DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

DATE: July 11, 2006

TO: NDA 21-937 (ATRIPLA® Tablets)

FROM: Russell Fleischer, PA-C, MPH
Senior Clinical Analyst, DAVP

THROUGH: Katherine Laessig, MD
Medical Team Leader, DAVP

RE: Clinical Review of new NDA

1.0 Resume

This NDA was submitted to support the approval of ATRIPLA Tablets, a fixed dose combination containing efavirenz 600 mg (EFV), tenofovir disoproxil fumarate (TDF) 300 mg and emtricitabine (FTC) 200 mg administered once-daily for treatment of HIV-1 infection in adults. ATRIPLA Tablets represent a collaborative effort between Gilead Sciences and Bristol-Myers Squibb (in the US) and with Merck who controls marketing of efavirenz outside the US. ATRIPLA Tablets would be made available in the US as well as to the PEPFAR program for export to other countries.

The three components of ATRIPLA Tablets are approved for the same indication in the US (treatment of HIV-1 infection in adults) and they have demonstrated safety and efficacy when used a part of an antiretroviral regimen as the individual products. The current application is based on a demonstration of bioequivalence between the individual components and the fixed-dose combination, and provision of adequate chemistry, manufacturing and controls information.

2.0 Background on Agents

ATRIPLA is a fixed-dose tablet containing efavirenz 600 mg (EFV), tenofovir disoproxil fumarate (TDF) 300 mg and emtricitabine (FTC) 200 mg. Each component is currently approved for use in combination with other antiretroviral agents to treat HIV-1 infected adults; TDF+FTC make up the components of fixed-dose TRUVADA® Tablets.

The application does not contain any clinical data. However, the efficacy of the combination of FTC/TDF/EFV was established in a large clinical study (Gilead Sciences study GS-934). In this study 244 HIV-1 infected adult patients received

efavirenz/emtricitabine/tenofovir DF (as individual agents) for 48 weeks (see Medical Review of NDA 21-356/SE7-016). The results demonstrated 84% of patients with HIV RNA <400 c/mL, 80% with HIV RNA <50 c/mL, and a mean increase in CD4 cells of 190 cells/mm^3 after 48 weeks of therapy. Both the safety and resistance/cross-resistance profiles of FTC, TDF, and EFV have been well characterized in each of their respective NDA reviews and labeling.

3.0 Currently Available Treatment for Indication

There are currently 23 individual drugs approved in the US for the treatment of HIV infection.

The nucleoside reverse transcriptase inhibitors (NRTIs) were the first class of compounds to exhibit anti-HIV efficacy. Currently there are six NRTI's marketed in the US: zidovudine (Retrovir®), didanosine (Videx®), zalcitabine (Hivid®), stavudine (Zerit®), lamivudine (Epivir®), abacavir (Ziagen®), emtricitabine (Emtriva®), and tenofovir (Viread®, sometimes also referred to as a nucleotide). More recently introduced classes of antiretroviral agents include the non-nucleoside reverse transcriptase inhibitors (NNRTI), including delavirdine (Rescriptor®), nevirapine (Viramune®), and efavirenz (Sustiva®), the protease inhibitors (PI), represented by indinavir (Crixivan®), ritonavir (Norvir®), saquinavir (Invirase® and Fortovase®), nelfinavir (Viracept®), amprenavir (Agenerase®), fosamprenavir (Lexiva®), atazanavir (Reyataz®), tipranavir (Aptivus®), darunavir (Prezista®) and lopinavir/ritonavir fixed dose combination (Kaletra®), and the GP41 fusion inhibitor enfuvirtide (Fuzeon®).

There are four additional combination products that include two or more of the above individual constituents: Combivir® (lamivudine/zidovudine), Truvada® (emtricitabine/tenofovir), Epzicom® (lamivudine/abacavir) and Trizivir® (zidovudine/lamivudine/abacavir).

The current DHHS treatment guidelines recommend initiation of treatment with highly active antiretroviral therapy (HAART) that includes at least three drugs, including either a NNRTI or PI with two NRTIs, to attack various stages in the life-cycle of the virus to attempt long-term suppression of viral replication and increases in CD4 cell counts.

Although the introduction of HAART has led to significant improvement in morbidity and mortality, a substantial number of patients do not achieve or maintain adequate suppression of HIV viral replication. Side effects, drug interactions, frequent dosing, pill burden, and complex dietary requirements have been cited as dilemmas facing patients and clinicians.

There has been much interest in simplification of regimens that might improve tolerability and adherence and increase the feasibility of long-term effective control of disease. Although it has not been proven that ATRIPLA Tablets will meet these goals, its availability should offer an additional option for patients and clinicians to consider when designing a more simplified HAART regimen.

4.0 Data Contained in the NDA

Four bioequivalence studies (GS-US-177-0101, GS-US-185R-0102, GS-US-177-0103, and GS-US-177-0105) were conducted in a total of 192 non-HIV infected subjects. Each subject received, at one study visit, a single dose of the fixed-dose, triple-combination tablet (containing 600 mg of EFV, 200 mg of FTC and 300 mg of TDF) and, at another study visit, a single 600-mg tablet of EFV, a single 200-mg capsule of FTC, and a single 300-mg tablet of TDF, administered concurrently. Studies GS-US-177-0101, GS-US-185R-0102, and GS-US-177-0103 evaluated early formulations, and Study GS-US-177-0105 used the proposed commercial formulation of the EFV/FTC/TDF fixed-dose combination tablet. An additional study (GS-US-177-0104) in 48 non-HIV infected adults was conducted to evaluate another early formulation of the combination tablet.

- **Safety Review**

A total of 240 healthy adult volunteers received FTC, TDF and EFV in the clinical pharmacology studies as a fixed-dose combination and as single agents. No deaths were reported in any of the clinical pharmacology studies.

There were no deaths, two serious adverse events (pregnancies) both leading to study discontinuation, one subject who discontinued due to elevated transaminase levels and one who was discontinued due to a positive urine screen for amphetamines. The most common clinical adverse events reported included: headache, dizziness, abdominal pain, nausea, vomiting, and rash; the frequencies were comparable between treatment arms and with the known adverse event profiles of the individual drugs.

Deaths

None.

Serious Adverse Events

Two SAEs, both pregnancies, were reported in Study 0105.

Subject 9 was a Hispanic female aged 37 years, and received EFV/FTC/TDF on Day 1. She did not receive any concomitant medications during the study. On Day 22, she had a positive qualitative serum hCG test. Pregnancy was confirmed by quantitative serum hCG tests on post-dose Days 22 and 28. She stated she was using only condoms at the time of conception, rather than two forms of contraception as instructed. The subject was informed of the positive pregnancy test on Day 28 and was withdrawn from the study by the investigator on the same day. She did not receive the Day 29 study drug dose. She was contacted 80 days after dosing for pregnancy follow-up and reported that she had gone to the emergency room with a spontaneous abortion 78 days after dosing. She had continued vaginal bleeding for 4 days with low blood pressure and lower abdominal pain. Eighty-six days after dosing, she returned to the emergency room because she had a recurrence of low blood pressure and vaginal bleeding. An ultrasound

revealed a small, irregular sac within the uterus that was consistent with a missed abortion. A quantitative hCG test at the time yielded a value of 18.5 mIU/mL, which the investigator considered to be essentially within the normal range and inconsistent with pregnancy. The investigator considered the spontaneous abortion as a Grade 1 important medical event that was related to study drug.

Subject 13 was a Hispanic female aged 22 years, and received the Reference Treatment on Day 1. She did not receive any concomitant medications during the study. She had no prior pregnancies, births, or abortions, and no relevant medical history. The subject tested negative for hCG at screening and on Day 0 (predose). On Day 8, one week after receiving study drug, she had a positive qualitative serum hCG test. She reported that she had used condoms and a spermicide for contraception. Pregnancy was confirmed by quantitative serum hCG tests on Days 9 and 12. She was withdrawn from the study by the investigator on Day 10. She was contacted on Day 53 for pregnancy follow-up. She reported that she had normal menses on Day 30. Spontaneous abortion was suspected, and a serum hCG test conducted on Day 57 was negative. The investigator considered the spontaneous abortion as a Grade 1 important medical event that was related to study drug.

Discontinuations due to Any Reasons

No subjects discontinued from studies 0101, 0102 or 0103 because of adverse events. In Study GS-US-177-0104, one subject was discontinued because of Grade 1 increased AST and ALT after dosing with concurrent EFV/FTC/TDF on Day 1.

Subject 42 was withdrawn from study 0105 by the Investigator because of a positive amphetamine test on Day 28 (classified as "failed check-in laboratory value") and did not receive the Day 29 study drug dose. This subject tested negative for drugs of abuse at screening and Day 0 (predose) and received only a single administration of study drug on Day 1.

General Adverse Events

There were no clinically relevant changes in laboratory parameters in any subject in any study.

Clinical adverse events were consistent with the established profiles for each of the components of ATRIPLA. The most common treatment-related events included: headache, dizziness, abdominal pain, nausea and vomiting, and rash. All AEs were Grade 1 in severity, except for one Grade 2 headache and one Grade 2 rash.

Clinical Pharmacology

Four bioequivalence studies comparing the pharmacokinetics of various formulations of EFV/FTC/TDF administered as a fixed dose combination to the individual components were conducted. Study GS-US-185R-0105 provides the data supporting bioequivalence between the fixed dose combination and individual components.

Study 0105 was a phase 1 pharmacokinetic study conducted in 48 healthy adult volunteers between 18 and 45 years of age to evaluate the bioequivalence of a fixed dose triple combination tablet with concurrent administration of the individual dosing forms. Subjects were randomized to receive a fixed dose combination tablet containing EFV 600 mg/FTC 200 mg/TDF 300 mg or the individual dosing forms on day 1 in the fasted state. Following a cross-over design, subjects received the other forms on day 29 again in the fasted state. The pharmacokinetic results are detailed in Table 1.

Table 1. Statistical Comparison of Pharmacokinetic Parameters

Parameter[a]	Test	Reference	Geometric Least Squares Mean Ratio (%)	90% Confidence Interval
Efavirenz	**(n=44)**		**(n=44)**	
Cmax (ng/mL)	2190.20	2192.55	99.89	93.37, 106.88
AUC0-last (ng•h/mL)	120841.0	126231.3	95.73	90.50, 101.26
AUCinf (ng•h/mL)	137106.6	144030.3	95.19	88.92, 101.91
Emtricitabine	**(n=45)**		**(n=45)**	
Cmax (ng/mL)	2066.48	2325.96	88.84	84.02, 93.94
AUC0-last (ng•h/mL)	10523.83	10740.78	97.98	94.90, 101.16
AUCinf (ng•h/mL)	10694.43	10916.98	97.96	94.86, 101.16
Tenofovir	**(n=45)**		**(n=45)**	
Cmax (ng/mL)	307.25	335.93	91.46	84.64, 98.83
AUC0-last (ng•h/mL)	1845.03	1858.15	99.29	91.02, 108.32
AUCinf (ng•h/mL)	2218.24	2208.41	100.45	93.22, 108.23

a Subjects 9, 13, and 42 did not complete the study and were not part of the pharmacokinetic analysis set. In addition, subject 46 did not meet the pharmacokinetic analysis criteria and was excluded from the pharmacokinetic analysis set for EFV.

Source: Module 5.3.1.2, GS-US-177-0105 Clinical Study Report, Section 11.1, Table 6

Three subjects were withdrawn from the study: two because of pregnancy (see Serious Adverse Events above) and one because of a positive amphetamine test.

Dosage and Administration

The recommended adult dose of ATRIPLA Tablets is one tablet, once daily, on an empty stomach.

There is significant drug-drug interactions associated with the co-administration of EFV, FTC, or TDF with other medications. Certain of these drugs will be contraindicated for co-administration with ATRIPLA Tablets and will be listed in the label.

Chemistry, Manufacturing and Controls

For a detailed discussion of Chemistry, Manufacturing and Controls, please see Dr. Lunn's review.

In the US, ATRIPLA Tablets will be supplied as a tablet The tablets are approximately 20 mm in length and 10.4 mm in width. ATRIPLA tablets will be pink, film-coated tablets printed with "123" on one side and blank on the other.

An alternative trade dress is also proposed for export. For this tablet

The daily recommended dose of ATRIPLA tablets is one tablet one time per day taken without regard to meals. The composition of ATRIPLA Tablets is provided in Table 2.

Table 2. Composition of ATRIPLA Tablets

Component	Weight (mg)/ Tablet
Efavirenz	600.0
Croscarmellose Sodium	
Hydroxypropyl Cellulose	
Magnesium Stearate	
Microcrystalline Cellulose	
Sodium Laurel Sulfate	
Emtricitabine	200.0
Tenofovir DF	300.0
Total Weight	1550.0

The process used to manufacture the commercial product is equivalent to the process used to manufacture the product used in the pivotal bioequivalence study. The regulatory specification for ATRIPLA Tablets includes description, identification, assay, content uniformity, chromatographic impurity/degradation products, dissolution, and microbial attributes.

ATRIPLA Tablets are supplied in HDPE bottles containing 30 tablets and a silica gel desiccant. The storage recommendation is "Store at 25°C (77°F), excursions permitted to

15-30°C (59-86°F)." The expiration dating period is 24 months.

All pre-approval inspections of drug substance and drug product manufacturing and testing sites were determined to be acceptable by the Office of Compliance.

Pharmacology/Toxicology

The Pharmacology and Toxicology profiles of the three components of ATRIPLA Tablets have been well characterized.

Human Reproduction and Pregnancy Data

FTC and TDF are pregnancy Category B and EFV is Category D. Subjects in the clinical pharmacology studies were to have negative pre-study pregnancy tests and were to agree to use two forms of adequate birth control. Despite these efforts, two pregnancies were reported, both within three weeks of receiving study drug and both resulting in spontaneous abortions. It is not possible to rule out an association between the spontaneous abortion described above and receipt of the study medications. The labeling for ATRIPLA will contain the pregnancy language from each individual product; no new warnings or precautions are necessary.

Special Populations

Pediatrics

ATRIPLA Tablets is a fixed-dose combination of FTC/TDF/EFV, and has not been studied in either pharmacology or clinical studies. Therefore, ATRIPLA is not suitable for use in patients less than 18 years of age.

Hepatic Impairment

FTC and EFV have not been formally evaluated in patients with abnormal hepatic function. TDF has been studied in non-HIV infected patients with moderate to severe hepatic impairment and showed no substantial alterations in TDF pharmacokinetics. FTC is not significantly metabolized by liver enzymes, so the impact of liver impairment should be limited. Therefore, no dose adjustment should be necessary.

FTC and TDF both have in vitro activity against hepatitis B virus (HBV), and although not currently indicated for this use, might be administered to HIV/HBV co-infected patients. The FTC and TDF labels contain a WARNING related to the risk of severe acute exacerbations of hepatitis B following discontinuation of these agents; this WARNING will be included in the ATRIPLA Tablets label.

Renal Impairment

ATRIPLA Tablets are a fixed-dose combination and is not suitable for use in patients with creatinine <50 mL/min.

FTC and TDF are principally eliminated by the kidneys, but <1% of EFV is. EFV has not been fully evaluated in patients with renal impairment. Pharmacokinetic data for TDF and FTC indicate that dose interval adjustment is necessary for patients with moderate or severe renal impairment (CL_{cr} < 50 mL/min) and those with ESRD requiring hemodialysis. In patients with mild renal impairment, the pharmacokinetics of TDF and FTC are not substantially altered to warrant dose adjustment. TDF is associated with cases of acute renal failure and Fanconi syndrome.

Geriatrics

Clinical studies of EFV, FTC and/or TDF did not include sufficient numbers of elderly subjects (i.e., aged >65 years) to allow evaluation of efficacy and safety in this population. Similarly, the pharmacokinetics of EFV, FTC, and TDF have not been fully evaluated in patients >65 years. Since elderly patients are more likely to have decreased renal function, the EFV/FTC/TDF fixed-dose combination tablet should be used with caution when treating patients over the age of 65 years.

5.0 Label Review

The proposed labeling was reviewed and found to contain substantial information about all three components of ATRIPLA Tablets. The labeling was edited to remove certain redundancies and to increase the prominence of a number of important attributes of the products. The applicant agreed to these revisions and the labeling was acceptable to DAVP.

6.0 Recommended Regulatory Action

This NDA supports the once-daily administration of ATRIPLA Tablets, a fixed-dose combination tablet containing EFV 600 mg, FTC 200 mg and TDF 300 mg, for use as a complete or component of a multi-drug regimen for treatment of HIV-1 infection in adults. The recommended adult dose of ATRIPLA Tablets is one tablet taken once-daily on an empty stomach. The findings from clinical pharmacology study 0105 support the conclusion that the proposed commercial formulation of ATRIPLA Tablets is bioequivalent to the individual components. In addition, the application contained adequate provisions for manufacturing, clinical data on use of the combination, and labeling. This application should be approved.

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/s/

Russell Fleischer
7/12/2006 11:03:36 AM
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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

DATE: 06/16/06

FROM: Katherine A. Laessig, M.D.
Division of Antiviral Drug Products, HFD-530

TO: Division File

SUBJECT: Group Leader Memo for NDA 21-937 (Atripla® Tablets)

1.0 Background

The applicant, Gilead Sciences, has submitted this package to support the approval of Atripla Tablets, a fixed dose combination (FDC) containing efavirenz (EFZ) 600 mg, emtricitabine (FTC) 200 mg, and tenofovir disoproxil fumarate (TDF) 300 mg for the treatment of HIV-1 infection. This drug product is the result of collaboration between 3 pharmaceutical companies, including Gilead Sciences, Bristol Myers Squibb, and Merck. Atripla will be administered as one pill once daily, and represents the only complete regimen for HIV that is available as a single pill. All 3 components have been approved for the treatment of HIV individually, based on substantive evidence of efficacy and safety. The basis for the approval of Atripla tablets is the demonstration of bioequivalence of Atripla with the individual components in study GS-US-177-105.

2.0 Summary

Clinical evidence for the use of the combination of EFZ/FTC/TDF is derived from study 934, which was the basis of traditional approval for TDF, and for another FDC containing FTC/TDF, known as Truvada®. Study 934 evaluated 511 HIV-1 infected subjects who were randomized 1:1 to receive EFZ/FTC/TDF or zidovudine (AZT), lamivudine (3TC), and EFZ for 96 weeks. The primary efficacy analysis was performed at week 48, demonstrating 84% of study subjects had HIV RNA < 400 copies/ml for the EFZ/FTC/TDF arm compared to 73% in the AZT/3TC/EFZ arm. The most common treatment-related adverse events for the TDF/FTC arm were nausea, fatigue, dizziness, and diarrhea. The most common laboratory abnormalities observed for the TDF/FTC arm were fasting cholesterol > 240 mg/dL, increases in CK, and serum amylase.

Two SAEs were reported in the bioequivalence study 0105. Both were pregnancies that ended in spontaneous abortions in the first trimester. One subject in 0105 was withdrawn by the investigator for a positive amphetamine test on study day 28. There were no clinically relevant changes in laboratory parameters in any subject. The most common treatment related events were consistent with the known safety profiles for the component drugs and included headache, dizziness, abdominal pain, nausea, vomiting, and rash.

3.0 Recommendation

This NDA containing the results of study 0105 establishes the bioequivalence of the FDC Atripla to the individual component drugs. Previous evidence of the clinical benefit of the combination of EFZ/FTC/TDF has been demonstrated in study 934. Therefore, I concur with the findings of the clinical review by Russell Fleischer, PA-C, MPH, and recommend that this application be approved.

Katherine A. Laessig, M.D.

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/s/

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7/12/2006 10:28:52 AM
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