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APPLICATION NUMBER:

203791Orig1s000

SUMMARY REVIEW

Decisional Memorandum to the File

Date	April 4, 2013
From	Jeffrey Murray, M.D., M.P.H.
Subject	Deputy Director
NDA #	203791
Applicant	Bioalliance
Date of Submission	Original: March 13, 2012 Major Amendment: January 3, 2013
PDUFA Goal Date	Original: January 11, 2013 Major Amendment: April 12, 2013
Proprietary Name / Established (USAN) names	Sitavig (acyclovir)
Dosage forms / Strength	Mucoadhesive Buccal Tablet (MBT) 50 mg
Proposed Indication(s) (original)	1. The treatment of recurrent orofacial herpes simplex virus (HSV) infections in immunocompetent patients, (b) (4)
Recommended:	Approval

1. Introduction

This memorandum summarizes the main review issues and regulatory decision for NDA 203791 a 505(b)(2) application for a 50 mg mucoadhesive buccal tablet of acyclovir Lauriad for the treatment recurrent orofacial herpes simplex virus infections (cold sores) in immunocompetent patients (#1 above). The tablet is also referred to as acyclovir Lauriad MBT, trade name Sitavig. Refer to the Clinical/Statistical review and addendum prepared by Drs. Alivisatos and Zeng and the Cross-Discipline Team Leader memorandum and addendum prepared by Dr. Struble for details regarding the review of this application. NDA 203791 was submitted under 505(b)2 and relies on FDA's previous findings of safety and efficacy for Zovirax cream, and Zovirax capsules, tablet and suspension. Zovirax cream is approved for the treatment of recurrent herpes labialis. Acyclovir Lauriad MBT is applied to the upper gum just above the incisor tooth on the same side as the recurrent herpes labialis lesion (or symptoms). Following a single dose, Acyclovir Lauriad MBT provides release of acyclovir in the buccal cavity with deployment to the lip region via wetting of the lips.

As stated in Dr. Struble's and Alivisatos's addenda the applicant submitted a major amendment in response to a discipline review letter from the Division of Antiviral Products (DAVP). The amendment triggered a three-month extension of the review clock. In brief, the critical deficiency outlined in the discipline review letter related to the strength of the primary endpoint analysis of the single clinical trial supporting the treatment indication. The applicant satisfactorily responded to the critical deficiency in addition to other issues related to the phase 3 trial design as will be discussed below. In the major amendment the applicant withdrew three related indications (numbers 2-4 in the above table).

2. CMC

2.1. General Product Quality considerations

Prefer to the CMC review prepared by Drs. Shrikant Pagay and Fuqiang Liu. As stated in their review, "This NDA has provided adequate information to assure the identity, strength, purity, and quality of the drug product. The drug master file for acyclovir drug substance supporting this NDA is adequate."

2.2. Facilities Review/Inspection

The Office of Compliance has issued an overall recommendation of 'Acceptable' based on the satisfactory cGMP status of the manufacturing facilities.

3. Microbiology/Virology

Refer to the review prepared by Dr. Lalji Mishra. The applicant submitted and relied on published data to describe the mechanism of action of acyclovir and the antiviral activity of acyclovir against various isolates of herpes simplex viruses. In addition the applicant submitted a clinical report from their phase 3 trial (BA2005/21/02) comparing quantitative HSV-1 DNA in the saliva of a subset of patients treated with acyclovir Lauriad MBT vs. placebo. This report suggests that treatment exhibited antiviral activity after a single dose of the MBT.

4. Nonclinical Pharmacology/Toxicology

Please refer to the review prepared by Dr. Lansita. The applicant primarily relied on historical experience with oral acyclovir including published literature reports and FDA's previous findings of safety for acyclovir capsules to support the nonclinical portion of the application. Historical experience with oral acyclovir would overestimate any safety concerns with the proposed 50 mg MBT that has much lower systemic bioavailability of acyclovir than the approved doses of acyclovir capsules. In addition the applicant conducted a single-dose local tolerance study in hamsters with 50 mg of acyclovir Lauriad administered to the jugal mucosa. There were no notable or significant safety findings in the hamster study.

5. Clinical Pharmacology/Biopharmaceutics

In addition to a phase 3 trial, the application also contained a pharmacokinetic study (BA 2004/21/01). Refer to the review prepared by Dr. Leslie Chinn for details regarding this study. In brief, it was a three-way cross-over trial of three treatments: acyclovir Lauriad MBT 50 mg, acyclovir Lauriad MBT 100 mg, and 200 mg acyclovir tablet (Zovirax). Compared to the 200 mg acyclovir tablet, the 50 mg and 100 mg MBTs yielded markedly lower plasma concentrations. AUC exposures were 88% lower for the 50 mg MBT compared to the 200 mg oral tablet. In contrast to systemic exposures, salivary acyclovir concentrations were much higher with the MBTs than the oral tablet. Salivary AUC values were 12961 higher for the 50 mg MBT as compared to the oral tablet. The applicant estimates that salivary concentrations remained above the in vitro HSV IC_{50} for 32 hours after application.

Pharmacokinetic study BA 2004/21/01 demonstrates that acyclovir Lauriad MBT exerts an antiviral effect by providing drug locally to the site of developing herpes lesions and not by a systemic effect. Therefore this study provides a "bridge" for FDA to consider its previous findings of topical Zovirax cream in support of this 505(b)2 application. However, salivary or lip concentrations are not sufficient for approval; clinical trial data are needed. Bioequivalence trials are typically not considered sufficient to support a formulation change for topical drugs.

6. Clinical/Statistical

Please refer to the clinical reviews and addendum (prepared by Drs. Alivisatos and Zeng) and cross discipline team leader addendum (prepared by Dr. Struble) for a detailed discussion of the primary endpoint and analysis. In brief, after some confusion over endpoint terminology and over which of several possible endpoints should be considered primary, DAVP and the applicant agreed that duration of episode (DOE) assessed in the intent-to-treat (ITT) population should be the primary endpoint analysis. As compared to time to healing in patients who develop typical vesicular lesions, DOE allows one to evaluate the effect of the intervention in everyone who initiates treatment at onset of symptoms and takes into account aborted lesions. This analysis is consistent with the analyses conducted for Zovirax cream and is consistent with the Agency's preference for ITT analyses.

6.1. Phase 3/Essential Clinical Studies

The applicant conducted one phase 3 trial in which patients with a history of cold sores, defined as at least four episodes in the preceding 12 months, were randomized to initiate acyclovir Lauriad MBT or a placebo at the onset of symptoms. To be included patients were required to have prodromal symptoms in at least 50% of their prior episodes.

A total of 1721 patients were randomized 1:1 to receive a single dose of acyclovir Lauriad MBT or placebo. Of the 1721 randomized, 775 initiated treatment (378 in the acyclovir Lauriad MBT group and 397 in the placebo group), of which 521 developed a primary vesicular lesion.

In the analysis supporting approval and summarized in the label, the median time to healing (DOE) using Hodges-Lehmann estimates (FDA statistician's preferred approach) was 5.49 days for acyclovir Lauriad MBT and 6.00 days for placebo with a median difference of 0.58 days (p-value 0.0289) favoring acyclovir Lauriad MBT. These results were similar to the treatment benefit previously observed for Zovirax cream.

6.2. Safety

The product was tolerated and there are no significant safety issues.

6.3. Issues needing resolution

As stated in Dr. Alivisatos's review, the applicant satisfactorily responded to deficiencies outlined in the clinical/statistical discipline review letter in addition to the primary analysis. Issues addressed included:

- Concerns about the frequency of data collection on lesion assessment and how it affected the treatment estimate. In the phase 3 trial, lesion assessment was recorded once daily, in prior studies, diary cards included twice daily assessments
- Concerns about protocol violations including the use of prohibited medications in eleven patients with vesicular lesions
- Lack of consistency in subgroup analyses for time to lesion healing
- (b) (4)
- (b) (4)

The applicant satisfactorily addressed concerns regarding the conduct of the phase 3 trial and demonstrated that the concerns listed in the first two bullet points above did not affect the overall results of efficacy for the duration of episode in the ITT population. The applicant showed that subgroup analyses with respect to adhesion time of the MBT and initiation of therapy was

reasonably consistent across subgroups when evaluating duration of episode in the ITT population. With respect to the last three bullet points the applicant [redacted] (b) (4)

7. Risk Management

This application does not require a REMS. There are no specific risks that need to be mitigated.

8. Summary of Regulatory Issues

- This is a 505(b)2 application which relies on FDA's previous findings of the acyclovir cream (Zovirax) approval to support efficacy of acyclovir Lauriad MBT, a new formulation of acyclovir that delivers drug topically to the site of recurrent herpes lesions. Acyclovir cream, but not acyclovir oral capsules have a herpes labialis treatment indication. Previous knowledge of the active moiety's efficacy, when delivered topically (acyclovir cream), offer sufficient supportive evidence to allow one clinical trial to be conducted to demonstrate efficacy of the new formulation. This is consistent with guidance to industry that states that single clinical trials are acceptable when accompanied by supportive evidence. Bioequivalence studies are not sufficient to show efficacy because of the limitations and uncertainties in assessing quantitative levels of drug in skin or saliva. As recommended by the Division for herpes labialis product development, the clinical trial conducted compared acyclovir Lauriad MBT to placebo and not acyclovir cream. A noninferiority margin for a comparison to acyclovir cream is not feasible because the treatment effect is modest and variable, requiring an exceedingly small noniferiority margin that precludes the ability to conduct informative active controlled trials.
- An initial discipline review letter outlined several deficiencies including a critical deficiency regarding the primary endpoint analysis. As part of a major amendment, the applicant satisfactorily addressed concerns outlined in the Division's discipline review letter.

9. Advisory Committee Meeting

An advisory committee meeting was not conducted or needed.

10. DSI Audits

Clinical Inspections found the data acceptable for review.

11. Conclusions and Recommendations

11.1. Regulatory Action

Acyclovir Lauriad Mucoadhesive Buccal Tablets 50 mg should be approved for the treatment of recurrent orofacial herpes simplex virus in immunocompetent patients.

11.2. Postmarketing Trials

Under PREA, the applicant will be required to conduct trials in 100 pediatric patients greater than 6 years to less than or equal to 17 years (distributed over the age range) with recurrent orofacial herpes simplex ages. The primary assessment will be for safety; however, data to assess duration of episode will also be collected for comparison with that of adults.

11.3. Labeling

The applicant accepted all the changes proposed by DAVP. In the clinical trials sections the primary analysis is described in an abbreviated fashion as follows:

“The mean and median durations of the recurrent herpes labialis episode (ITT population, n=771) were at least half a day shorter in patients treated with SITAVIG compared with patients treated with placebo.”

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/s/

JEFFREY S MURRAY
04/10/2013