

**CENTER FOR DRUG EVALUATION AND RESEARCH**

**Application Number** 21-205

**MEDICAL REVIEW(S)**

NDA 21-205

NDA submitted: 17 Dec 99  
Review completed: 17 Jun 00  
Revisions completed: 2 Jul 00

**Medical Officer's Review**

**Applicant:** Glaxo Wellcome Inc.  
Five Moore Drive  
Research Triangle Park, NC 27709

**Drugs:** Generic: abacavir sulfate (Trizivir constituent)  
Generic: lamivudine (Trizivir constituent)  
Generic: zidovudine (Trizivir constituent)  
Trade: Trizivir™

**Route:** Oral

**Dosage forms:** Fixed-dose combination tablet: abacavir 300 mg/lamivudine 150 mg/zidovudine 300 mg

**Proposed indication:**

**Related INDs:** IND — abacavir sulfate/lamivudine/zidovudine tablets  
IND — abacavir tablets and oral solution  
IND — lamivudine tablets and oral solution  
IND — zidovudine capsules and tablets  
IND — lamivudine/zidovudine tablets  
IND — abacavir tablets, amprenavir capsules, adefovir dipivoxil tablets and efavirenz capsules  
IND — lamivudine for chronic hepatitis B

**Related NDAs:** NDA 20-977 (Ziagen® tablets)  
NDA 20-978 (Ziagen® oral solution)  
NDA 20-564 (Epivir® tablets)  
NDA —  
NDA 19-655 (Retrovir® capsules)  
NDA 19-910 (Retrovir® syrup)  
NDA 19-951 (Retrovir® injection)  
NDA 20-857 (Combivir® tablets)  
NDA 21-003 EPIVIR®-HBV™ (lamivudine) Tablets  
NDA 21-004 EPIVIR®-HBV™ (lamivudine) Oral Solution  
NDA 20-518 Retrovir® (zidovudine) tablets  
NDA 21-205 Trizivir® (abacavir sulfate/lamivudine/zidovudine) Tablets

**Related documents:** Minutes of meetings: Pre-NDA meeting, 21 Sept 1999

**Major amendments:** Safety Update (16 Mar 2000)

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**I. Summary**

This application is submitted to support marketing approval for a fixed dose combination oral tablet that includes three nucleoside analogs, abacavir sulfate (ABC) 300 mg (marketed as Ziagen®), lamivudine (3TC) 150 mg (marketed as Epivir®), and zidovudine (ZDV) 300 mg (marketed as Retrovir®). The application provides evidence that Trizivir is bioequivalent to concomitant administration of each of its constituent drugs. The primary clinical concern in the review of this application relates to hypersensitivity reactions (HSR) caused by abacavir. These have been observed in up to 8% of abacavir recipients in clinical trials, and were observed in a similar proportion (7.2%) of Trizivir recipients. If abacavir hypersensitivity reactions are not suspected, quickly identified, and abacavir-containing therapy immediately stopped, these reactions may rapidly progress to a life-threatening condition or fatal outcome.

The following main points were considered in assessing the Trizivir risk-benefit relationship, as a basis for a decision on this application for marketing approval: (i) Trizivir is not urgently needed to treat HIV infection. Its constituent nucleoside analogs are currently approved. (ii) Trizivir-associated benefits appear to relate primarily to convenience and may be marginal. (iii) The risks of death and of life-threatening HSR, particularly in patients rechallenged with abacavir, are expected to be at least as great, and may be greater, in Trizivir vs Ziagen recipients. Differences in patient and/or prescriber populations could affect rates of these serious HSR-related outcomes. (iv) Abacavir-related risks that may be differentially expressed in Trizivir vs Ziagen recipients during product marketing can only be assessed following Trizivir approval. (v) Increases in deaths or abacavir rechallenge in Trizivir vs Ziagen recipients may outweigh any benefit associated with availability of Trizivir. It is incumbent upon the applicant to demonstrate that the already worrisome safety profile of abacavir (ZIAGEN) is not worsened when abacavir is marketed in the Trizivir formulation. Because of these concerns, the relative risk of rechallenge and death in Trizivir vs Ziagen recipients during Trizivir marketing needs to be determined.

It is recommended that Trizivir approval should be made contingent on evidence that the applicant will conduct a prospective epidemiological study. This study should be appropriately designed to evaluate rates of abacavir HSR-related death and abacavir rechallenge in Trizivir and Ziagen recipients, so that the risk of these serious outcomes with Trizivir marketing can be evaluated. The applicant should obtain prior FDA agreement as to study design, and provide evidence that this study will undertaken and completed in a timely manner.

**II. Introduction and Background** This application is submitted in support of marketing approval for a fixed dose combination oral tablet that includes three nucleoside analogs, abacavir sulfate (ABC) 300 mg, lamivudine (3TC) 150 mg, and zidovudine (ZDV) 300 mg. Each of these drugs and doses have individually been approved, and the fixed dose combination oral tablet, Combivir®, which contains lamivudine (150 mg) and zidovudine (300 mg) has also been approved. Further, the combination of ABC, 3TC, and ZDV has been studied in three Phase III clinical trials; these studies have been used to provide evidence that ABC is effective in this combination. The Applicant bases this application upon human bioequivalence and *in vitro* dissolution data. No new clinical efficacy data is provided. A limited amount of clinical safety information is included.

The applicant intends that Trizivir will be used for the treatment of HIV infection when therapy is warranted, either alone or in combination with other antiretroviral agents. The applicant notes that for those patients whose HIV therapy regimen includes ABC, 3TC, and ZDV, this new tablet would reduce the total daily tablet intake for these three drugs from six to two tablets daily. The applicant concludes that this tablet can be administered twice daily without regard to meals.

**III. Other reviews** Please refer to the Biopharmaceutics review (Dr. P. Rajagopalan)

**IV. Summary of NDA clinical section.**

**A. Study AZL 10001** An Evaluation of the Bioequivalence of a Combined Formulated Tablet (300/150/300 mg abacavir/lamivudine/zidovudine) Compared to ZIAGEN (abacavir) 300 mg Tablet, EPIVIR (lamivudine) 150

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mg Tablet, and RETROVIR (zidovudine) 300 mg Tablet Administered Concurrently and the Effect of Food on Absorption in Healthy Volunteers.

This is the principle study submitted in this application in support of the marketing application for approval of TRIZIVIR. It is a randomized, open-label, single-dose comparison of pharmacokinetics of three treatments, conducted in 24 healthy volunteers. Study treatments were: (1) ABC/3TC/ZDV combination tablet (300 mg/150mg/300mg), fasting; (2) ABC 300 mg tablet/3TC 150 mg tablet/ZDV 300 mg tablet, fasting; (3) ABC/3TC/ZDV combination tablet (300 mg/150mg/300mg), fed. Each subject was to receive each treatment, with 24-hour PK sampling, and then an intervening 3-day wash-out period between treatments. See the Biopharmaceutics review for a summary of the study results and its conclusions. Although the washout period between study drugs was 24 hours less than specified in the protocol, the Biopharmaceutics reviewer concluded that the abbreviated washout period did not significantly affect the results of this study.

**Study results - safety.** There were no deaths or serious adverse events. Five of 25 subjects had a total of 8 adverse events, including nausea (2 subjects), back (2 subjects) or neck pain (1 subject), cough (1 subject), dizziness (1 subject), rash on neck (1 subject). For clinical chemistries, hematology and vital signs, mean and median parameters for the study population are within the normal range.

**B. Study AZL 10002 An Evaluation of the Steady-State Pharmacokinetics of abacavir, lamivudine, and zidovudine Following Administration of a Combined Formulated Tablet (300/150/300 mg abacavir/lamivudine/zidovudine) versus ZIAGEN (300 mg abacavir) and COMBIVIR (150/300 mg lamivudine/zidovudine) in Subjects with HIV-1 Infection**

This open-label multiple dose, descriptive study was required by French regulatory authority and was conducted in France. A three-page summary of this study is provided. Twelve HIV-infected males, ≥ 18 years of age were enrolled. The duration of the study was approximately 10 days, not including screening. Subjects stayed in the study unit for the 12-hour PK evaluations. All subjects received Treatments 1 and 2: Treatment 1: current treatment including COMBIVIR with ZIAGEN (abacavir) BID; Treatment 2: triple combination tablet BID for at least 7 days. Pharmacokinetic sampling was performed over 12 hours on 2 occasions - before switching to the triple combination tablet, and after at least 7 days of treatment with the triple combination tablet.

**Study results - safety.** The study summary notes that "only non serious, not drug-related and mild in intensity adverse events were reported. No study drug interruption or discontinuation was required due to an adverse event. No remarkable changes in hematology, clinical chemistry, vital signs (blood pressure, heart rate) or ECG occurred."

**C. Clinical Trials and Safety Update** No clinical trial study reports are submitted in this application. As summarized in the original application, ongoing clinical trials in which the abacavir/lamivudine/zidovudine triple combination tablet is being used are listed below:

1. Studies, projected enrollments, study design, population and regulatory role, are summarized as follows:

Study	N	design	population	regulatory role
AZL 30002 (48 wks)	200	2 NRTIs+PI vs 2 NRTIs+NNRTI vs 2 NRTIs+ABC	HIV+ HIV RNA <50	non-IND
ESS 40005 (24 wks)	230	ABC,3TC,ZDV vs ABC/3TC/ZDV	HIV+, on ABC, 3TC, ZDV HIV RNA <400	US: IND,(Phase 4)
French ATU	300	ABC/3TC/ZDV (non-comparative, O/L)	named-patient	France, pre-approval (expanded access)
Maint. Study	150	AZT/3TC+ABC vs 3-ARTs (incl PI)	HIV RNA <50	Switzerland

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A 90-day Safety Update, which was submitted as an Amendment to this NDA on 16 Mar 2000. This Update lists 6 studies as contributing to data in this Update, which provides the available safety information on Trizivir in these ongoing studies. This information is summarized as follows:

**2. Extent of exposure and adverse event overview, by study.**

Study	Enrolled (N)	Treated with Trizivir (N)	Treatment duration	Deaths	Serious AE's	HSR	Lab AE's (Gr 3/4)	Pregnancies
AZL 30002	219	111	8 wks (median)	0	12	8	8	0
AZLF30002 (rollover from CNAF30002)	25	11	2 wks (median)	0	0	0	0	0
AZL30003 (rollover from AZL10002)	12	0	0	0	0	0	0	0
ESS 40005 (24 wks)	88	43	≥ 8 wks (n=16)	0	0	0	4	1
French ATU	0	0		0	0	0	0	0
Maint. Study	164	2	1 week	0	0	0	0	0

**Comment:** The information on exposure is not provided in a comparable fashion for all studies. At least 70 patients had exposures of 8 weeks or greater, and a total of 167 patients were exposed to the abacavir/lamivudine/zidovudine fixed-dose combination tablet. Information on this fixed-dose combination tablet is very limited and of short duration. Because most hypersensitivity reactions to abacavir occur within the first 6 weeks of therapy, more than 70 patients have exposures that could detect abacavir-related hypersensitivity reactions.

**3. Drop-outs due to adverse events, regardless of relation to study treatment.** The report notes that no patients were discontinued from study participation due to adverse events. Eight patients (in AZL30002) who received TZV experienced abacavir-related hypersensitivity reactions and were switched to an alternative drug regimen, but remained on the study.

**4. Serious adverse events.** Twelve patients in study AZL30002 had serious adverse events; of these, 8 had events resembling abacavir hypersensitivity reactions while receiving Trizivir therapy. These events, which occurred from 2 days to 6 weeks of initiation of Trizivir, were similar to those seen in abacavir recipients, were attributed to abacavir present in the three-drug fixed-combination Trizivir tablet, and improved following discontinuation of Trizivir. Three patients had serious adverse events (pulmonary embolism, suicide attempt, vomiting and diarrhea) prior to taking study therapy. One patient, whose study therapy consisted of indinavir, d4T, and nevirapine, developed a renal calculus, which was attributed to indinavir.

**Comment:** These 8 hypersensitivity events occurred in 111 Trizivir recipients. This is a hypersensitivity rate of 7.2 %, within the range (3-8%) observed in abacavir studies. It is likely that hypersensitivity in these patients is due to abacavir in Trizivir. The event of vomiting and diarrhea may be causally related to the three nucleoside analogs present in Trizivir. The serious adverse events of pulmonary embolism and suicide attempt do not appear to relate to Trizivir.

**5. Grade 3/4 laboratory abnormalities.** Eight patients in study AZL30002 each had one Grade 3 or 4 laboratory event; seven were in patients on current treatment (not including Trizivir), and one in a Trizivir recipient. One of 111 Trizivir recipients and one of 108 current therapy (not containing Trizivir) recipients each had Grade 3 elevations of triglycerides. Four patients in study ESS40005 had Grade 3 or 4 laboratory elevations at entry. Each of these events were present at screening and/or baseline, and following entry into the study, there was no change in the severity of their laboratory values from baseline.

**Comment:** This data indicates no excess Grade 3/4 laboratory abnormalities in Trizivir recipients.

6. **Pregnancy.** A single pregnancy was reported in these studies (study ESS40005). The patient, who had a negative pregnancy test on screening, was receiving abacavir and Combivir (3TC/ZDV). Three months after starting study medication, she was found to be pregnant. Study medication was discontinued, and nevirapine was initiated. The outcome of the pregnancy was unknown at the time of the report.

## **V. Reviewer's Assessment**

### **A. Summary of evidence supporting approval.**

Trizivir is a fixed-dose combination oral tablet which contains abacavir sulfate, lamivudine, and zidovudine. Each constituent drug is marketed as an oral tablet (as Ziagen, Epivir, and Retrovir, respectively). In addition, Combivir, a fixed-dose combination tablet which contains lamivudine and zidovudine, is also approved for marketing.

In this application, evidence supporting the efficacy and safety of the three-drug fixed-dose combination tablet, Trizivir, which contains abacavir, lamivudine and zidovudine, is: (i) each individual product (abacavir, lamivudine, and zidovudine) has been shown to be safe and effective, and (ii) the combination tablet, Trizivir, has been shown to be bioequivalent to abacavir, lamivudine and zidovudine when administered concurrently as individual tablets. The single-dose bioequivalence study which provides this evidence is thus the key study supporting approval of Trizivir.

Safety information on Trizivir itself, provided in an update of ongoing clinical studies utilizing Trizivir, was submitted during the course of the review. In this update, at least 70 patients had exposures of 8 weeks or greater, and a total of 167 patients were exposed to the abacavir/lamivudine/zidovudine fixed-dose combination tablet. Thus, although the safety data with Trizivir itself is very limited, there is no reason to expect the safety profile for Trizivir to be different from that associated with use of the components singly. The safety interpretation regarding Trizivir is largely based on studies in which combination therapy with abacavir, lamivudine, and zidovudine was used. However, the application lacks data which addresses reviewers' concerns that the perceived convenience of Trizivir may increase the known risks due to abacavir HSR in certain circumstances.

### **B. Risks and benefits of Trizivir.**

1. **Risk.** Each of the three nucleoside analogs in Trizivir has significant safety concerns associated with its use. The Trizivir-associated risk of primary reviewer concern relates to HSR in abacavir recipients.

a. **Abacavir and HSR.** The most clinically significant is a hypersensitivity reaction (HSR) caused by abacavir sulfate. Safety concerns with HSR are: (i) the high rate of occurrence (6% of patients in clinical trials), (ii) the severity of HSR (which can be life-threatening or fatal), (iii) accurate identification of HSR, because of overlapping symptoms between HSR and other diseases, overlapping adverse events associated with drugs likely to be taken by HIV-infected patients, and variability in HSR presentation, (iv) the more rapid onset and increased severity of HSR with rechallenge, (v) the occurrence of life threatening or fatal HSR in patients who, having stopped abacavir for reasons other than HSR, develop HSR following abacavir reintroduction, (vi) the critical importance of early recognition of HSR and prompt termination of abacavir therapy to improving the clinical outcome of HSR in abacavir recipients.

In Ziagen recipients, the critical elements for reducing the risk of fatal outcomes from abacavir HSR include early recognition of, and appropriate response to, HSR symptoms by both the patient and the health care

professional. Several elements appear necessary for the safe use of abacavir: (i) education (including information dissemination and comprehension) that enhances the prompt recognition of HSR symptoms, (ii) clear understanding that prompt termination of abacavir is the only effective means thus far identified to reduce the risk of life-threatening and fatal outcome, (iii) recognition that symptoms of HSR may be similar to, or overlap, symptoms with other concurrent diseases (such as infection, flu-like illness, gastrointestinal illness), and that abacavir must be terminated early even if these symptoms may have an alternate, disease-related explanation, (iv) recognition that once abacavir HSR has developed, abacavir must never again be reintroduced, because very severe HSR may then develop within hours, and may be fatal, and (v) recognition that interruption of abacavir therapy, followed by abacavir reintroduction, may likewise be followed by rapid-onset, very severe HSR, which may be fatal. From the experience with Ziagen, it is to be anticipated that these same elements will be critical to enhance the safe use of Trizivir.

b. *HSR in Trizivir recipients.* There is very little safety data on which to base an evaluation of the risk of abacavir-related HSR in Trizivir recipients. In study AZL30002, eight of 111 Trizivir recipients (7.2 %) developed abacavir HSR, which is consistent with the 6% rate (range, 3-8%) of HSR observed in abacavir studies overall. There is no evident reason that the abacavir-host interaction should be biologically different in Trizivir vs Ziagen recipients, and thus it is not surprising that rates of HSR in clinical trials are similar, regardless of the formulation of abacavir.

Trizivir will represent a more convenient way to provide its three constituent nucleoside analogues, because it will provide a 3-drug antiretroviral regimen with 1 tablet, twice a day. This added convenience raises several additional safety concerns.

First, because of the convenience of Trizivir, physicians and other health care providers who are less experienced in the treatment of HIV infection (and may thus be less attuned to abacavir HSR safety concerns), may undertake the treatment of HIV-infected patients, when otherwise they might not. Lack of experience by the health care provider may lead to delay in the recognition of HSR, delay in the termination of abacavir, and more frequent abacavir rechallenge. Any or all of these factors could lead to the more frequent progression of abacavir HSR to life-threatening illness and/or death.

Second, the patient population that will be targeted in Trizivir marketing may differ from that thus far targeted for treatment with Ziagen (abacavir). Trizivir may be more frequently used in certain populations for whom compliance with antiretroviral therapy is perceived to be a problem (e.g., individuals marginalized for socioeconomic reasons, of limited ability to comprehend the abacavir safety information provided, having limited familiarity with the English language, or prisoners). Because communication and comprehension of symptoms of abacavir HSR, and the need to stop taking abacavir when symptoms occur and never re-start abacavir-containing therapy are so critical to the prevention of life-threatening and fatal HSR, this is a significant safety concern.

Third, Trizivir therapy may be used more frequently as initial therapy of HIV infection than is presently the case. Trizivir is likely to be promoted for treating previously untreated HIV-infected individuals because it spares use of an HIV-1 protease inhibitor until a later stage in the patient's infection. Yet, at present, the three-drug combination of abacavir/lamivudine/zidovudine is not regarded as "first line" antiretroviral therapy in treatment guidelines provided by <sup>DHHS</sup> ~~the~~ <sup>the</sup> DHHS. There is less evidence that this triple combination regimen provides a durable virologic response than is available for certain other 3-drug antiretroviral regimens. This is an efficacy concern, not a safety issue, but does represent a risk of Trizivir therapy.

2. *Benefit.* No direct comparison of efficacy of the 3-drug, fixed-dose combination, Trizivir, to concurrent administration of abacavir plus lamivudine plus zidovudine as individual tablets, or to abacavir plus Combivir (the fixed-dose combination tablet containing lamivudine and zidovudine) has been made. Efficacy of Trizivir is based solely on pharmacokinetic information.

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The chief advantage of the Trizivir three-drug fixed-dose combination tablet over its individual constituents is one of convenience. That is, there is a reduced pill burden compared to administration of the approved constituent drugs. The antiretroviral effect provided by Trizivir (1 tablet, BID) could be provided by either: (i) Ziagen (abacavir), 1 tablet BID plus Combivir, (lamivudine plus zidovudine), 1 tablet BID, for a total of 4 pills per day, or (ii) Ziagen (abacavir), 1 tablet BID plus Epivir (lamivudine), 1 tablet BID plus Retrovir (zidovudine), 1 tablet BID, for a total of 6 pills per day.

There are those patients for whom Trizivir may provide a less complex and thus more convenient regimen, a potential advantage over existing formulations of abacavir, lamivudine and zidovudine. But it is unlikely that this represents a substantial proportion of HIV-infected patients.

### C. Assessment of Trizivir-associated risks and benefits.

1. Trizivir is not urgently needed to treat HIV infection. Its constituent nucleoside analogs are currently approved for marketing.
2. Potential Trizivir-associated benefits appear to relate primarily to convenience and appear to be marginal, relative to use of already approved formulations of its constituent nucleoside analogs.
3. Death, and rechallenge-associated HSR are the most severe outcomes associated with abacavir HSR; each is largely preventable through adequate patient and provider education. Risks associated with Trizivir marketing are expected to be at least as great, and may be greater, than those associated with Ziagen. These relative risks will not be established unless and until Trizivir is approved. Nevertheless, the reviewers have significant concerns regarding these potential risks, as summarized above. Increases in rates of abacavir rechallenge or HSR-related death in Trizivir recipients over those in Ziagen recipients are likely to outweigh any possible benefit associated with availability of Trizivir.
4. It is incumbent upon the applicant to demonstrate that the already worrisome safety profile of abacavir (ZIAGEN) is not worsened when abacavir is provided in the Trizivir formulation. A means to permit evaluation of the relative risk of rechallenge and death in Trizivir vs Ziagen recipients during Trizivir marketing needs to be established prior to Trizivir approval (see below).

### D. Post-marketing evaluation of Trizivir safety.

As a basis for any decision regarding continued marketing of Trizivir, accurate information regarding the relative safety of Trizivir and Ziagen will be needed to identify risks attributable to marketing of these products. In consultation with FDA epidemiologists, it is clear that passively collected data using the FDA's MedWatch system cannot be used to establish relative rates of HSR-related death and abacavir rechallenge in Ziagen vs Trizivir recipients, because a denominator cannot be established.

Therefore, only a prospective epidemiological study can provide these rates. Such a study will be most useful if it is designed to capture information on patient populations and providers that are differentially treated with, or prescribe, Trizivir vs Ziagen. The study should capture information such that risk of life-threatening HSR and death in Trizivir vs Ziagen recipients can be determined.

To assure that this study will be promptly undertaken, completed and reported in a timely manner, an approvable action will be taken on this new drug application. Approval should be made contingent upon: submission of an appropriately designed and powered prospective epidemiological study; FDA review and agreement on the protocol; evidence that study sites and investigators have been engaged; and an appropriate plan for interim reports and for submission of the final study report, as agreed to by the FDA.

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**VI. Recommendation**

Based on the bioequivalence of Trizivir to concomitant administration of the constituent drugs that are already marketed, this application is approvable. Given the concern regarding abacavir hypersensitivity reactions in Trizivir recipients regarding whether abacavir hypersensitivity reactions, and particularly fatal ones, may be more frequent in Trizivir than in Ziagen recipients, it is recommended that Trizivir approval be made contingent on evidence that an appropriate prospective epidemiological study will be undertaken and its results reported to the FDA in a timely manner.

  
John R. Martin, M.D.  
Medical Officer, HFD-530

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concurrences:

HFD-530/DivDir/ HJolson  
HFD-530/TL/TCvetkovich

cc:

NDA  
HFD-530  
HFD-530/DivDir/ HJolson  
HFD-530/TL/TCvetkovich  
HFD-530/CSO/MTruffa  
HFD-530/Chem/RKambhampati  
HFD-530/Micro/LMishra  
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