the IC 50 of HSV-1.

Based on the pathogenesis of the disease, the current treatments available, and clinical data recently reported, an early high dose, short duration antiviral therapy is a logical strategy to treat herpes labialis. This adhesive technology provides an early and extended release of the active ingredient in the oral cavity and in the lips, which reaches adequate concentrations within the first hour after application and also provides a convenient mode of administration allowing a once daily regimen, self-administration, and better compliance.

The applicant submitted this NDA to provide efficacy and safety information on the use of a single dose of acyclovir Lauriad 50 mg muco-adhesive buccal tablet.

Protocol BA 2005/21/02

The objective of this study was to demonstrate the efficacy of a single dose of acyclovir Lauriad 50 mg muco-adhesive buccal tablet versus a single dose of matching placebo on the primary vesicular lesion of labial herpes.

The secondary objectives of this study were to evaluate: 1) the duration of herpetic symptoms, 2) the duration of the episode, and 3) the incidence of and time to labial herpetic recurrence during the nine months following treatment.

This protocol was a randomized, double-blind, single dose multicenter study comparing acyclovir Lauriad 50mg muco-adhesive buccal tablet single dose treatment versus matching placebo (randomization in a 1:1 ratio) in immunocompetent patients suffering from recurrent herpes labialis.

The review division requested inspection of three clinical investigators, including two domestic site inspections and one foreign site for the pivotal protocol Study BA2005/21/02. The consult to OSI states that these sites were chosen because, “The enrollment of large numbers of study subjects, significant primary efficacy results pertinent to decision-making and the first approval of this new NDA and most limited experience with this drug has been at foreign sites”.

II. RESULTS (by protocol/site):

Name of CI, location, and site #	Protocol and # of subjects	Inspection Dates	Final Classification
Mathew G. Davis, M.D. Rochester Clinical Research, Inc. 500 Helendale Rd, Suite 120 Rochester, NY 14609 Site #709	Protocol BA2005/21/02 Number of subjects: 84 Treated:44 vs 46 (at site)	7/16-20/2012	NAI
Maurice Archuleta, M.D. Clinical Research Front Range 6306 West 38 th Ave Wheat Ridge, CO 80033 Site #706	Protocol BA2005/21/02 Number of subjects: 54 Treated:22 vs. 23(at site)	6/18-7/3/2012	VAI
Maciek Kozima, M.D. Nzoz Praktyka Lekarska iga gilas Mirkiewicz Ul.Jugoslowianska 65 d Wroclaw 50-354 Poland Site #705	Protocol BA 2005/21/02 Number of subjects:186 Treated: 54 vs.58(at site)	9/17-20/2012	Pending (Preliminary classification NAI)

Key to Classifications

NAI = No deviations

VAI = Deviation(s) from regulations

OAI = Significant deviations for regulations. Data unreliable.

Pending = Preliminary classification based on e-mail communication from the field; the EIR has not been received from the field and complete review of EIR is pending.

1. **Matthew Davis, M.D.**
Rochester, NY 14609

a. What Was Inspected: At this site, 84 subjects were screened, seven subjects were reported as screen failures, 77 subjects were randomized, and 46 subjects completed the study. Review of the Informed Consent Documents, for all subjects records reviewed, verified that subjects signed informed consent prior to enrollment.

The medical records/source documents for 30 subjects were reviewed in depth, including drug accountability records, vital signs, IRB files, laboratory results, inclusion/exclusion criteria, and use of concomitant medications. Source documents for all 30 subjects were compared to case report forms and data listings, to include primary efficacy endpoint and adverse events.

b. General observations/commentary: At the conclusion of the inspection, no Form FDA 483 was issued to Dr. Davis. The medical records reviewed were found to be in order, organized, and the data verifiable. There were no deaths and no evidence of under-reporting of adverse events. There were no known limitations to the inspection.

c. Assessment of Data Integrity: The data, in support of the clinical efficacy and safety at Dr. Davis’s site are considered reliable and appear acceptable in support of the application.

2. **Maurice Archuleta, M. D.**
Wheat Ridge, CO 80033

a. What Was Inspected: At this site, a total of 54 were screened, 12 subjects were reported as screen failures, 23 subjects were randomized, 15 subjects did not have an outbreak and returned unused drug, two subjects were reported as lost to-follow-up, two subjects withdrew consent, and 23 subjects received treatment and completed the study. Review of the Informed Consent Documents, for all subjects reviewed, verified that subjects signed consent forms prior to enrollment.

The medical records/source data for all subjects enrolled were reviewed including drug accountability records, vital signs, laboratory results, IRB records, prior and current medications, adverse events, and inclusion/exclusion criteria. Source documents were compared to CRFs and data listings for primary efficacy endpoints and adverse events listing.

b. General Observations/Commentary: At the conclusion of the inspection, a one item Form FDA 483 was issued to Dr. Maurice Archuleta because the investigational drug disposition records were not adequate. The drug accountability records at the site were incomplete and lacked accounting for at least 6 kits. In a letter dated July 16, 2012, the clinical investigator provided accounting for most of the kits and agreed that the record keeping was not adequate. In addition to the above observation, the FDA investigator discussed additional inspectional findings with the clinical investigator which were not cited on the FDA 483. The discussion included, but was not limited to the following:

Protocol violations

1. The protocol required a serum pregnancy test to be performed as part of Visit 1. For Subjects 0001 and 0006 a urine pregnancy test was performed instead of a serum pregnancy test.
2. The protocol required that subjects were to be seen within 24 hours after occurrence of symptoms and application of treatment. Subjects 0004, 0006, and 029 had their assessment for Visit 3 out of window i.e. 2 days post outbreak.
3. The protocol prohibits the use of NSAIDs or aspirin during the study. Subject 0006 took prohibited medications (Advil and ibuprofen).
4. Protocol amendment 2 was approved by the IRB on January 15, 2008. The amendment required oral examination to be performed from this date at Visit 1 and if the subject experienced an outbreak, at Visits 3, 4, 5, and Visit 7 if applicable. Our investigation noted that for at least 16 subjects the oral examination (Gingival Index) was not performed at certain visits.

Inadequate drug accountability records

Our investigation found inadequate accounting for all the medication dispensed. Ultimately, Drug kit # 0874 was the only kit not accounted for during the inspection. The clinical investigator stated that Kit #0874 was not dispensed and this was confirmed by a note from the sponsor confirming unopened kit return in Dr. Archuleta's response letter of July 16, 2012. The clinical investigator acknowledged that an error was made in the total count of 45 kits contrary to the total number of 39 kits listed in the monitoring report.

Inadequate record keeping

1. The inspectional findings noted conflicting information for Subject 0005. The document showed that laboratory tests were not received, but were noted as collected on the 24 hour work sheet. Data verification laboratory sheets indicate that Subject 0005 was a no show for Visit 2. Our investigation found that the documents were filled out for Subject 0005 before the subject arrived to the visit. In addition, Subject 9039 Visit 2 CRF was filled out in advance of the visit. When the clinical investigator was asked about the unacceptable practice of prefilled out CRFs, the clinical investigator provided no explanation. Note: the two subjects withdrew consent.
2. For at least 21 subjects' records, the case report forms (CRFs) for Visit 1 documented the duration of episodes of previous herpes outbreaks. However, there was no source documentation to support the recorded information on the CRFs.

During the inspection, the clinical investigator informed the FDA field investigator that he dismissed all of his research staff and no longer performs clinical studies. There were no known limitations to the inspection. There were no deaths and no evidence of under-reporting of adverse events.

Dr. Maurice Archuleta responded to the inspectional findings in a letter dated July 16, 2012. OSI finds his response acceptable/adequate.

c. Assessment of Data Integrity: Despite deficiencies in record availability, adherence to the protocol, and record keeping and drug accountability records, these appear to be isolated instances and it is unlikely that these errors significantly impacted the outcome of the study. Thus, the data generated at Dr. Archuleta's site in support of clinical efficacy and safety are considered acceptable and may be used in support of the pending application.

3. **Maciek Kozina, M.D.**
Wroclaw, Poland

Note: Observations noted below for the site are based on an e-mail communication from the field; the establishment Inspection Report (EIR) has not been received from the field and complete review of the EIR is pending. An inspection summary addendum will be generated if conclusions change upon receipt and review of the EIR.

a. What Was Inspected: At this site, a total 186 subjects were screened, 50 subjects were reported as screen failures, 136 subjects were randomized into the study, and 58 subjects completed the study. Review of the Informed Consent Documents, for all subjects records reviewed, verified that all subjects signed consent forms prior to enrollment.

The medical records/source documents for all subjects were partially reviewed for primary/secondary endpoints and informed consent. The medical records/source documents for 26 subjects were reviewed in depth, including drug accountability records, vital signs, IRB files, laboratory test results, inclusion/exclusion criteria, and use of concomitant medications. Source documents for subjects were compared to case report forms and data listings, to include primary efficacy endpoints and adverse events

b. General Observations/Commentary: At the conclusion of the inspection, no Form FDA 483 was issued to Dr. Kozina. However, our field investigator found that one subject received the prohibited medication “aspirin” throughout the study. The medical records reviewed were found to be in order, organized, and the data verifiable. There were no deaths and no evidence of under-reporting of adverse events. There were no known limitations to the inspection.

c. Assessment of Data Integrity: The data, in support of the clinical efficacy and safety at Dr. Kozina’s site are considered reliable and appear acceptable in support of the pending application.

III. OVERALL ASSESSMENT OF FINDINGS AND GENERAL RECOMMENDATIONS

Three clinical investigator sites were inspected in support of this application. The inspection of Drs. Davis and Kozina revealed no regulatory violations, and the classifications for these inspections are noted above. The classification for the inspection of Dr. Archuleta is Voluntary Action Indicated (VAI). The final classification for Dr. Kozina’s site will be determined upon review of the establishment inspection report (EIR). An inspection summary addendum will be generated if conclusions change upon receipt and review of the EIR. While regulatory violations were identified during the inspection of Dr. Archuleta, the findings are not likely to critically impact primary efficacy and safety analyses; therefore, OSI does not consider the effect of the violations on overall data integrity to be significant. Overall, the data submitted from these three sites are considered acceptable in support of the pending application.

{See appended electronic signature page}

Antoine El-Hage, Ph.D.
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

CONCURRENCE:

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/s/

ANTOINE N EL HAGE
12/05/2012

SUSAN LEIBENHAUT
12/05/2012

SUSAN D THOMPSON
12/05/2012

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management**

Label, Labeling and Packaging Review

Date: November 9, 2012

Reviewer: Morgan Walker, Pharm.D., M.B.A.
Division of Medication Error Prevention and Analysis

Team Leader: Irene Z. Chan, Pharm.D., BCPS
Division of Medication Error Prevention and Analysis

Deputy Director: Kellie Taylor, Pharm.D., MPH
Division of Medication Error Prevention and Analysis

Drug Name and Strength: Sitavig (Acyclovir) Buccal Tablets. 50 mg

Application Type/Number: NDA 203791

Applicant: BioAlliance Pharma

OSE RCM #: 2012-1450

*** This document contains proprietary and confidential information that should not be released to the public.***

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1 INTRODUCTION

This review evaluates the proposed blister label, carton and insert labeling for Sitavig (Acyclovir) Buccal Tablets, 50 mg, for areas of vulnerability that can lead to medication errors.

1.1 PRODUCT INFORMATION

The following product information is provided in the March 12, 2012 submission.

- Proprietary Name: Sitavig
- Active Ingredient: Acyclovir
- Indication of Use: Treatment of recurrent orofacial herpes and (b) (4)
- Route of Administration: Buccal
- Dosage Form: Buccal Tablets
- Strength: 50 mg
- Dose: Apply one 50 mg buccal tablet as a single dose to the upper gum region
- How Supplied: Unit-of-use blisters. Each blister contains 1 tablet. Two blisters are packaged in one carton.
- Storage: Store at 20°C to 25°C (68°F to 77°F), excursions permitted to 15°C to 30°C (59°F to 86°F)

2 METHODS AND MATERIALS REVIEWED

DMEPA searched the FDA AERS database for Oravig (Miconazole) medication error reports since Oravig utilizes the same dosage form as Sitavig and is administered in the same manner. We reviewed medication errors associated with Oravig that could be applicable to our review of Sitavig. We also reviewed the Sitavig labels and package insert labeling submitted by the Applicant.

2.1 SELECTION OF MEDICATION ERROR CASES

We searched the FDA Adverse Event Reporting System (FAERS) database using the strategy listed in Table 1.

Table 1: AERS Search Strategy	
Date	October 4, 2012
Drug Names	Oravig (trade name)
MedDRA Search Strategy	Medication Errors (HLGT) Product Packaging Issues HLT Product Label Issues HLT Product Quality Issues (NEC) HLT

The AERS database search identified three reports. After individual review, all three reports were not included in the final analysis for the following reasons:

- Duplicate cases
- Adverse medication event unrelated to medication error

2.2 LABELS AND LABELING

Using the principles of human factors and Failure Mode and Effects Analysis,¹ along with post marketing medication error data, the Division of Medication Error Prevention and Analysis (DMEPA) evaluated the following:

- Blister Label submitted March 12, 2012 (Appendix B)
- Carton Labeling submitted March 12, 2012 (Appendix C)
- Insert Labeling submitted March 12, 2012

2.3 PREVIOUSLY COMPLETED REVIEWS

DMEPA previously completed a proprietary name review in OSE Review # 2011-3286, dated January 30, 2011, for Sitavig (Acyclovir) Buccal Tablets, 50 mg (IND 77812), and # 2012-1449, dated September 20, 2012, for Sitavig (Acyclovir) Buccal Tablets, 50 mg (NDA 0203791). The proposed proprietary name, Sitavig, was found acceptable in both reviews.

3 INTEGRATED SUMMARY OF MEDICATION ERROR RISK ASSESSMENT

A review of the insert labeling did not find any areas of vulnerability from a medication error perspective. However, a review of the blister label, carton labeling, and blister packaging identified the following areas of vulnerability:

- Blister Label and Carton Labeling
 - The established name is inadequately prominent
 - The active ingredient and the dosage form statements are not presented in the same font
 - The proprietary name is in all uppercase letters instead of title case, which decreases the readability of the proprietary name
 - The quantity statement “2 x 1 tablets” is confusing because it is not clear whether there are one or two tablets in the blister and how many blisters are in the carton
 - There is no barcode on the label
 - There is no manufacturer or statement of the place of business on the label

¹ Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

- Blister Label
 - The statement “pill-off” is misspelled
- Carton Labeling
 - The usual dosage statement only refers to the patient package insert instead of the entire insert labeling. There may be information in the insert labeling that is not in the patient package insert that health care professionals may need to refer to for dosage and administration information
 - There are no storage requirements
- Blister Packaging
 - There are two pockets on the discarded portion of the blister packaging that do not contain anything in them. This may be misleading to patients, as they may think that there is actual drug in them

DMEPA sent the Applicant an information request (IR) on October 11, 2012 asking for the following information:

“Please clarify the packaging for Sitavig. Does it contain 1 tablet per blister card and 2 blisters per carton? Also, please provide rationale for the two empty blisters on the blister card that appear to get discarded.”

The Applicant provided the following response in an email dated October 22, 2012:

“We confirm that the carton contains 2 blisters and each blister contains 1 tablet of Sitavig. The packaging of the product required a child resistant (b) (4) blister. The tablet was placed on one side of the blister card with the precut zone in order to propose a peel off blister. On each blister, 2 (b) (4) are required to be able to stack 2 blisters per carton.”

DMEPA considered the Applicant’s rationale for the packaging presentation, and we are still concerned that the packaging presentation with the two empty blisters that are acting as (b) (4) may cause confusion for patients. However, we recognize that at this advanced stage of product development, it may not be feasible for the Applicant to re-design the packaging. Therefore, we recommend improved directions for patients on the blister label.

We provide recommendations in section 4.1 below regarding the label, labeling and packaging.

4 CONCLUSIONS AND RECOMMENDATIONS

DMEPA concludes that the proposed insert labeling is acceptable from a medication error perspective. However, we identified areas of confusion on the proposed blister label, carton labeling, and blister packaging. We provide recommendations below, and we recommend they be implemented prior to approval of the NDA.

4.1 COMMENTS TO THE APPLICANT

A. General Comment

The current presentation of the net quantity for the blister and the carton as well as the packaging for the blister is confusing. The net quantity statement does not provide a clear presentation of how many tablets are actually in the blister or the carton. In addition, having two empty pockets is misleading and may cause patients to think there is something wrong with their package if they try to open and see nothing in them. This may result in patients throwing the packaging away and pose a risk of occurrences of dose omission medication errors. We recommend you consider re-designing your blister packaging to minimize this risk of confusion; however, we recognize that at this advanced stage of product development, it may not be feasible for you to re-design the packaging. Therefore, if you are unable to revise your blister packaging, we recommend improved directions for patients on the blister label. We provide recommendations in section C below.

B. Blister Label and Carton Labeling

- Ensure that the established name is at least half the size of the proprietary name. Ensure the established name has prominence commensurate with the proprietary name taking into account all pertinent factors including typography, layout, contrast and other printing features per 21 CFR 201.10(g)(2).
- Revise the proprietary name from all uppercase (TRADENAME) to title case (Tradename) for improved readability.
- Ensure that there is a barcode on the label per 21 CFR 201.25.
- Ensure that the manufacturer information and statement of the place of business are included per 21 CFR 201.1(h)(1).

C. Blister Label

- Ensure that the print on the back of the blisters is not printed directly on the foil backing. Black print directly on foil will not provide sufficient contrast for readability. Additionally, the dimpling on the foil may obscure the print.
- Revise the net quantity statement to read “1 tablet”.
- Revise the “pill-off” statement to read “peel-off”.
- Given the small size of the blister label, ensure the directions for patients on how to access the single tablet are printed large enough to allow for improved readability.
- In order to avoid patient confusion regarding the two empty pocket (b) (4) on the blister packaging, we recommend including a step (e.g. between steps 1 and 2) that shows that these should be discarded and do not contain medicine.

D. Carton Labeling

- Revise the net quantity statement to say “2 blisters, each blister contains one 50 mg buccal tablet”. Additionally, on the principal display panel, move the net quantity statement to the upper right corner away from the statement of strength.
- Place the dosage form statement (Buccal Tablets) immediately next to the active ingredient statement (Acyclovir). Additionally, ensure the same font is utilized for both the active ingredient and the dosage form.
- Revise the usual dosage statement to the following, “See package insert for dosing and administration information.”
- Ensure that the storage requirements are present on the back panel.

E. Blister Packaging

- Consider revising the packaging such that there are no empty pockets on the blister. This may help with confusion so that patients will not think that they have not received any medication in their blister by peeling or breaking the wrong side.

If you have further questions or need clarifications, please contact Danyal Chaudhry, project manager, at 301-796-3813.

APPENDICES

APPENDIX A. DATABASE DESCRIPTIONS

Adverse Event Reporting System (AERS)

The Adverse Event Reporting System (AERS) is a computerized information database designed to support the FDA's post-marketing safety surveillance program for drug and therapeutic biologic products. The FDA uses AERS to monitor adverse events and medication errors that might occur with these marketed products. The structure of AERS complies with the international safety reporting guidance ([ICH E2B](#)) issued by the International Conference on Harmonisation. Adverse events in AERS are coded to terms in the Medical Dictionary for Regulatory Activities terminology (MedDRA).

AERS data do have limitations. First, there is no certainty that the reported event was actually due to the product. FDA does not require that a causal relationship between a product and event be proven, and reports do not always contain enough detail to properly evaluate an event. Further, FDA does not receive all adverse event reports that occur with a product. Many factors can influence whether or not an event will be reported, such as the time a product has been marketed and publicity about an event. Therefore, AERS cannot be used to calculate the incidence of an adverse event in the U.S. population.

2 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

MORGAN A WALKER
11/15/2012

IRENE Z CHAN
11/15/2012

KELLIE A TAYLOR
11/20/2012

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy Initiatives
Division of Medical Policy Programs**

REVIEW DEFERRAL MEMORANDUM

Date: October 11, 2012

To: Debra B. Birnkrant, MD
Director
Division of Antiviral Products (DAVP)

Through: LaShawn Griffiths, MSHS-PH, BSN, RN
Associate Director for Patient Labeling
Division of Medical Policy Programs (DMPP)

Barbara Fuller, RN, MSN, CWOCN
Team Leader, Patient Labeling
Division of Medical Policy Programs (DMPP)

From: Karen Dowdy, RN, BSN
Patient Labeling Reviewer
Division of Medical Policy Programs (DMPP)

Subject: Review Deferred: Patient Package Insert (PPI) and
Instructions for Use (IFU)

Drug Name (established name): SITAVIG (acyclovir)

Dosage Form and Route: buccal tablet

Application Type/Number: NDA 203-791

Applicant: BioAlliance Pharma

1 INTRODUCTION

On March 12, 2012, BioAlliance Pharma submitted for the Agency's review New Drug Application (NDA) 203-791 for SITAVIG (acyclovir) buccal tablets with the proposed indication for treatment of recurrent orofacial herpes and [REDACTED] (b) (4). On March 14, 2012, the Division of Antiviral Products (DAVP) requested that the Division of Medical Policy Programs (DMPP) review the Applicant's proposed Patient Package Insert (PPI) and Instructions for Use (IFU) for SITAVIG (acyclovir) buccal tablets.

This memorandum documents the DMPP review deferral of the Applicant's proposed Patient Package Insert (PPI) and Instructions for Use (IFU) for SITAVIG (acyclovir) buccal tablets.

2 CONCLUSIONS

Due to outstanding clinical and statistical deficiencies, DAVP plans to issue a Complete Response (CR) letter. Therefore, DMPP defers comment on the Applicant's patient labeling at this time. A final review will be performed after the Applicant submits a complete response to the Complete Response (CR) letter. Please send us a new consult request at such time.

Please notify us if you have any questions.

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/s/

KAREN M DOWDY
10/11/2012

BARBARA A FULLER
10/11/2012

LASHAWN M GRIFFITHS
10/11/2012

**FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion
Division of Professional Drug Promotion
Division of Consumer Drug Promotion**

*****Pre-decisional Agency Information*****

Memorandum

Date: October 10, 2012

To: Sohail Mosaddegh, PharmD, Regulatory Project Manager
Division of Antiviral Products (DAVP)

From: Jessica Fox, PharmD, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: NDA 203791
SITAVIG (acyclovir) Buccal Tablet

OPDP acknowledges receipt of DAVP's March, 14, 2012, consult request for the review of proposed product labeling for SITAVIG (acyclovir) Buccal Tablet, NDA 203791. OPDP notes an email correspondence from DAVP dated October 10, 2012, indicating that this application will be receiving a complete response. Therefore, OPDP will provide comments on proposed substantially complete labeling for this application during a subsequent review cycle. OPDP requests that DAVP submits a new consult request during the subsequent review cycle.

Thank you for the opportunity to provide comments on the proposed product labeling. If you have any questions, please contact Jessica Fox at (301) 796-5329 or at Jessica.Fox@fda.hhs.gov.

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/s/

JESSICA M FOX
10/10/2012

REGULATORY PROJECT MANAGER PLR FORMAT LABELING REVIEW

To be completed for all new NDAs, BLAs, Efficacy Supplements, and PLR Conversion Supplements

Application: NDA 203791

Name of Drug: SITAVIG (acyclovir) buccal tablet, 50mg

Applicant: BioAlliance Pharma

Labeling Reviewed

Submission Date: March 12, 2012 (SPL converted to PDF)

Receipt Date: March 12, 2012

Background and Summary Description

New NDA 203791 (SITAVIG), is a 505(b)2 that was submitted on March 12, 2012. This NDA relies on Zovirax Cream 5%, Xerese, and the published literature for pharmacokinetic (PK) and non-clinical data. A clinical study done by the applicant and published literature is used for safety/efficacy. Sitavig is a new dosage form (slow release buccal tablet) of acyclovir for the treatment of recurrent herpes labialis (cold sores) or herpes simplex virus (HSV).

Review

The submitted labeling was reviewed in accordance with the labeling requirements listed in the “Selected Requirements for Prescribing Information (SRPI)” section of this review. Labeling deficiencies are identified in this section with an “X” in the checkbox next to the labeling requirement.

In addition, the following labeling issues were identified:

HIGHLIGHTS OF PRESCRIBING INFORMATION

1. The date of the initial U.S. approval should be bolded (eg. **1982**).
2. You have requested a pediatric deferral for pediatric subjects greater than (b) (4) years of age. Therefore, you need to update the indication sections of the labeling to adequately reflect the patient population for which you are seeking an indication.
3. Reformat the WARNINGS AND PRECAUTIONS section to ensure that the title and at least one line of text remain together.

4. Under USE IN SPECIFIC POPULATIONS, remove the Pregnancy and Pediatric Use information.

FULL PRSCRIBING INFORMATION: CONTENTS*

5. Section headings must be in bold type and should appear in upper-case letters. For example, replace “**Indications and Usage**” with “**INDICATIONS AND USAGE**”.
6. Change the statement at the end of the Table of Contents to “*Sections or subsections omitted from the Full Prescribing Information are not listed”.
7. Although the subsection headings were indented, consider using the formatting provided below

- 1 INDICATIONS AND USAGE**
- 2 DOSAGE AND ADMINISTRATION**
 - 2.1 Basic Dosing Information
 - 2.2 Administration Instructions
- 3 DOSAGE FORMS AND STRENGTHS**
- 4 CONTRAINDICATIONS**
- 5 WARNINGS AND PRECAUTIONS**
 - 5.1 Hypersensitivity

FULL PRESCRIBING INFORMATION

8. Use consistent spacing when separating the headings from the text or subsection. Please see the spacing used for sections 1, 10, and 11 versus other sections.
9. Section 17’s heading should be followed by the following statement:
See FDA-approved patient labeling (Patient Information).
10. If the package insert and patient package insert are separate documents, the manufacturer information must appear at the end of the PI.

PATIENT LABELING:

11. Change the title of this section from “FDA-Approved Patient Labeling” to “Patient Information”.

Conclusions/Recommendations

All labeling deficiencies identified in the SRPI section of this review and identified above will be conveyed to the applicant in the 74-day letter. The applicant will be asked to resubmit labeling that addresses all identified labeling deficiencies by June 08, 2012. The resubmitted labeling will be used for further labeling discussions.

Regulatory Project Manager

Date

Chief, Project Management Staff

Date

SELECTED REQUIREMENTS FOR PRESCRIBING INFORMATION (SRPI):

- **Revision Date**

- A placeholder for the revision date, presented as “Revised: MM/YYYY or Month Year,” must appear at the end of HL. The revision date is the month/year of application or supplement approval.

- **Contents: Table of Contents (TOC)**

- All section headings must be in **bold** type, and subsection headings must be indented and not bolded.

- **Patient Counseling Information**

- Must reference any FDA-approved patient labeling, including the type of patient labeling. The statement “See FDA-approved patient labeling (insert type of patient labeling).” should appear at the beginning of Section 17 for prominence. For example:

- “See FDA-approved patient labeling (Patient Information)”

10 Page(s) 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/

SOHAIL MOSADDEGH
05/16/2012

KAREN D WINESTOCK
05/17/2012

REGULATORY PROJECT MANAGER PLR FORMAT LABELING REVIEW

To be completed for all new NDAs, BLAs, Efficacy Supplements, and PLR Conversion Supplements

Application: NDA 203791

Name of Drug: SITAVIG (acyclovir) buccal tablet, 50mg

Applicant: BioAlliance Pharma

Labeling Reviewed

Submission Date: March 12, 2012 (SPL converted to PDF)

Receipt Date: March 12, 2012

Background and Summary Description

New NDA 203791 (SITAVIG), is a 505(b)2 that was submitted on March 12, 2012. This NDA relies on Zovirax Cream 5%, Xerese, and the published literature for pharmacokinetic (PK) and non-clinical data. A clinical study done by the applicant and published literature is used for safety/efficacy. Sitavig is a new dosage form (slow release buccal tablet) of acyclovir for the treatment of recurrent herpes labialis (cold sores) or herpes simplex virus (HSV).

Review

The submitted labeling was reviewed in accordance with the labeling requirements listed in the “Selected Requirements for Prescribing Information (SRPI)” section of this review. Labeling deficiencies are identified in this section with an “X” in the checkbox next to the labeling requirement.

In addition, the following labeling issues were identified:

HIGHLIGHTS OF PRESCRIBING INFORMATION

1. The date of the initial U.S. approval should be bolded (eg. **1982**).
2. You have requested a pediatric deferral for pediatric subjects greater than (b)₍₄₎ years of age. Therefore, you need to update the indication sections of the labeling to adequately reflect the patient population for which you are seeking an indication.
3. Reformat the WARNINGS AND PRECAUTIONS section to ensure that the title and at

least one line of text remain together.

4. Under USE IN SPECIFIC POPULATIONS, remove the Pregnancy and Pediatric Use information.

FULL PRSCRIBING INFORMATION: CONTENTS*

5. Section headings must be in bold type and should appear in upper-case letters. For example, replace “**Indications and Usage**” with “**INDICATIONS AND USAGE**”.
6. Change the statement at the end of the Table of Contents to “*Sections or subsections omitted from the Full Prescribing Information are not listed”.
7. Although the subsection headings were indented, consider using the formatting provided below

- 1 INDICATIONS AND USAGE**
- 2 DOSAGE AND ADMINISTRATION**
 - 2.1 Basic Dosing Information
 - 2.2 Administration Instructions
- 3 DOSAGE FORMS AND STRENGTHS**
- 4 CONTRAINDICATIONS**
- 5 WARNINGS AND PRECAUTIONS**
 - 5.1 Hypersensitivity

FULL PRESCRIBING INFORMATION

8. Use consistent spacing when separating the headings from the text or subsection. Please see the spacing used for sections 1, 10, and 11 versus other sections.
9. Section 17’s heading should be followed by the following statement:
See FDA-approved patient labeling (Patient Information).
10. If the package insert and patient package insert are separate documents, the manufacturer information must appear at the end of the PI.

PATIENT LABELING:

11. Change the title of this section from “FDA-Approved Patient Labeling” to “Patient Information”.

Conclusions/Recommendations

All labeling deficiencies identified in the SRPI section of this review and identified above will be conveyed to the applicant in the 74-day letter. The applicant will be asked to resubmit labeling that addresses all identified labeling deficiencies by June 08, 2012. The resubmitted labeling will be used for further labeling discussions.

Regulatory Project Manager

Date

Chief, Project Management Staff

Date

SELECTED REQUIREMENTS FOR PRESCRIBING INFORMATION (SRPI):

- **Revision Date**

- A placeholder for the revision date, presented as “Revised: MM/YYYY or Month Year,” must appear at the end of HL. The revision date is the month/year of application or supplement approval.

- **Contents: Table of Contents (TOC)**

- All section headings must be in **bold** type, and subsection headings must be indented and not bolded.

- **Patient Counseling Information**

- Must reference any FDA-approved patient labeling, including the type of patient labeling. The statement “See FDA-approved patient labeling (insert type of patient labeling).” should appear at the beginning of Section 17 for prominence. For example:
 - “See FDA-approved patient labeling (Patient Information)”

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

/s/

SOHAIL MOSADDEGH
05/16/2012

KAREN D WINESTOCK
05/16/2012

RPM FILING REVIEW

(Including Memo of Filing Meeting)

To be completed for all new NDAs, BLAs, and Efficacy Supplements [except SE8 (labeling change with clinical data) and SE9 (manufacturing change with clinical data)]

Application Information		
NDA # 203791 BLA#	NDA Supplement #:S- BLA Supplement #	Efficacy Supplement Type SE-
Proprietary Name: SITAVIG Established/Proper Name: acyclovir Dosage Form: Buccal Tablet Strengths: 50 mg		
Applicant: BioAlliance Pharma Agent for Applicant (if applicable): Jim Carter, US agent		
Date of Application: March 12, 2012 Date of Receipt: March 12, 2012 Date clock started after UN:		
PDUFA Goal Date: January 12, 2013	Action Goal Date (if different): January 11, 2013	
Filing Date: 05/11/12	Date of Filing Meeting: 04/23/12	
Chemical Classification: (1,2,3 etc.) (original NDAs only) type-3		
Proposed indication(s): SITAVIG is indicated in adults (b) (4) for the treatment of recurrent orofacial herpes simplex virus infections in immunocompetent patients (b) (4)		
Type of Original NDA: AND (if applicable)	<input type="checkbox"/> 505(b)(1)	<input checked="" type="checkbox"/> 505(b)(2)
Type of NDA Supplement:	<input type="checkbox"/> 505(b)(1)	<input type="checkbox"/> 505(b)(2)
<i>If 505(b)(2): Draft the "505(b)(2) Assessment" form found at: http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499 and refer to Appendix A for further information.</i>		
Review Classification:	<input checked="" type="checkbox"/> Standard	
<i>If the application includes a complete response to pediatric WR, review classification is Priority.</i>	<input type="checkbox"/> Priority	
<i>If a tropical disease priority review voucher was submitted, review classification is Priority.</i>	<input type="checkbox"/> Tropical Disease Priority Review Voucher submitted	
Resubmission after withdrawal? <input type="checkbox"/>	Resubmission after refuse to file? <input type="checkbox"/>	
Part 3 Combination Product? <input type="checkbox"/> <i>If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults</i>	<input type="checkbox"/> Convenience kit/Co-package <input type="checkbox"/> Pre-filled drug delivery device/system <input type="checkbox"/> Pre-filled biologic delivery device/system <input type="checkbox"/> Device coated/impregnated/combined with drug <input type="checkbox"/> Device coated/impregnated/combined with biologic <input type="checkbox"/> Drug/Biologic <input type="checkbox"/> Separate products requiring cross-labeling <input type="checkbox"/> Possible combination based on cross-labeling of separate products <input type="checkbox"/> Other (drug/device/biological product)	

<input type="checkbox"/> Fast Track <input type="checkbox"/> Rolling Review <input type="checkbox"/> Orphan Designation <input type="checkbox"/> Rx-to-OTC switch, Full <input type="checkbox"/> Rx-to-OTC switch, Partial <input type="checkbox"/> Direct-to-OTC Other:	<input type="checkbox"/> PMC response <input type="checkbox"/> PMR response: <input type="checkbox"/> FDAAA [505(o)] <input type="checkbox"/> PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] <input type="checkbox"/> Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) <input type="checkbox"/> Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)			
Collaborative Review Division (<i>if OTC product</i>):				
List referenced IND Number(s): IND 77812, DMF (b) (4)				
Goal Dates/Product Names/Classification Properties	YES	NO	NA	Comment
PDUFA and Action Goal dates correct in tracking system? <i>If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.</i>	Yes			
Are the proprietary, established/proper, and applicant names correct in tracking system? <i>If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into tracking system.</i>		No		Product name is listed as acyclovir Buccal tablet
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug)? <i>For NDAs/NDA supplements, check the Application and Supplement Notification Checklists for a list of all classifications/properties at: http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163970.htm</i> <i>If no, ask the document room staff to make the appropriate entries.</i>	Yes			standard
Application Integrity Policy	YES	NO	NA	Comment
Is the application affected by the Application Integrity Policy (AIP)? <i>Check the AIP list at: http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</i> <i>If yes, explain in comment column.</i>		No		
<i>If affected by AIP, has OC/DMPQ been notified of the submission? If yes, date notified:</i>				
User Fees	YES	NO	NA	Comment
Is Form 3397 (User Fee Cover Sheet) included with authorized signature?	Yes			

<p><u>User Fee Status</u></p> <p><i>If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send Unacceptable for Filing (UN) letter and contact user fee staff.</i></p>	<p>Payment for this application:</p> <p><input checked="" type="checkbox"/> Paid <input type="checkbox"/> Exempt (orphan, government) <input type="checkbox"/> Waived (e.g., small business, public health) <input type="checkbox"/> Not required</p>																			
<p><i>If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.</i></p>	<p>Payment of other user fees:</p> <p><input checked="" type="checkbox"/> Not in arrears <input type="checkbox"/> In arrears</p>																			
<p>505(b)(2) (NDAs/NDA Efficacy Supplements only)</p>	<p>YES</p>	<p>NO</p>	<p>NA</p>	<p>Comment</p>																
<p>Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?</p>		<p>No</p>																		
<p>Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? [see 21 CFR 314.54(b)(1)].</p>		<p>No</p>																		
<p>Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug [see 21 CFR 314.54(b)(2)]?</p> <p><i>If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the (b)(2) review staff in the Immediate Office of New Drugs</i></p>		<p>No</p>																		
<p>Is there unexpired exclusivity on the active moiety (e.g., 5-year, 3-year, orphan or pediatric exclusivity)? Check the <i>Electronic Orange Book</i> at: http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm</p> <p>If yes, please list below:</p> <table border="1" data-bbox="203 1446 1349 1587"> <thead> <tr> <th>Application No.</th> <th>Drug Name</th> <th>Exclusivity Code</th> <th>Exclusivity Expiration</th> </tr> </thead> <tbody> <tr> <td>NDA 22436</td> <td>Xerese</td> <td>NC</td> <td>7/31/12</td> </tr> <tr> <td></td> <td></td> <td></td> <td></td> </tr> <tr> <td></td> <td></td> <td></td> <td></td> </tr> </tbody> </table>	Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration	NDA 22436	Xerese	NC	7/31/12									<p>Yes</p>			
Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration																	
NDA 22436	Xerese	NC	7/31/12																	
<p><i>If there is unexpired, 5-year exclusivity remaining on the active moiety for the proposed drug product, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 108(b)(2). Unexpired, 3-year exclusivity will only block the approval, not the submission of a 505(b)(2) application.</i></p>																				
<p>Exclusivity</p>	<p>YES</p>	<p>NO</p>	<p>NA</p>	<p>Comment</p>																
<p>Does another product (same active moiety) have orphan exclusivity for the same indication? Check the <i>Orphan Drug Designations and Approvals</i> list at: http://www.accessdata.fda.gov/scripts/opdlisting/ood/index.cfm</p>		<p>No</p>																		

<p>If another product has orphan exclusivity, is the product considered to be the same product according to the orphan drug definition of sameness [see 21 CFR 316.3(b)(13)]?</p> <p><i>If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy</i></p>				
<p>Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? (<i>NDAs/NDA efficacy supplements only</i>)</p> <p>If yes, # years requested: 3</p> <p><i>Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i></p>	Yes			
<p>Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use (<i>NDAs only</i>)?</p>		No		
<p>If yes, did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)?</p> <p><i>If yes, contact Mary Ann Holovac, Director of Drug Information, OGD/DLPS/LRB.</i></p>				

Format and Content				
<p><i>Do not check mixed submission if the only electronic component is the content of labeling (COL).</i></p>	<input type="checkbox"/> All paper (except for COL) <input checked="" type="checkbox"/> All electronic <input type="checkbox"/> Mixed (paper/electronic) <input checked="" type="checkbox"/> CTD <input type="checkbox"/> Non-CTD <input type="checkbox"/> Mixed (CTD/non-CTD)			
<p>If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?</p>				
Overall Format/Content	YES	NO	NA	Comment
<p>If electronic submission, does it follow the eCTD guidance?¹ If not, explain (e.g., waiver granted).</p>	Yes			
<p>Index: Does the submission contain an accurate comprehensive index?</p>	Yes			
<p>Is the submission complete as required under 21 CFR 314.50 (<i>NDAs/NDA efficacy supplements</i>) or under 21 CFR 601.2 (<i>BLAs/BLA efficacy supplements</i>) including:</p>		No		Subgroup analysis by gender, age and

1

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf>

<input checked="" type="checkbox"/> legible <input checked="" type="checkbox"/> English (or translated into English) <input checked="" type="checkbox"/> pagination <input checked="" type="checkbox"/> navigable hyperlinks (electronic submissions only)				race can not be located. Info found (05/04/12).
If no, explain.				
BLAs only: Companion application received if a shared or divided manufacturing arrangement?				
If yes, BLA #				
Forms and Certifications				
<i>Electronic forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise, paper forms and certifications with hand-written signatures must be included. Forms include: user fee cover sheet (3397), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674); Certifications include: debarment certification, patent certification(s), field copy certification, and pediatric certification.</i>				
Application Form	YES	NO	NA	Comment
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)?	Yes			
<i>If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].</i>				
Are all establishments and their registration numbers listed on the form/attached to the form?	Yes			
Patent Information (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?	Yes			
Financial Disclosure	YES	NO	NA	Comment
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)?	Yes			
<i>Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].</i>				
<i>Note: Financial disclosure is required for bioequivalence studies that are the basis for approval.</i>				
Clinical Trials Database	YES	NO	NA	Comment
Is form FDA 3674 included with authorized signature?		Yes		
<i>If yes, ensure that the application is also coded with the supporting document category, "Form 3674."</i>				
<i>If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant</i>				
Debarment Certification	YES	NO	NA	Comment
Is a correctly worded Debarment Certification included with authorized signature?	Yes			

<p><i>Certification is not required for supplements if submitted in the original application; If foreign applicant, both the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].</i></p> <p><i>Note: Debarment Certification should use wording in FDCA Section 306(k)(1) i.e., “[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.” Applicant may not use wording such as, “To the best of my knowledge...”</i></p>				
Field Copy Certification (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
<p>For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included?</p> <p><i>Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)</i></p> <p><i>If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.</i></p>			NA	

Controlled Substance/Product with Abuse Potential	YES	NO	NA	Comment
<p><u>For NMEs:</u> Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)?</p> <p><i>If yes, date consult sent to the Controlled Substance Staff:</i></p> <p><u>For non-NMEs:</u> <i>Date of consult sent to Controlled Substance Staff:</i></p>			NA	

Pediatrics	YES	NO	NA	Comment
<p><u>PREA</u></p> <p>Does the application trigger PREA?</p> <p><i>If yes, notify PeRC RPM (PeRC meeting is required)²</i></p> <p><i>Note: NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.</i></p>	Yes			PERC scheduled

² <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027829.htm>

If the application triggers PREA , are the required pediatric assessment studies or a full waiver of pediatric studies included?		No		
If studies or full waiver not included , is a request for full waiver of pediatric studies OR a request for partial waiver and/or deferral with a pediatric plan included? <i>If no, request in 74-day letter</i>				
If a request for full waiver/partial waiver/deferral is included , does the application contain the certification(s) required by FDCA Section 505B(a)(3) and (4)? <i>If no, request in 74-day letter</i>	No			Pediatric plan not submitted but has been requested
BPCA (NDAs/NDA efficacy supplements only): Is this submission a complete response to a pediatric Written Request? <i>If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)³</i>	No			
Proprietary Name	YES	NO	NA	Comment
Is a proposed proprietary name submitted? <i>If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."</i>		No		OSE will recommend timeline for "resubmission"
REMS	YES	NO	NA	Comment
Is a REMS submitted? <i>If yes, send consult to OSE/DRISK and notify OC/OSI/DSC/PMSB via the DCRMSRMP mailbox</i>		No		
Prescription Labeling	<input type="checkbox"/> Not applicable			
Check all types of labeling submitted.	<input checked="" type="checkbox"/> Package Insert (PI) <input checked="" type="checkbox"/> Patient Package Insert (PPI) <input checked="" type="checkbox"/> Instructions for Use (IFU) <input type="checkbox"/> Medication Guide (MedGuide) <input checked="" type="checkbox"/> Carton labels <input checked="" type="checkbox"/> Immediate container labels <input type="checkbox"/> Diluent <input type="checkbox"/> Other (specify)			
	YES	NO	NA	Comment
Is Electronic Content of Labeling (COL) submitted in SPL format? <i>If no, request applicant to submit SPL before the filing date.</i>	Yes			
Is the PI submitted in PLR format? ⁴	Yes			Under RPM format review

³ <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027837.htm>

If PI not submitted in PLR format , was a waiver or deferral requested before the application was received or in the submission? If requested before application was submitted , what is the status of the request? <i>If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.</i>				
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to OPDP?	Yes			
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (send WORD version if available)	Yes			
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office (OBP or ONDQA)?	Yes			
OTC Labeling	<input type="checkbox"/> Not Applicable			
Check all types of labeling submitted.	<input type="checkbox"/> Outer carton label <input type="checkbox"/> Immediate container label <input type="checkbox"/> Blister card <input type="checkbox"/> Blister backing label <input type="checkbox"/> Consumer Information Leaflet (CIL) <input type="checkbox"/> Physician sample <input type="checkbox"/> Consumer sample <input type="checkbox"/> Other (specify)			
	YES	NO	NA	Comment
Is electronic content of labeling (COL) submitted? <i>If no, request in 74-day letter.</i>				
Are annotated specifications submitted for all stock keeping units (SKUs)? <i>If no, request in 74-day letter.</i>				
If representative labeling is submitted, are all represented SKUs defined? <i>If no, request in 74-day letter.</i>				
All labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEPA?				
Other Consults	YES	NO	NA	Comment
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team) <i>If yes, specify consult(s) and date(s) sent:</i>	Yes			DSI
Meeting Minutes/SPAs	YES	NO	NA	Comment
End-of Phase 2 meeting(s)?		No		

4

<http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/StudyEndpointsandLabelingDevelopmentTeam/ucm025576.htm>

Date(s):				
<i>If yes, distribute minutes before filing meeting</i>				
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? Date(s): 04/29/2010, 08/11/2010, CMC pre-NDA 06/09/2011	Yes			Copies made
<i>If yes, distribute minutes before filing meeting</i>				
Any Special Protocol Assessments (SPAs)? Date(s):		No		
<i>If yes, distribute letter and/or relevant minutes before filing meeting</i>				

ATTACHMENT

MEMO OF FILING MEETING

DATE: April 23, 2012 (Updated May 11, 2012)

BLA/NDA/Supp #: 203791

PROPRIETARY NAME: SITAVIG

ESTABLISHED/PROPER NAME: acyclovir

DOSAGE FORM/STRENGTH: Buccal tablets 50 mg

APPLICANT: BioAlliance Pharma

PROPOSED INDICATION(S): SITAVIG is indicated in adults (b) (4) for the treatment of recurrent orofacial herpes simplex virus infections in immunocompetent patients. (b) (4)

BACKGROUND: New 505(b)2 NDA (203791, Sitavig) submitted 03/12/12 that relies on Zovirax, Xerese, and acyclovir for PK and non-clinical data. A clinical study done by the sponsor and published literature is used for safety/efficacy. Sitavig is a new dosage form of acyclovir (slow release buccal tablet) for the treatment of HSV.

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Sohail Mosaddegh	Y
	CPMS/TL:	Karen Winestock	Y

Cross-Discipline Team Leader (CDTL)	Kimberly Struble		Y
Clinical	Reviewer:	Regina Alivastos	Y
	TL:	Kim Struble	Y
Social Scientist Review (<i>for OTC products</i>)	Reviewer:		
	TL:		
OTC Labeling Review (<i>for OTC products</i>)	Reviewer:		
	TL:		
Clinical Microbiology (<i>for antimicrobial products</i>)	Reviewer:	Lalji Mishra	N
	TL:	Julian O'Rear	Y
Clinical Pharmacology	Reviewer:	Leslie Chinn	Y
	TL:	Shirley Seo	Y
Biostatistics	Reviewer:	Wen Zeng	Y
	TL:	Greg Soon	N
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Janice Lansita	Y
	TL:	Hanan Ghantous	N
Biopharmaceutics	Reviewer:	Tapash Ghosh	Y
	TL:		
Product Quality (CMC), Drug Product	Reviewer:	Shirkant Pagay	Y
	TL:	Stephen Miller	
Product Quality (CMC), Drug Substance	Reviewer:	Fuqiang Liu	Y
	TL:	Stephen Miller	Y
Quality Microbiology (<i>for sterile products</i>)	Reviewer:		
	TL:		
CMC Labeling Review	Reviewer:		
	TL:		

Facility Review/Inspection	Reviewer:		
	TL:		
OSE/DMEPA	Reviewer:	TBD	
	TL:		
OSE/DRISK (REMS)	Reviewer:		
	TL:		
OC/OSI/DSC/PMSB (REMS)	Reviewer:		
	TL:		
OMP/ Marketing and Advertising Consumer Reviewer	Reviewer:	Oluwaseun Asante	N
	TL:		
OMP/ Marketing and Advertising Professional Reviewer	Reviewer:	Jessica Fox	N
	TL:		
CDER/OSE/DRISK Patient labeling	Reviewer:	Latonia Ford	N
	TL:	Barbara Fuller	Y
Other attendees			

FILING MEETING DISCUSSION:

GENERAL	
<ul style="list-style-type: none"> 505(b)(2) filing issues? <p>If yes, list issues:</p>	<input type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
<ul style="list-style-type: none"> Per reviewers, are all parts in English or English translation? <p>If no, explain:</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> Electronic Submission comments <p>List comments:</p>	<input type="checkbox"/> Not Applicable
CLINICAL	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE

<p>Comments:</p>	<input type="checkbox"/> REFUSE TO FILE <input checked="" type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> Clinical study site(s) inspections(s) needed? <p>If no, explain:</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> Advisory Committee Meeting needed? <p>Comments:</p> <p><i>If no, for an original NME or BLA application, include the reason. For example:</i></p> <ul style="list-style-type: none"> <i>this drug/biologic is not the first in its class</i> <i>the clinical study design was acceptable</i> <i>the application did not raise significant safety or efficacy issues</i> <i>the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease</i> 	<input type="checkbox"/> YES Date if known: <input checked="" type="checkbox"/> NO <input type="checkbox"/> To be determined Reason:
<ul style="list-style-type: none"> Abuse Liability/Potential <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<p>CLINICAL MICROBIOLOGY</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input checked="" type="checkbox"/> Review issues for 74-day letter
<p>CLINICAL PHARMACOLOGY</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> Clinical pharmacology study site(s) inspections(s) 	<input type="checkbox"/> YES

needed?	<input checked="" type="checkbox"/> NO
BIOSTATISTICS Comments:	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input checked="" type="checkbox"/> Review issues for 74-day letter
NONCLINICAL (PHARMACOLOGY/TOXICOLOGY) Comments:	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input checked="" type="checkbox"/> Review issues for 74-day letter
IMMUNOGENICITY (BLAs/BLA efficacy supplements only) Comments:	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
PRODUCT QUALITY (CMC) Comments:	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input checked="" type="checkbox"/> Review issues for 74-day letter
<u>Environmental Assessment</u> <ul style="list-style-type: none"> • Categorical exclusion for environmental assessment (EA) requested? If no, was a complete EA submitted? If EA submitted, consulted to EA officer (OPS)? Comments:	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO
<u>Quality Microbiology (for sterile products)</u> <ul style="list-style-type: none"> • Was the Microbiology Team consulted for validation of sterilization? (NDAs/NDA supplements only) Comments:	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO

<p><u>Facility Inspection</u></p> <ul style="list-style-type: none"> • Establishment(s) ready for inspection? ▪ Establishment Evaluation Request (EER/TBP-EER) submitted to OMPQ? <p>Comments:</p>	<p><input type="checkbox"/> Not Applicable</p> <p><input checked="" type="checkbox"/> YES <input type="checkbox"/> NO</p> <p><input type="checkbox"/> YES <input type="checkbox"/> NO</p>
<p><u>Facility/Microbiology Review (BLAs only)</u></p> <p>Comments:</p>	<p><input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE</p> <p><input type="checkbox"/> Review issues for 74-day letter</p>
<p><u>CMC Labeling Review</u></p> <p>Comments:</p>	<p><input type="checkbox"/> Review issues for 74-day letter</p>
REGULATORY PROJECT MANAGEMENT	
<p>Signatory Authority: DAVP</p> <p>21st Century Review Milestones (see attached) (listing review milestones in this document is optional):</p> <p>Comments:</p>	
REGULATORY CONCLUSIONS/DEFICIENCIES	
<p><input type="checkbox"/></p>	<p>The application is unsuitable for filing. Explain why:</p>
<p><input checked="" type="checkbox"/></p>	<p>The application, on its face, appears to be suitable for filing.</p> <p><u>Review Issues:</u></p> <p><input type="checkbox"/> No review issues have been identified for the 74-day letter.</p> <p><input checked="" type="checkbox"/> Review issues have been identified for the 74-day letter. List (optional):</p> <p><u>Review Classification:</u></p> <p><input checked="" type="checkbox"/> Standard Review</p> <p><input type="checkbox"/> Priority Review</p>

ACTIONS ITEMS	
<input type="checkbox"/>	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug).
<input type="checkbox"/>	If RTF, notify everybody who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER).
<input type="checkbox"/>	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
<input type="checkbox"/>	BLA/BLA supplements: If filed, send 60-day filing letter
<input type="checkbox"/>	If priority review: <ul style="list-style-type: none"> • notify sponsor in writing by day 60 (For BLAs/BLA supplements: include in 60-day filing letter; For NDAs/NDA supplements: see CST for choices) • notify OMPQ (so facility inspections can be scheduled earlier)
<input checked="" type="checkbox"/>	Send review issues/no review issues by day 74
<input checked="" type="checkbox"/>	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
<input type="checkbox"/>	BLA/BLA supplements: Send the Product Information Sheet to the product reviewer and the Facility Information Sheet to the facility reviewer for completion. Ensure that the completed forms are forwarded to the CDER RMS-BLA Superuser for data entry into RMS-BLA one month prior to taking an action [These sheets may be found at: http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027822]
<input checked="" type="checkbox"/>	Other Contact sponsor regarding referencing IND (b) (4) ((b) (4) IND) but not IND 77812 (Sitavig)

Regulatory Project Manager

Date

Chief, Project Management Staff

Date

Appendix A (NDA and NDA Supplements only)

NOTE: The term "original application" or "original NDA" as used in this appendix denotes the NDA submitted. It does not refer to the reference drug product or "reference listed drug."

An original application is likely to be a 505(b)(2) application if:

- (1) it relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application,
- (2) it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval, or
- (3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

- (1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies),
- (2) No additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application, and.
- (3) All other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely

for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

- (1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2),
- (2) The applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement, or
- (3) The applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your OND ADRA or OND IO.

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

/s/

SOHAIL MOSADDEGH
05/14/2012

KAREN D WINESTOCK
05/15/2012