

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-752

MEDICAL REVIEW



MEMORANDUM OF TELEPHONE CONFERENCE

Date of Meeting: July 26, 2004

NDA: 21-752

Drug: Tenofovir DF/Emtricitabine

Sponsor: Gilead Sciences, Inc.

Between: Representatives of the FDA
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And: Representatives of Gilead Sciences
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Subject: Teleconference held to discuss implications of Division of Scientific Investigation's (DSI) review of Gilead's study GS-US-104-0172 (fed portion).

Background: Following completion of DSI's audit of Gilead's bioequivalence study GS-US-104-0172, the Division received the recommendation not to accept the fed portion of this study due to the absence of documentation to show that the study subjects were dosed within five minutes of completion of the meal. The inspector further commented that the study participants were instructed to save the last bite of the meal until five minutes before the administration of the study drug. Thus, most of the meal may have been consumed well before drug administration. A teleconference was scheduled with Gilead to discuss the possible impact on study results.

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Discussion:

The Division inquired as to whether Gilead received a copy of the form 483 issued to _____ where the study was conducted, and, given this recommendation, how the results support the current wording in the labeling advising that the medication can be administered with or without food.

Gilead stated that they had seen the form containing the results of the inspection and did not agree with the inspector's interpretation. The Sponsor believes that even though the subjects were instructed to save their last bite of food until five minutes before administration of the drug, the results of this study were the same as the results from the previous study and have no impact on the administration instructions in the labeling. The Sponsor also stated that it is now common practice to instruct subjects in the fed leg of these types of studies to save their last bite until five minutes prior to medication administration.

The Division stated that our interpretation of the guidance is that subjects are to eat their meal over the course of thirty minutes and not to save a bite until five minutes before taking the medication. The Division's concern is that without knowing how long it took participants to complete their meals, the effect of food may be underestimated.

Gilead stated that they understand the Division's position regarding the correct procedure for conduction of the food effect study but believes that the impact on the results do not affect the administration instructions for Truvada.

The Division requested that Gilead provide their justification for this position and following internal discussion would provide them with a decision on whether an additional study would be required.

Resolution:

Immediately following the teleconference, the Division discussed the issue internally and agreed that the impact of improper conduct of the trial was negligible and would not require the Sponsor to conduct an additional food effect study.

The Sponsor was contacted on July 27, 2004 and notified that the Division does not recommend an additional study but advised the Sponsor to consider our interpretation of the guidance in conducting future food effect studies.

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/s/

Jeff O'Neill
8/10/04 01:05:33 PM
CSO

NDA 21-752 Clinical Pharmacology telecon with Gilead 07-26-04. Hard
copy sign-off 8/10/04

Kathrine Laessig
8/11/04 10:54:06 AM
MEDICAL OFFICER

CLINICAL REVIEW

NDA 21-752

Truvada™ Tablets
Fixed-Dose Combination of Tenofovir
Disoproxil Fumarate and Emtricitabine

For: Treatment of HIV-1 Infection
in Adults

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1.0 Recommendations

1.1 Recommendation on Approvability

Based on review of the materials submitted in this NDA, it is recommended that the fixed dose combination (FDC) of Viread® (tenofovir disoproxil fumarate, TDF) and Emtriva® (emtricitabine, FTC) known as Truvada™ Tablets receive accelerated approval.

Truvada™ was granted “priority review” because FDA believes that where adequate evidence of safety and efficacy already exists for the use of certain individually approved HIV drugs in combination, the path to regulatory approval of a[n] FDC or co-packaged product is straightforward. FDA is prepared to move swiftly to evaluate such products when applications for them are submitted for approval. The approval recommendation is based on the demonstration of bioequivalence between tenofovir disoproxil fumarate and emtricitabine when administered separately and together (see 21 CFR 320.25(g)), safety data for the combination, and extrapolated efficacy data from a drug with substantial similarities to Emtriva.

Efficacy from completed studies in which FTC/TDF have been administered to HIV-1 infected adults are not available. FTC and currently marketed lamivudine (3TC) share a number of structural and functional similarities (e.g., both are cytosine analogues, and they share common resistance and safety profiles). Data from a study in which TDF was co-administered with 3TC and from a study in which FTC and 3TC were compared suggest similar efficacy between FTC and 3TC. Based on these findings, the Division was willing to extrapolate data from 3TC to FTC. However, since FTC/TDF studies are ongoing, there are no data to confirm that the extrapolation is valid. Therefore, pending the results of ongoing studies in treatment naïve patients, it will be recommended that Truvada Tablets be used as an alternate for patients who might require a once daily regimen.

Interim safety and resistance data on the co-administration of FTC and TDF to treatment naïve HIV-1 infected adults who received TDF/FTC were requested by FDA. Safety data reviewed in this application suggested no apparent new adverse events or increases in the frequency or severity of adverse events over those that are known to occur with each individual product.

Resistance to FTC occurs quickly and is manifested by the emergence of the M184V/I mutation. Resistance to TDF appears to emerge slower, but the TDF-related K65R mutation results in loss of susceptibility to not only TDF but potentially most nucleoside reverse transcriptase inhibitors (NRTIs). Finally, emerging clinical trials data suggest that TDF/FTC should not be used as a component of a triple NRTI regimen because of higher rates of virologic failure.

Viread® is currently approved under subpart H and confirmatory trials are ongoing; therefore, it is necessary to extend accelerated approval to Truvada Tablets as it would not be appropriate to grant a traditional approval to a fixed-dose combination while one component is approved under a more restrictive regulation.

1.2 Recommendation on Phase 4 Studies and/or Risk Management Steps

A patient package insert for Truvada™ Tablets will be distributed with each prescription.

The following post-marketing commitments were agreed to by the applicant:

1. The applicant will provide 48-week efficacy, safety and resistance data from completed studies (GS-03-934 and Abbott M02-418) in which TDF and FTC were or are being administered in combination or as Truvada Tablets.

Completion = two years from NDA approval date.

2. The applicant will evaluate the use of Truvada Tablets in patients with significant renal impairment, defined as CrCl <30 mL/min.

Completion time = fifteen months from NDA approval date.

3. The applicant will conduct a stability study on alternate trade dress (light blue) emtricitabine/tenofovir DF tablets under long-term conditions (30°C/65% RH) as well as accelerated conditions (40°C/75% RH) and submit the data in the next annual report.

Completion time = fifteen months from NDA approval date.

In addition to the above Phase IV commitments, for seeking approval of alternate trade dress (light blue) emtricitabine/tenofovir DF tablets for marketing in Climactic Zone III and IV countries, in addition to the usual stability studies under long-term (30°C/65% RH) and accelerated conditions (40°C/75% RH), the applicant will conduct a stress stability study on one batch of tablets that are stored for three months at 50°C/ambient humidity and at 25°C/80% RH conditions as recommended in the FDA Guidance for Industry document entitled *Q1F Stability Data Package for Registration Applications in Climatic Zones III and IV (June 2004)*.

2.0 Summary of Clinical Findings

2.1 Overview of Clinical Program

Emtriva® (emtricitabine, FTC) Capsules are approved for use in combination with other antiretroviral agents to treat HIV-1 infection in patients >18 years of age (NDA 21-500). The approval was based on the demonstration of antiviral and immunologic activity in HIV-1 infected patients who received FTC-containing regimens for 48 weeks.

Accelerated approval was granted for Viread® (tenofovir disoproxil fumarate, TDF) Tablets for use in combination with other antiretroviral agents to treat HIV-1 infection in patients >18 years of age based on evidence of the antiviral activity of TDF when added to a stable background regimen for 24-48 weeks (NDA 21-356).

The current application includes the following data:

- Results from two human Biopharmaceutics studies demonstrating bioequivalence between TDF and FTC following administration of each drug separately and as a FDC.
- Summary safety and resistance data from ongoing clinical studies sponsored by the applicant (Study GS-01-934) and Abbott Laboratories (Study M02-418), in which TDF and FTC are being co-administered as individual agents or as a fixed-dose combination.
- Long-term (144-week) safety data was submitted from an ongoing study in which TDF and lamivudine (3TC, Epivir®) are being co-administered (Study GS-99-903); lamivudine and emtricitabine are similar in structure, clinical antiviral activity and safety profiles; therefore, the Division agreed to consider efficacy and safety data from TDF/3TC to be extrapolated to TDF/FTC.
- Post marketing-safety data for each product.

2.2 State of Armamentarium for Indication

There are currently 21 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 8 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). Additional classes of antiretroviral agents include the non-nucleoside reverse transcriptase inhibitors (NNRTI), including delavirdine (Rescriptor®), nevirapine (Viramune®), and efavirenz (Sustiva®), and the protease inhibitors (PI), represented by indinavir (Crixivan®), ritonavir (Norvir®), saquinavir (Invirase® and Fortovase®), nelfinavir (Viracept®), amprenavir (Agenerase®), fosamprenavir (Lexiva®), atazanavir (Reyataz®), and lopinavir/ritonavir fixed dose combination (Kaletra®). The first drug in a new class of GP41 fusion inhibitors, enfuvirtide (Fuzeon®), was approved in early 2003.

The current standard is to treat 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 to achieve 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, and adherence issues such as dosing, pill burden, and complex dietary requirements have been cited as dilemmas facing patients and clinicians.

There has been much interest in the possibility that simplification of regimens might improve tolerability and adherence and increase the feasibility of long-term effective control of disease. Although there are no compliance data available, one Truvada Tablet provides two important components of multi-drug antiretroviral therapy that could have utility as an option for clinicians to consider when designing more simplified HAART regimens.

Emtriva is a cytosine NRTI with the same chemical structure as lamivudine (3TC) except for a fluoride residue at position 5 on the pyrimidine ring. In cells, emtricitabine is phosphorylated to a 5'-triphosphate (FTC-TP) much the same way as 3TC is phosphorylated to its active triphosphate (3TC-TP). Both agents are approved for once daily administration, and FTC and 3TC share a common resistance profile. In comparative clinical studies, Emtriva demonstrated similar efficacy and safety as 3TC (see NDA 21,500 study FTC-303). Therefore, at the time the Emtriva NDA was submitted, the Division determined that Emtriva did not appear to offer any significant advantages over the already marketed Epivir, so the application was granted traditional approval and reviewed on a standard review timeline (10 months).

Based on the aforementioned characteristics of FTC and 3TC, the Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents developed by the panel on Clinical Practices for Treatment of HIV Infection convened by the Department of Health and Human Services (DHHS) state that FTC may be used as an alternative to lamivudine as a component of HAART therapy.

21 CFR 300.50 describes FDA's policy for the approval of fixed combination prescription drugs for humans. The rule states in pertinent part, "Two or more drugs may be combined in a single dosage form when each component makes a contribution to the claimed effects and the dosage of each component (amount, frequency, duration) is such that the combination is safe and effective for a significant patient population requiring such concurrent therapy as defined in the labeling for the drug." 21 CFR 300.50(a). This has been interpreted to require a factorial analysis of proposed combination ingredients that demonstrates that the combination is more effective than each component of the combination alone. For HIV drugs, however, it would not be feasible, or ethical, to study the efficacy of an FDC in a clinical study with a factorial design in which the entire combination would be compared to its individual components. This type of study design would require HIV-infected individuals to be exposed to suboptimal regimens that could quickly result in drug resistance not only to the drug or drugs under study, but in many cases to other antiretroviral drugs from within the same class. Suboptimal therapy may jeopardize the success of future therapeutic options for those patients exposed to single or dual antiretroviral treatment due to the emergence of resistance and the potential for cross-resistance.

Efficacy data from completed studies in which FTC/TDF have been administered are not available. Based on similarities between FTC and 3TC as outlined above, as well as data from a study in which TDF was co-administered with 3TC (Study GS-99-903), it was deemed that this application did not require complete study data of the FDC upon which to render a regulatory decision. However, data from study GS-01-934, in which patients are receiving TDF/FTC will be submitted to support the traditional approval of TDF, and those data will provide evidence of the safety and efficacy of the combination contained in Truvada Tablets.

2.3 Chemistry, Manufacturing and Controls

Truvada™ Tablets will be supplied as size blue capsule-shaped, film-coated tablets with “701” embossed on one side “GILEAD” on the other. The daily recommended dose is one tablet one time per day. The composition of Truvada is provided in Table 1.

Table 1. Composition of Truvada™ Tablets

Component	Quantity per Tablet
Tenofovir dipovoxil fumarate	300 mg
Emtricitabine	200 mg
Croscarmellose sodium	
Microcrystalline cellulose, NF	
Lactose monohydrate, NF	
Pregelatinized starch, NF	
Magnesium stearate, NF	
Purified water, USP	As needed
Core Tablet Weight	1000 mg

Source: Truvada™ Tablets Application Summary, Section 2.3.P.

Truvada Tablets will be packaged in — high density polyethylene (HDPE) bottle with a child-resistant screw cap; each bottle will contain 30 tablets. Bottle can be stored at room temperature: 25°C [77°F], with excursions permitted to 15-30°C [59-86°C].

The applicant submitted an amendment to provide for an alternative trade dress for export outside the United States. The differences between the export and US dress are that the export is a slightly different blue color (lighter) and can be stored up to 30° C. For marketing of the alternative trade dress in Zone III and IV countries, in addition to the usual stability studies under long-term (30°C/65% RH) and accelerated conditions (40°C/75% RH), a stress stability study on one batch of tablets that are stored for three months at 50°C/ambient humidity and at 25°C/80% RH conditions as recommended in the FDA Guidance for Industry document entitled *Q1F Stability Data Package for Registration Applications in Climatic Zones III and IV (June 2004)* is necessary.

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

2.4 Summary of Human Pharmacology

2.4.1 Steady-State Pharmacokinetics

Study FTC-114 was a phase 1 study conducted to evaluate the steady-state pharmacokinetics of FTC and TDF administered alone and in combination in healthy volunteers. Nineteen otherwise healthy male and female volunteers were randomized to receive each of three treatments for seven days with no washout period between treatments (21 days total). The treatments included: FTC 200 mg once daily, TDF 300 mg once daily, and FTC 200mg with TDF 300 mg once daily.

The results demonstrated that TDF had no clinically significant effect on the pharmacokinetics of FTC, and vice versa.

2.4.2 Bioequivalence and Food Effect

Study GS-US-104-172 was a phase 1 pharmacokinetic study conducted in healthy volunteers to evaluate the bioequivalence of the combined TDF/FTC tablet to concomitant TDF and FTC, as well as the effect of food on pharmacokinetics. In this study, 44 otherwise healthy male and female volunteers received single doses of the combination TDF/FTC tablet and TDF and FTC administered concurrently in the fasted state and following low fat and high fat meals.

- **Bioequivalence**

The data demonstrate that bioequivalence was achieved based on similar tenofovir exposure and half-life following administration of the combination TDF/FTC tablet and TDF. Likewise bioequivalence was achieved between the combination TDF/FTC tablet and FTC.

- **Food Effect**

The results of study GS-104-172 demonstrated that Truvada Tablets can be administered without regard to food intake. Administration of the TDF/FTC combination tablet with a high-fat or low-fat meal led to increased tenofovir T_{max} , 16% and 13.5%, respectively, compared to administration in the fasted state. Tenofovir AUC was similarly increased following a high-fat or low-fat meal, 35% or 34%, compared with the fasted state. The pharmacokinetics of FTC was unchanged.

3.0 Integrated Summary of Efficacy

The NDA contained interim efficacy data from two ongoing studies, GS-01-934 and Abbott M02-418. Since the studies have not been completed and data sets were not available for review, it was not possible to assess the efficacy of antiretroviral combinations in which FTC and TDF are being co-administered. The ongoing studies are investigating use of FTC/TDF in treatment naïve patients; therefore, there are no data on response to treatment in antiretroviral therapy experienced patients.

Study GS-01-934 is an ongoing phase 3 study comparing the safety and efficacy of Truvada™ Tablets to Combivir® (FDC of 3TC/ZDV, GlaxoSmithKline) in combination with efavirenz in treatment naïve adults. This study was initiated to provide long-term efficacy data to support traditional approval of TDF. The study has fully enrolled 500 patients, but data is only available on a proportion who have completed 16 weeks of treatment (n=188).

Study M02-418, conducted by Abbott Laboratories, was a phase 3 study comparing the safety and efficacy of Kaletra® (FDC lopinavir 800 mg/ritonavir 200 mg) QD versus BID in combination with TDF and FTC in treatment naïve adults. Treatment was for 48 weeks. A total of 190 patients were enrolled. The study is complete and has been submitted by Abbott to the

Kaletra NDA. According to the sponsor's analysis, both treatment arms produced similar proportions of patients with HIV-1 RNA <50 c/mL through week 48, approximately 70%.

Previously, 48-week efficacy data from ongoing study GS-99-903 in which TDF/3TC/EFV is being compared to d4T/3TC/EFV in treatment naïve patients have been submitted and reviewed in NDA 21-356. The antiviral and immunologic activity of the two regimens was similar. In addition, efficacy data reviewed in NDA 21-500 for Emtriva® demonstrated similar antiviral and immunologic activity in patients who were randomized to either remain on a 3TC-containing regimen or switch to FTC.

Based on interim data from study GS-01-934, and recently submitted but not reviewed data from study Abbott M02-418, it is not possible to reach a conclusion about the antiviral or immunologic activity for the combination of TDF and FTC. The applicant has committed to submit 48-week efficacy data from studies M02-418 and GS-01-934 for review at which time specific statistical analyses will be conducted to determine the extent of efficacy conveyed by TDF/FTC in combination with other antiretroviral agents. Given the similarities between FTC and 3TC, the 48-week data from study GS-99-903 suggest that exchanging these agents in a regimen with TDF and either a PI or NNRTI would not likely lead to a detrimental efficacy outcome. Until such time as data from TDF/FTC studies are completed, submitted and reviewed, the Truvada™ Tablets label will carry a statement about the lack of efficacy information for the combination of TDF and FTC, but will describe similarities between FTC and 3TC and that the efficacy of the combination of TDF/3TC is expected to be similar to that of Truvada.

4.0 Integrated Summary of Safety

4.1 Brief Statement of Conclusions

Because patients in HIV studies receive multiple drugs that cause adverse events, it is often difficult to tease out the specific adverse events related to the drug of interest. In the case of TDF and FTC, however, the safety review benefits from the availability of adverse events from numerous studies in which the products have been administered to healthy volunteers and HIV-1-infected patients. Both Emtriva™ and Viread® are approved products with well characterized safety profiles. From the data reviewed in this NDA, there does not appear to be an increase in the frequency or severity of adverse events known to occur with each product, as listed in the respective package inserts.

In summary, both agents have well defined and somewhat overlapping adverse event profiles. Based on the limited non-validated summary safety data reviewed in this application, there do not appear to be any signals for new adverse events when FTC and TDF or TDF and 3TC are co-administered (as a surrogate for FTC), or for increased frequency or severity of known adverse events for the individual drugs.

The long-term safety data from study GS-99-903 suggests that over time more patients experience bone demineralization on a TDF containing regimen compared to a stavudine containing regimen, but there was no apparent increase in fractures compared to the control regimen. The duration of the two controlled studies (GS-01-934 and M02-418) were too short to

confirm the findings of study GS-99-903; the applicant will continue to monitor for such toxicities in clinical studies and in post-marketing surveillance.

Abnormalities of renal toxicity (defined as increased creatinine and/or decreased phosphorous) were reported infrequently among patients in studies Abbott M02-418 and GS-01-934; but the number of patients was relatively small and the duration was short, 24-48 weeks. Preliminary review of long-term data from study GS-99-903 suggests no substantial increase in renal toxicity following 144 weeks of exposure to TDF. Until such time as these findings can be confirmed, and the TDF labeling changed to reduce the precautions related to renal toxicity, patients who receive TDF and FTC should continue to be diligently followed for emergence of renal toxicity.

The labeling for each agent contains a boxed warnings related to nucleoside-related toxicities (i.e., hepatotoxicity, lactic acidosis, rash), and post-treatment exacerbation of hepatitis noted in patients with hepatitis B virus infection who discontinue antiviral therapy. These warnings will be included in the Truvada Tablets label. In addition, wording regarding the potential for bone toxicity and long-term renal abnormalities will be retained in the Truvada Tablets label.

4.2 Description of Patient Exposure

The safety data base consists of information on the following:

- Adverse clinical and laboratory events among 62 healthy volunteer subjects in single and multiple dose clinical pharmacology studies (studies GS-US-104-172 and FTC-114).
- Deaths, serious adverse events, adverse events which led to study drug discontinuation, moderate and severe adverse events and laboratory abnormalities for 190 HIV-1-infected patients who received TDF/FTC in combination with Kaletra for 48 weeks in Abbott study M02-418.
- Deaths, serious adverse events, adverse events which led to study drug discontinuation, selected hepatic and renal laboratory parameters and the incidence of bone fractures and hyperpigmentation for 93 HIV-1 infected patients who received TDF/FTC/EFV for 24 weeks in study GS-01-934 (data cut off April 24, 2004).
- Deaths, serious adverse events, adverse events which led to study drug discontinuation, selected hepatic and renal laboratory parameters and the incidence of bone fractures and hyperpigmentation for 299 HIV-1 infected patients who received TDF/3TC/EFV for 144 weeks in study GS-99-903 (data cut off April 24, 2004).
- Post-marketing surveillance safety data.

Of note, information from studies GS-99-903, GS-934-01, and M02-418 are summaries of unaudited safety data.

4.3 General Adverse Events

- **FTC**

Common adverse events listed in the Emtriva label include headache, diarrhea, nausea and rash. Other events listed include abdominal pain, asthenia, malaise, pain, dyspepsia, vomiting, neuropathy, arthralgia, myalgia, dizziness, insomnia, paresthesia, increased cough, pharyngitis, rhinitis, pruritis, skin discoloration (primarily in non-Caucasians), and depressive disorders. Significant (Grade 3 and 4) increases in AST and ALT levels, increased triglycerides, and neutropenia, have previously been reported to occur in approximately 10% of FTC-treated patients.

Skin discoloration was reported to occur in 13% (176/1348) of patients in the Emtriva™ registration studies, and was described as hyperpigmentation on the palms and soles predominantly occurring in black patients. The mechanism and clinical significance of skin discoloration remain unknown, and the Emtriva labeling includes this information. The applicant is evaluating the nature of these lesions as part of a post-marketing commitment.

- **TDF**

As described in the Viread label, the most common clinical and laboratory adverse events reported among patients receiving TDF include nausea, diarrhea, flatulence, and dizziness. Other events listed in the labeling include asthenia, headache, abdominal pain, anorexia, and mild elevations of triglycerides, creatine kinase, and ALT/AST levels.

A long term safety concern is the potential for bone abnormalities, defined as decreased bone mineral content and density. A mechanism for bone toxicity has not yet been established

Tenofovir is primarily eliminated via the kidney. Based on preclinical and clinical data TDF should not be administered to patients with renal insufficiency until further data becomes available. Also the label includes a statement that co-administration of tenofovir with drugs that decrease or compete for renal clearance may increase serum concentrations of tenofovir (see **Special Populations: Renal Impairment**).

- **Combination TDF and FTC**

The following section summarizes safety data from completed human pharmacology and ongoing clinical studies.

In the two clinical pharmacology studies conducted in healthy volunteers, the most common adverse events reported included nausea, vomiting, diarrhea, flatulence, abdominal pain, headache and somnolence. One case of maculopapular rash was reported that led to study discontinuation; the rash resolved one week later. There was no substantial increase in the frequency of adverse events when FTC and TDF were administered together.

In Abbott M02-418, no deaths were reported. Serious adverse events were twice as common in the BID compared to the QD arm (15% versus 5%); however, there was no specific pattern of events in either arm. Discontinuations due to adverse events were similar between arms; more patients discontinued from the QD arm for diarrhea and nausea than from the BID arm (10 versus 0). General adverse events reported in >5% of patients included diarrhea, nausea and vomiting. Diarrhea occurred in 16% of QD patients and 5% of BID patients. The higher frequency of diarrhea in the QD arm was likely due to the higher single dose of ritonavir and the increased burden of excipients administered in the QD dose. Grade 3 and 4 laboratory abnormalities included elevated AST and ALT levels, increased triglycerides, increased cholesterol, glucose, and amylase levels. The frequency of each abnormality was generally <5%, and occurred with similar frequency between the QD and BID arms.

In study GS-01-934 no deaths have occurred, three patients have experienced serious adverse events (retractable hiccups, appendicitis, and non-Hodgkin lymphoma), and two of these patients discontinued study medications due to their adverse events. One case of skin hyperpigmentation was reported on the knuckles of both hands, palmar side of fingers, shin of both legs and soles of both feet, 24 weeks after starting study medications; the patient continues to be on study medications and the skin lesions are being monitored. No Grade 3 or 4 laboratory abnormalities have thus far been reported. One patient experienced a traumatic rib fracture; otherwise no bone-related events have been reported. Five patients have experienced Grade 1 or 2 increases in urine protein and decreased phosphorous; however, no clinical renal events were reported. Similarly, few patients experienced Grade 1 or 2 elevations in AST/ALT; again, no hepatic-related clinical events were reported.

In study GS-99-903, five patients in the TDF/3TC/EFV arm have died; the causes of death appear related to advanced HIV disease rather than drug induced toxicity. Overall 81/299 patients experienced Grade 3 or 4 adverse events. Events that occurred in at least 2% of patients included bacterial infection, rash, depression, fever, pneumonia, and fracture. Serious adverse events were reported by 50 patients; of which four appeared related to study drugs: anemia, peripheral neuritis, bronchitis and gynecomastia. Other events were consistent with the known adverse events profiles of the agents in the regimen and advanced HIV disease. Discontinuations due to adverse clinical events or laboratory abnormalities have been relatively low, 6% and 2%, respectively. Grade 3 and 4 laboratory abnormalities include increased amylase, creatine kinase, AST and ALT, and triglyceride levels, decreased neutrophil counts, and hematuria. Overall, these findings were comparable to those reported by patients the control group receiving d4T/3TC/EFV.

With respect to bone abnormalities, in study GS-99-903 five patients in the TDF treatment arm experienced fractures compared to 11 in the control arm; all five fractures in the TDF arm were determined to be due to trauma. Mean change from baseline in bone mineral density, however, is higher among patients receiving the TDF-based regimen; -2.2 ± 3.9 versus -1.0 ± 4.6 in the control arm ($p < 0.001$).

Renal toxicity does not appear to increase as duration of exposure to TDF increases. Specifically, through week 144, Grade 2 or greater increases in creatinine 1%, glycosuria 2%, proteinuria 6%, and Grade 2 or greater decreases in phosphorous of 1%, have been reported.

Post-marketing data summarizing adverse events reported to the applicant since Viread's approval, October 31, 2001, and December 31, 2003, was reviewed. Of the 570 reports submitted, 230 were reports of events related to the renal/urinary system. Specifically, there were 49 cases of increased creatinine, 16 cases of hypophosphatemia, 42 cases of renal insufficiency, 51 cases of acute renal failure, 6 cases of chronic renal failure, and 32 cases of Fanconi's syndrome. The timing of events varied greatly between one day and over one year of exposure. In some cases, symptoms abated following cessation of TDF, but in most cases the outcome of the event(s) was unknown. Based on the limited data provided for each case, it was not possible to rule out TDF's contribution to these events. Therefore, the Truvada Tablet labeling will carry the same precautions about long-term monitoring of renal function as described in the Viread label.

Emtriva has only been approved since July 2003; therefore, very few postmarketing reports have been generated. Review of these few cases did not reveal any new patterns of adverse events that could be considered reasonably associated with the use of the product.

4.4 Resistance

At the Pre-NDA meeting, the applicant agreed to submit data related to resistance (primarily related to K65R mutation) from ongoing studies GS-01-934 and Abbott M02-418, as well as long-term data from study GS-99-903.

Resistance to emtricitabine emerges rapidly both *in vitro* (within three few passages) and *in vivo* within a few weeks of monotherapy. The pattern of resistance is typically manifested by a change at codon 184 of the reverse transcriptase with methionine being substituted with valine or isoleucine (M184V/I). Resistance to tenofovir occurs slower and is mediated by the emergence of the K65R mutation. In addition, it appears that the K65R mutation also conveys decreased susceptibility to most NRTIs (e.g., produces cross resistance).

Results of a 5 day *in vitro* combination activity study demonstrates that the antiviral effect of the combination is synergistic. In >5 day studies the FTC-directed M184 mutation in reverse transcriptase appears with loss of susceptibility to FTC and only TDF is active. Over time, the TDF-directed K65 mutation in reverse transcriptase appears with loss of susceptibility to TDF and FTC and all other NRTIs (except perhaps AZT) and NNRTIs.

In summary, the mutations conveying resistance to FTC and TDF are well characterized. Truvada Tablets will be used in regimens with at least one other potent agent preferably from a different class of antiretroviral agents (e.g., an NNRTI or PI). If resistance to FTC emerges, which occurs rapidly, TDF and other agent(s) would potentially be sufficiently potent to compensate for the loss of FTC. If however, the K65R mutation emerges, resistance to both FTC and TDF will occur; thus, leaving the patient on essentially monotherapy, and reduce the options for use of other NRTIs. Therefore, the labeling will include statements related to the potential for the occurrence of the K65R mutation and the potential for cross-resistance to other NRTIs.

Finally, the efficacy of triple NRTI regimens has been studied in which TDF and 3TC were components. Unfortunately, these regimens were not sufficiently efficacious to support a recommendation that they be routinely used. The label will recommend that Truvada Tablets not be used as a component of a triple NRTI regimen.

5.0 Dosing

The adult dose of Truvada™ Tablets is one capsule daily administered without regard to food intake. The dose is based on the currently approved doses of TDF (300 mg QD) and FTC (200 mg QD) and is supported by pharmacokinetic data demonstrating bioequivalence between FTC and TDF given separately and together in a fixed-dose combination.

The doses of TDF and FTC were established in their respective development programs and approved in each product's NDA. Studies to support the approval of Truvada Tablets demonstrated bioequivalence between administration of TDF and FTC as individual drugs and as a fixed-dose combination, with no impact on the pharmacokinetics of either product in either the fed or fasted state.

Patients with CrCl <30 mL/min and those on hemodialysis should not receive Truvada™ Tablets (see **Special Populations: Renal Impairment**).

6.0 Special Populations

6.1 Renal Impairment

- **FTC**

Urinary excretion is the primary mode of elimination of emtricitabine, and as creatinine clearance decreases emtricitabine exposures increase. Emtriva™ is dialyzable and hemodialysis removes approximately 30% of an emtricitabine dose over a 3-hour dialysis period starting within 1.5 hours of emtricitabine dosing. It is not known whether emtricitabine can be removed by peritoneal dialysis. These findings supported Emtriva dosing based on creatinine clearance (CrCl): 200 mg every 24 hours for CrCl \geq 50 mL/min, 200 mg every 48 hours for CrCl 30-49 mL/min, 200 mg every 72 hours for CrCl 15-29 mL/min, and for patients with CrCl <15 mL/min and those requiring hemodialysis, 200 mg every 96 hours. On hemodialysis days, Emtriva should be administered following the dialysis procedure.

- **TDF**

Tenofovir is principally eliminated via the kidney and no studies have been conducted in patients with creatinine clearance <30 mL/min. Preclinical studies demonstrated renal toxicities (renal tubular toxicity, interstitial nephritis, increased creatinine, BUN, glycosuria, proteinuria, phosphaturia, calciuria, and Fanconi-like syndrome) in various animal species. Studies in patients with renal insufficiency yielded the following recommendations based on CrCl: 300 mg every 24 hours for CrCl \geq 50 mL/min, 300 mg every 48 hours for CrCl 30-49 mL/min, and 300 mg twice per week for CrCl 15-29 mL/min. For patients requiring hemodialysis, the recommendation is 300 mg every seven days after 12 hours of dialysis.

- **Combination of TDF and FTC**

In Study GS-99-903, in which TDF is being co-administered with lamivudine, after 144 weeks of treatment approximately 5% (13/296) of patients have had episodes of Cr \geq 1.5 mg/dL and 7% (22/296) have had phosphorous levels $<$ 2.2 mg/dL at some point.

Five patients in study GS-934-01 have experienced Grade 1 or 2 increases in urine protein and decreased phosphorous; however, no clinical renal events were reported. In Abbott M02-481, three patients experienced Cr $>$ 1.5 mg/dL; two of whom experienced acute renal failure. One patient had diabetic nephropathy and the other had acute tubulointerstitial nephritis. After study drug discontinuation, Cr returned to $<$ 1.7 gm/dL in both patients.

No new data on the use of FTC or TDF in patients with renal insufficiency were submitted in this NDA. For patients with CrCl \geq 30 mL/min, the dosing recommendations are consistent and would support concomitant use of the two agents. However, once the CrCl is $<$ 30 mL/min, the recommendations diverge with TDF requiring a longer time span between dosing. Therefore, as proposed by the applicant, Truvada™ Tablets are not recommended for use in patients with CrCl $<$ 30 ml/min or those receiving hemodialysis.

In summary, no conclusions about long term renal safety of the combination of TDF/FTC can yet be reached. Patients should continue to be diligently monitored during treatment with Truvada Tablets.

6.2 Pediatric Use

Clinical trials of both drugs to determine appropriate doses, safety and efficacy in pediatric patients are ongoing. There are no data on the use of Truvada Tablets in pediatric patients. The applicant requested a waiver based on the arguments that the individual products are currently under study in pediatric patients, and it is not possible to modify Truvada Tablets to accommodate weight-based dosing. In younger pediatric patients the argument that Truvada Tablets cannot be manipulated to provide weight-based dosing is legitimate. In adolescents, however, who may weigh close to their adult counterparts, it may be possible to dose Truvada Tablets at its full strength, which could translate into improved adherence. Therefore, a deferral of pediatric studies was issued and the need for additional studies in this population will be revisited once appropriate doses of TDF and FTC in pediatric patients have been determined.

6.3 Use During Pregnancy

Both FTC and TDF are classified as Pregnancy Category B. Therefore, Truvada™ Tablets will receive the same classification with the recommendation that it should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

7.0 Labeling Review

The applicant's proposed label included information culled from the Emtriva and Viread labels with the inclusion of the data demonstrating bioequivalence between the each drug compared to when they are administered as a FDC. The following revisions were made to the Truvada label:

- The Indication and Usage was revised to provide guidance to clinicians about potential uncertainties associated with Truvada Tablets. This section reads:

“Truvada is indicated in combination with other antiretroviral agents (such as non-nucleoside reverse transcriptase inhibitors or protease inhibitors) for the treatment of HIV-1 infection in adults. Safety and efficacy studies using Truvada tablets or using VIREAD and EMTRIVA in combination are ongoing.

Both components of TRUVADA have been studied individually, as part of multidrug regimens and have been found to be safe and effective. Since EMTRIVA and lamivudine (3TC) are comparable in their structure, resistance profiles, and efficacy and safety as part of multidrug regimens, existing data from the use of lamivudine and tenofovir in combination have been extrapolated to support use of TRUVADA Tablets for the treatment of HIV-1 infection in adults (see **Description of Clinical Studies and Adverse Events**). Therefore, in treatment naïve patients, TRUVADA should be considered as an alternative to a regimen of VIREAD and EPIVIR for those patients who might benefit from a once-daily regimen. In treatment experienced patients, the use of TRUVADA should be guided by laboratory testing and treatment history (see **Microbiology**).

Additional important information regarding the use of TRUVADA for the treatment of HIV-1 infection:

- There are no study results demonstrating the effect of TRUVADA on clinical progression of HIV-1.
- It is not recommended that TRUVADA be used as a component of a triple nucleoside regimen.
- In Clinical Studies, the description of studies GS-99-907 and FTC-301A from the Emtriva and Viread labels were deleted as they presented data on regimens and populations not applicable to the use of Truvada. The descriptions of studies GS-99-903 and FTC-303 were retained as they provide data suggesting the similarity between FTC and 3TC with respect to efficacy.
- In Adverse Reactions, the applicant provided separate tables depicting adverse events for each product. The tables were deleted and replaced with text describing each product's common adverse events and laboratory abnormalities with a statement that the type, frequency, and severity of these events do not appear increased when FTC and TDF are co-administered as part of a multi-drug regimen.
- The applicants' proposal that Truvada Tablets are not recommended for use in patients with CrCl <30 ml/min or those receiving hemodialysis was acceptable.

8.0 Conclusions and Recommendation

8.1 Conclusions

The pharmacokinetic and safety data support co-administration of emtricitabine and tenofovir as the fixed-dose combination to be called Truvada™ Tablets as a component of a multi-drug antiretroviral regimen. Pharmacokinetics data demonstrate bioequivalence between TDF/FTC

administered either as individual agents or as a fixed-dose combination. The CMC data demonstrate that the applicant can consistently manufacture Truvada Tablets; and the stability data support 24 months expiry. Safety data on the combination suggests no apparent increase in the types, frequency or severity of toxicities known to be related to each individual product as listed in their respective labels. Preliminary efficacy data suggests that the combination of TDF/FTC, in combination with non-nucleoside reverse transcriptase inhibitors or protease inhibitors is likely to provide antiviral and immunological activity comparative to similar currently approved regimens; final assessment of efficacy will be based on review of completed studies.

Resistance to FTC occurs quickly and is manifested by the emergence of the M184V/I mutation. Resistance to TDF appears to emerge slower, but the TDF-related K65R mutation results in loss of susceptibility to not only TDF but all nucleoside reverse transcriptase inhibitors (NRTIs). Overall, these data suggest that the TDF/FTC combination may have a low genetic barrier for the emergence of mutations that can lead to virologic failure. Finally, emerging clinical trials data suggest that TDF/FTC should not be used as a component of a triple NRTI regimen because of higher rates of virologic failure.

8.2 Recommendation

Based on the review of the safety and pharmacokinetic data submitted in NDA 21-752, this reviewer recommends, from a clinical perspective, that Truvada™ Tablets be approved for use in HIV-1 infected adults as a component of multi-drug regimens containing at least one drug from another class of antiretroviral agents.

Because tenofovir disoproxil fumarate (Viread®) is currently approved under subpart H and confirmatory trials are ongoing, it is necessary to extend accelerated approval to Truvada Tablets as it would not be appropriate to grant traditional approval to Truvada™ Tablets while one component of the tablet is approved under a restrictive regulation.

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/s/

Russell Fleischer
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Kathrine Laessig
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Debra Birnkrant
8/2/04 11:46:15 AM
MEDICAL OFFICER

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

DATE: 07/20/04

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

TO: Division File

SUBJECT: Group Leader Memo for NDA 21-752 SN 000 TRUVADA™ tablets
(emtricitabine 200 mg/tenofovir disoproxil fumarate 300 mg fixed
dose combination)

1.0 Background

TRUVADA is the tradename for emtricitabine (FTC) 200 mg/tenofovir disoproxil fumarate (TDF) 300 mg fixed dose combination tablets. The individual components, TDF, tradename VIREAD™, and FTC, tradename EMTRIVA™, have previously been granted accelerated and traditional approval, respectively. Both components are indicated for the treatment of HIV-1 infection in adults, in combination with other antiretroviral therapy. All products are marketed by the innovator, Gilead Sciences, Inc.

Subsequent to the filing of this marketing application in March 2004, the Division of Antiviral Drug Products drafted guidance for industry entitled, "Fixed Dose Combination and Co-packaged Drug Products for Treatment of HIV." In general, this application conforms to the specifications required for marketing approval, as outlined in the draft guidance. Safety and efficacy data exist for both components individually, and although clinical trials using TDF and FTC are still ongoing at this time, efficacy results from studies using TDF and lamivudine (3TC), an approved product with many similarities to FTC, are being extrapolated to support the use of the TDF/FTC combination.

2.0 Summary of Study Results

The bioequivalence of the TDF/FTC FDC to the individual components has been demonstrated in 2 studies, GS-US-104-172 and FTC-114. The results of these studies demonstrate comparable pharmacokinetic exposures for the FDC and the individual components, FTC and TDF, as well as the absence of an interaction between the 2 components, or a food effect.

As noted above, clinical trials using the combination of TDF and FTC are currently being conducted, and are not available at the time of this review. However, clinical trial data from Gilead Sciences study 903, which evaluated the efficacy and safety of TDF and 3TC in combination with efavirenz, have previously been reviewed and demonstrate the safety and efficacy of the combination. FTC and 3TC have many features in common, as both are cytidine analogs, select for the M184I/V mutation, and have similar tolerability and activity profiles, as demonstrated in Gilead Sciences study 301 which was submitted in support of the marketing approval of FTC. Therefore, results of study 903 can be extrapolated to TDF/FTC.

Gilead is sponsoring a 500 patient, phase 3 trial that will compare the safety and efficacy of the FTC/TDF FDC to that of the AZT/3TC FDC (Combivir™, marketed by GlaxoSmithKline), both in combination with efavirenz. This study, 934, will be submitted in support of the traditional approval of tenofovir. An additional study being sponsored by Abbott Laboratories study M02-418 examines the safety and efficacy of the FTC/TDF FDC combined with either bid or qd lopinavir/ritonavir (Kaletra™). The applicant has provided a summary of the M02-418 final study results. Although the nucleoside backbone of TDF/FTC FDC is the same in both arms, the performance of the regimens as described in the summary of results provided by the applicant, is comparable to that of historical controls of other Kaletra based regimens. The applicant has requested a letter of cross-reference from Abbott, which is pending at the time of this review.

Until study 934 is complete and the final study report has been submitted and reviewed by DAVDP, the package insert for TRUVADA will contain language explaining to providers that although data from trials using the combination of TDF and 3TC may be extrapolated to the combination of TDF and FTC, the FTC/TDF FDC may be considered an alternative to TDF and 3TC at the current time.

3.0 Summary of Safety

The safety profiles of TDF and FTC are well-established. The most common clinical and laboratory adverse events reported among patients receiving TDF include nausea, diarrhea, flatulence, and dizziness. Other events listed in the package insert include asthenia, headache, abdominal pain, anorexia, and mild elevations of triglycerides, creatine kinase, and ALT/AST levels. Common adverse events listed in the Emtriva label include headache, diarrhea, nausea and rash. Other events listed include abdominal pain, asthenia, malaise, pain, dyspepsia, vomiting, neuropathy, arthralgia, myalgia, dizziness, insomnia, paresthesia, increased cough, pharyngitis, rhinitis, pruritis, skin discoloration (primarily in non-Caucasians), and depressive disorders. Significant (Grade 3 and 4) increases in AST and ALT levels, increased triglycerides, and neutropenia, have previously been reported to occur in approximately 10% of patients receiving a combination regimen containing FTC.

Review of 16 week interim results on a subset of subjects from study 934 and summary final results from study M02-418 did not reveal any new pattern of AEs for the combination of FTC/TDF. Preliminary review of 144 week data from study 903, which used the combination of TDF and 3TC, also did not show any change in the toxicity profile. There was no increase in the rates of AEs noted in the bioequivalence studies evaluating the FDC product.

4.0 Recommendation

The results of studies 104-172 and FTC-114 establish the bioequivalence of the FDC to the individual components, TDF and FTC. Multiple similarities between FTC and 3TC allow the extrapolation of efficacy and safety results of TDF and 3TC to the combination of TDF and FTC. Lastly, preliminary results from study 934, and the summary of results of study M02-418 provide supporting evidence of safety and efficacy of the actual TDF/FTC product. Therefore, I concur with the findings of the clinical analyst review by Russell Fleischer, and recommend that this application be approved.

Katherine A. Laessig, M.D.

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this page is the manifestation of the electronic signature.**

/s/

Kathrine Laessig
8/2/04 11:40:53 AM
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