I. Recommendations

A. Recommendation on Approvability

Based on review of the materials submitted in this NDA, it is recommended that the application be approved.

This recommendation is based on a thorough review of a robust safety and efficacy database derived from multiple large clinical trials conducted in HIV infected patients. The efficacy data demonstrate that antiretroviral drug regimens including Emtriva plus two other agents are active and produce antiviral and immunologic activity, as measured by suppression of HIV-1 RNA and increases in CD4 cell counts, comparable to other triple drug regimens. Thus, Emtriva administered once daily represents an additional option for patients who might benefit from a once daily antiretroviral regimen.

B. Recommendation on Phase 4 Studies and/or Risk Management Steps

A patient package insert for Emtriva® will be distributed with each prescription.

The applicant has committed to further investigate the mechanism and clinical significance of the adverse event skin discoloration.

II. Summary of Clinical Findings

A. Brief Overview of Clinical Program

Emtriva® (emtricitabine, FTC, nee Coviracil®) is an antiviral agent intended for oral administration to treat HIV-1 in patients >18 years of age. The clinical development program for this indication consisted of two pivotal and 5 supportive studies. Throughout development more than 2500 HIV-1 infected patients have been exposed to Emtriva for more than 48 weeks at the dose proposed for approval: 200 mg QD. In addition, Emtriva has been investigated in pediatric patients with HIV-1 infection and in adults with chronic hepatitis B virus (HBV) infection.

B. Efficacy

Emtriva® is a cytosine NRTI. Emtricitabine has 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 as 3TC is phosphorylated to its active triphosphate. Since Emtriva is structurally similar to 3TC it was expected to produce similar antiviral activity and safety profile as 3TC.

The antiviral and immunologic activity of Emtriva was investigated in two large controlled studies (FTC-301A and FTC-303) and supported by several other controlled and uncontrolled studies. Across these studies, the regimens containing Emtriva were active.
Executive Summary Section

**Comparison to Epivir® (3TC, lamivudine [GlaxoSmithKline])**

Emtriva® was directly compared to 3TC in two studies. In study FTC-303, patients who had evidence of viral suppression (HIV RNA <400 c/mL) on a 3TC-containing regimen were randomized 2:1 to switch to Emtriva or remain on 3TC. At the end of the 48-week dosing period, the proportion of patients with continued suppression of HIV RNA to <400 c/mL (the primary endpoint) was 73% among patients who switched to Emtriva compared to 82% who remained on 3TC (p=0.05 for the difference). Similarly, a higher proportion of patients who remained on 3TC experienced suppression of their HIV RNA to <50 c/mL (75% versus 68%), and had corresponding increases in CD4 cell counts (+61 cells/mm³ versus +29 cells/mm³). The efficacy difference appears to have been driven by the higher rate of discontinuations from the Emtriva arm due to adverse events. Since this was an open label study and clinicians and their patients knew their treatment assignment, it is possible that they were sensitized to the occurrence of new adverse events leading to asymmetrical discontinuations from Emtriva.

FTC-302 was to serve as a pivotal study but was terminated early by the South African regulatory authorities for poor GCP adherence and multiple ethical digressions, for these reasons, DAVDP placed the study on CLINICAL HOLD. In this study, once daily Emtriva was compared directly to twice-daily 3TC among antiretroviral therapy-naïve patients. Due to communications problems between the applicant and the South Africans, the study continued and 48-week blinded data became available. Although not reviewed in detail, the overall results demonstrated less efficacy among patients treated with Emtriva than those who received 3TC. Specifically, the proportion of patients with HIV RNA <400 c/mL and <50 c/mL were 64% and 60% in the Emtriva arm and 71% and 64% in the 3TC arm, respectively. Thus, FTC-302 can be considered supportive of the overall conclusions of study FTC-303 in that there are no apparent efficacy advantages in favor of Emtriva over 3TC.

**Comparison to Zerit® (d4T, stavudine [Bristol-Myers Squibb])**

In study FTC-301A Emtriva® was directly compared to d4T on a background of didanosine (ddl) and efavirenz (EFV) in treatment naïve patients.

The regimen containing Emtriva produced better antiviral activity and safety than d4T, however, this may be related to the poor tolerability of d4T when used in combination with ddl. Similar results were observed when the combination of 3TC and zidovudine was compared to a regimen containing d4T+ddl in ACTG 384, and adds to the database of studies suggesting that the combination of d4T+ddl is no longer a preferred first line nucleoside backbone due to excessive toxicities. Further, given the results of studies FTC-302 and FTC-303, it is highly likely that if 3TC had been used in this study rather than Emtriva, similar results would have been obtained.

**Summary of Efficacy**

Despite *in vitro* data suggesting greater activity of Emtriva® compared to 3TC, there was no immunologic or antiviral advantage in favor of Emtriva over 3TC demonstrated in two clinical studies. At the time the phase 3 studies were initiated, Epivir® was approved only for twice daily
administration. Since then, Epivir has been approved for once-daily administration. Therefore, any potential advantage for Emtriva with respect to compliance due to once daily frequency of dosing is now moot. Regimens containing Emtriva either with or without d4T appear likely to be better tolerated than regimens containing d4T+ddI; a conclusion that has also been reached for regimens containing 3TC.

Finally, multi-drug regimens containing Emtriva were demonstrated to be active, thus, Emtriva represents an additional once-daily NRTI choice for clinicians and patients to consider when constructing a primary anti-HIV regimen. Emtriva unlikely has a role in patients who are doing well on a 3TC containing regimen. There are no data in more advanced patients (e.g., patients who have failed previous NRTI therapy) upon which to make a recommendation for use.

C. Safety

In HIV trials adverse event data were collected on the entire study drug regimen, which can make it difficult to specify an individual study drug as being related to a particular adverse event. However, in this case, Emtriva® has been administered as a monotherapy to patients with chronic hepatitis B virus (HBV) infection; thus, it was possible to identify certain adverse events related to Emtriva, and to assess their frequency and severity in the HIV studies.

Based on the review of the safety database, it can be concluded that Emtriva was generally well tolerated with a safety profile comparable to Epivir. The most common adverse events related to Emtriva included: headache, nausea, vomiting, diarrhea, rash, skin discoloration (primarily amongst non-Caucasians), and elevated ALT and AST.

Specific nucleoside-related toxicities (i.e., hepatotoxicity, lactic acidosis, rash) also occurred with comparable frequency and severity as 3TC. However, more patients discontinued from the d4T+ddI arm of FTC-301A due to pancreatitis and peripheral neuropathy, which likely led to the differential efficacy results.

Post treatment exacerbation of hepatitis was noted in HBV studies. Although FTC will not be indicated for HBV, a number of HIV infected patients are co-infected with HBV. Thus, some patients with HBV may actually receive FTC. In these cases, there is a potential concern that should a patient discontinue FTC (as anti-HIV therapy) they could experience an exacerbation of hepatitis. The labeling will carry a WARNING to alert clinicians to this possibility.

Resistance to Emtriva emerges rapidly both in vitro by a few passages of the virus in cells and in vivo by a few weeks of monotherapy. The pattern of resistance is similar to lamivudine and is typically manifested by a change at codon 184 of the reverse transcriptase with methionine being substituted with valine or isoleucine (M184V/I).

D. Dosing

The proposed Emtriva® dose is one-200 mg capsule administered once daily (QD). This dose was selected based on the results of 2 two-week monotherapy comparisons to 3TC. The
Executive Summary Section

The applicant concluded that this dose maintains antiviral concentrations above the IC_{90} for a significant portion of the dosing interval. Although this was potentially not the optimal dose of Emtriva, it is an active dose based on exposure-response relationships.

Emtriva is 4% protein bound; therefore, interactions with drugs that are protein mediated are unlikely. Emtriva exposure is increased 4-6.5 fold following ingestion of a full high fat high calorie meal; therefore, patients will be instructed to take Emtriva with a meal.

Patients with renal insufficiency can be dosed with Emtriva on an every 48-96 hour schedule (see Special Populations: Renal Impairment).

E. Special Populations

Ethnicity/Race

Approximately 72% of patients enrolled in Emtriva HIV-1 studies were Caucasian. There was no ethnicity-related differences in clinical outcomes between patients who received Emtriva or 3TC.

Non-Caucasians experienced higher rates of headache, increased AST and ALT, dizziness and skin discoloration. Conversely, Caucasians reported more insomnia and elevated triglyceride levels. The higher rates of increased ALT and AST among non-Caucasians was likely influenced by the overall high frequency of these events in study FTC-302 where >95% of the study population was non-Caucasian, and receiving nevirapine. The primarily Caucasian population in study FTC-303, the majority of who were receiving protease inhibitors, appeared to account for the higher overall frequency of elevated triglycerides.

No specific dosing modifications based on race/ethnicity are recommended in the labeling.

Gender

Males and females accounted for 58% and 42% of HIV-1 clinical trial enrollees, respectively. With respect to efficacy outcomes, in general females experienced more virologic failures compared to males. This may have been attributable to higher discontinuations among females due to adverse events from study FTC-303, and a low proportion of females (15%) in study FTC-301A. There was no gender difference between Emtriva and 3TC, overall.

The types of adverse events reported by males and females were similar, although more females discontinued from study FTC-303 because of adverse events. Males reported headache, constipation, pruritis, rash, and skin discoloration more frequently and females reported urogenital events more often. The overall frequency and severity of other adverse events were comparable.

No dosing modifications based on gender are recommended in the labeling.
Executive Summary Section

Age

Overall age did not affect clinical response. It was not possible to assess safety or efficacy in elderly patients (≥65 years of age) because they accounted for <1% of HIV-1 trial participants. Further, extremely few subjects 65 years of age and older were enrolled in pharmacokinetic studies. Although the numbers of elderly patients with HIV-1 infection is relatively small, there do not appear, from preclinical or clinical studies, any specific contraindications to using Emtriva in this age group. Therefore, no additional dosing modifications based on age are recommended in the labeling.

Renal Impairment

Emtriva® was administered to subjects with normal renal function and to those with End Stage Renal Disease (ESRD) requiring hemodialysis. Results demonstrate that urinary excretion is the primary mode of elimination, and as creatinine clearance decreases Emtriva 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 (blood flow rate of 400 mL/min and a dialysate flow rate of 600 mL/min). It is not known whether emtricitabine can be removed by peritoneal dialysis.

The following dosing schedule will be included in the labeling: 200 mg every 24 hours for CrCl ≥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.

Use During Pregnancy

Fifty-three pregnancies occurred in women exposed to Emtriva. The majority of pregnancies were electively terminated; however, 19 live healthy births were reported. There were six spontaneous abortions. In all cases, the patient was receiving multiple antiretroviral agents, including Emtriva. Therefore, the specific role of Emtriva in these outcomes could not be determined.

Results of preclinical reproductive and developmental toxicology studies demonstrated no adverse effects on fertility, reproductive performance, sperm count (male rats), mortality or developmental toxicity. The clinical data appear to suggest no specific risk to fetal development.
Executive Summary Section

However, since no adequate well-controlled studies have been conducted in pregnant females, Emtriva® is classified as Pregnancy Category B, with the recommendation that it should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Emtriva will be included in the ongoing Antiretroviral Pregnancy Registry.
I. Introduction and Background

A. Drug Established and Proposed Trade Name, Drug Class, Sponsor’s Proposed Indication(s), Dose, Regimens, Age Groups

Established name: Emtricitabine
Trade Name: Emtriva®
Chemical: 2’3’Dideoxy-5-flouro-3’tiacytadine (FTC)
Class: Nucleoside analogue
Proposed indication: Treatment of HIV-1 infection in adults (≥18 years of age)
Dose and regimen: 200 mg once-daily in combination with other antiretroviral agents
Dosage form: 200 mg capsules

B. State of Armamentarium for Indication

There are 18 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 6 NRTI’s marketed in the US: zidovudine (Retrovir®), didanosine (Videx®), zalcitabine (Hivid®), stavudine (Zerit®), lamivudine (Epivir®), abacavir (Ziagen®), 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®), and the protease inhibitors (PI), now represented by indinavir (Crixivan®), ritonavir (Norvir®), saquinavir (Invirase® and Fortovase®), nelfinavir (Viracept®), amprenavir (Agenerase®) and lopinavir/ritonavir fixed dose combination (Kaletra®). The most recently approved agents include a GP41 fusión inhibitor (Fuzeon®) and a PI (Reyataz®).

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 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 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 it has not been proven that Emtriva will meet these goals, its availability should offer an additional option for clinicians to consider when attempting to design a more simplified once daily HAART regimen.
C. Important Milestones in Product Development

Emtriva® (emtricitabine, FTC) is a cytosine NRTI with in vitro activity specific to HIV-1, HIV-2, and HBV. In cells, emtricitabine is phosphorylated to the 5'-triphosphate (FTC-TP) which is a competitive inhibitor of HIV-1 reverse transcriptase and HBV DNA polymerase. Emtricitabine has the same chemical structure as lamivudine (3TC) except for a fluoride residue at position 5 on the pyrimidine ring. Emtricitabine is reported to have a 10-fold greater in vitro potency than lamivudine.\(^1\) Resistance to emtricitabine is the same as described for lamivudine: a single mutation at codon 184 (M184V/I).

Burroughs Wellcome submitted the original IND for Emtriva\(^\text{TM}\) in January 1994. The rights were subsequently licensed to Triangle in 1995, with a new IND submitted in August 1997. In September 1997, the applicant conducted two Phase I two-week dose-ranging studies in HIV-infected patients (FTC-101 and FTC-102). The applicant relied on the results of these studies for selection of the proposed dose for use in Phase 3 studies. No Phase 2 studies were conducted.

Fast Track designation was conveyed in August 1998, based primarily on its potential for once daily administration.

On October 8, 1998, a development meeting was held to discuss the design and analysis plans for the applicant's proposed phase 3 studies. The Division could not concur with the proposed overall drug development plan. Specifically, the Division expressed numerous concerns about the utility of the current database from the two Phase 1 studies as the basis for selection of the dose for the Phase 3 studies and the risk to the applicant associated with such a selection. Concerns were raised about the small number of subjects enrolled, the limited duration of dosing, and whether the data on reductions in HIV-1 RNA demonstrated meaningful differences among the doses studied in FTC-101 and FTC-102. It was recommended that the applicant conduct additional dose finding studies or modify the proposed clinical trials to include additional doses of Emtriva. The applicant was encouraged to propose additional dose finding studies, taking into account trial design issues, practicality, and any ethical considerations associated with the conduct of such trials. Further, the Division expressed several reservations about the original designs of FTC-301 and FTC-303.

Study FTC-302 was initiated in September 1999 in the Republic of South Africa (RSA), and was to serve as the applicant's second pivotal study to support the approval of Emtriva. In December 1999, the applicant reported three liver-related deaths and a significant number of serious liver-related adverse events. The Medicines Control Council (MCC) of the RSA terminated the study for significant departures from accepted good clinical practices; the study was placed on CLINICAL HOLD in the US in February 2000. Due to lengthy negotiations between the applicant and the MCC, all patients completed 48 weeks of blinded treatment. Subsequently, the applicant requested that the CLINICAL HOLD be lifted; this request was denied based on \(---\) the conditions of the CLINICAL HOLD had not

---

\(^1\) Lamivudine is a NRTI currently marketed by GlaxoSmithKline under the trade names Epivir® and Epivir-HBV® and is one of the active ingredients in the fixed-dose combination products Combivir® and Trizivir®.
been met (see CLINICAL REVIEW METHODS: D. Were Trials Conducted in Accordance with Accepted Ethical Standards).

On July 3, 2002, a preNDA meeting was held during which the applicant described the data that would be included in an NDA for Emtriva. The application would include final (48-week) data from study FTC-303 and interim (24-week) data from study FTC-301A. Prior to the meeting, the applicant notified the Division that the interim data from study FTC-301A suggested that one of the blinded treatment arms appeared to convey better antiviral activity and safety compared to the other. Based on a recommendation from the study DSMB, the treatment arms were unblinded; the better performing arm was the arm containing Emtriva. The protocol was amended to offer the Emtriva-containing regimen to all patients. The study was continued until all patients had completed 48 weeks of treatment.

The Emtriva® NDA was submitted on September 3, 2002 and granted a standard review (10 months).

Midway through the review of the NDA Gilead Sciences purchased Triangle Pharmaceuticals, and became the applicant of record for this NDA. In addition, Gilead submitted the new trade name, Emtriva®, as a replacement for Coviracil®.

Indications Not Claimed in the NDA

D. Other Relevant Information

Emtriva is not approved in any other country.

E. Important Issues with Pharmacologically Related Agents

The risk of virologic failure is clearly an important factor in selecting an initial antiretroviral regimen. Other factors such as safety, toxicity, adherence, preservation of future treatment options, access, cost, and other issues also remain important in selecting the optimal first regimen for an individual patient.

A major issue with antiretroviral agents is emergence of resistance. Resistance is widely considered to be partially related to problems in adherence to combination therapy, with irregular gaps in use of individual drugs considered to promote risk of resistance due to periods when the full combination is not present at sufficient levels to block viral replication. A change from
twice daily to once daily dosing has been postulated to be associated with both lower and higher risk of resistance emergence. Specifically, once daily dosing could improve adherence. Conversely, once daily dosing could be detrimental if trough levels were low enough to permit viral replication and were low for prolonged periods with even single missed doses. Most NRTIs do not have the complex dietary requirements or large numbers of doses or pills associated with some other antiretrovirals, so the current application adds little to this issue (would change from one tablet twice daily to one or two tablets once daily, neither with dietary restrictions). Other issues with NRTIs include toxicities such as marrow suppression, neuropathy, pancreatitis, and lactic acidosis with prolonged use. Experience with other drugs does not suggest that number of doses per day is necessarily or uniformly linked to these toxicities, although there may be some associations with both total daily dose and duration of use.

A second major obstacle to long-term therapy is drug toxicity. The nucleoside analogues have both early and late toxicities. Examples of early toxicities include nausea and other gastrointestinal side effects, rash, and CNS side effects. Toxicities that have been related to some NRTIs include anemia, peripheral neuropathy, pancreatitis, lipoatrophy, and lactic acidosis. As a nucleoside analogue, many of these events were expected to occur during Emtriva therapy. The goal, therefore, is to select nucleoside analogues that produce lower frequency and severity of these toxicities. There is a growing body of evidence that the combination of didanosine (ddI) and stavudine (d4T) is falling out of favor as components of initial treatment for HIV infection due to the apparent higher risk of toxicities associated with these two agents. The risk of toxicities, and subsequent discontinuation, when ddI and d4T are used together has been found to be higher than when one of these drugs is used with other nucleoside analogues, such as lamivudine (3TC), thus leading to decreased efficacy. Emtriva, like 3TC, may provide a reasonable alternative for use in combination with ddI or d4T, rather than selecting the combination of ddI+d4T.

II. Clinically Relevant Findings From Chemistry, Animal Pharmacology and Toxicology, Microbiology, Statistics and/or Other Consultant Reviews

2.1. Chemistry

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

Emtriva® Tablets will be supplied as 200-mg, size 1 hard gelatin capsules with a light blue cap and white opaque body, printed with “200” in black ink on the cap and GILEAD and the cooperate logo in black on the body. The daily recommended dose of Emtriva is one 200-mg tablet one time per day. The composition of Emtriva Tablets is provided in Table 1.
Table 1. Composition of Emtriva® Tablets

<table>
<thead>
<tr>
<th>Component</th>
<th>Weight (mg)/Tablet</th>
</tr>
</thead>
<tbody>
<tr>
<td>Emtriva</td>
<td>200.0</td>
</tr>
<tr>
<td>Microcrystalline cellulose, NF</td>
<td></td>
</tr>
<tr>
<td>Crospovidone, NF</td>
<td></td>
</tr>
<tr>
<td>Povidone, USP</td>
<td></td>
</tr>
<tr>
<td>Magnesium Stearate, NF</td>
<td></td>
</tr>
<tr>
<td>Total Weight</td>
<td>400.0</td>
</tr>
</tbody>
</table>


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

The primary stability data generated on three commercial-representative batches indicate that the drug product is generally stable at 25°C/60% relative humidity (RH) for 24 months and at 40°C/75% (RH) for six months. Additionally, 24 months of supportive stability data on three lots of 200 mg tablets prepared using — mg of lactose monohydrate (instead of — mg), — mg of pregelatinized starch (instead of — mg) and no crospovidone (instead of — mg) was submitted. There was no significant time-dependent degradation, and all stability tests were within predetermined specifications. Therefore, the data submitted support a shelf-life of 24 months.

Emtriva Tablets will be packaged in a 60 mL — — bottle and a child-resistant cap lined with an induction line.

Bottle can be stored at room temperature: 25°C [77°F], with excursions permitted to 15-30°C [59-86°F].

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

2.2 Pharmacology/Toxicology

For a detailed discussion, please see Dr. Verma’s review. In this section, results of studies in which the drug substance, FTC, was used are reviewed.

FTC is phosphorylated to the 5'-monophosphate by cellular deoxycytidine kinase, to the 5'-diphosphate by deoxycytidine monophosphate kinase, and then to the 5'-triphosphate by nucleoside diphosphate kinase. The 5'-triphosphate of FTC competitively inhibits the incorporation of 2'-deoxycytidine 5'-triphosphate into the homopolymeric template primer r1-dC catalyzed by RT. Because the 5'-triphosphate of FTC does not contain a 3'-hydroxyl group, its incorporation into nascent viral DNA results in the chain termination.
3TC undergoes the same phosphorylation process. FTC and 3TC have similar structures with the exception that FTC contains a single fluorine moiety. The fluorine moiety is negatively charged, as are strands of DNA. Thus, FTC may not interact as well with DNA as 3TC.

Animal studies demonstrated:

- The NOEL ranged between 200 mg/kg to 1000 mg/kg depending on species. Based on a body surface area factor, equivalent human doses would be between 4000 mg/day and 10,000 mg/day for a 60 kg person. The daily dose of Emtriva for adults is 200 mg; therefore, the lowest animal dose provides for an approximately 50-fold margin for safety.

- Unchanged FTC represented the great majority of radioactivity present in urine and feces (70-95%), indicating that FTC is not extensively metabolized.

- FTC has a low extent of binding to human plasma at therapeutic concentrations, 4%. Because of the low extent of binding to human plasma at therapeutic concentrations, drug interactions mediated by protein binding displacement are not expected.

- FTC did not affect heart rate or blood pressure, any respiratory functions, urine output, pH or electrolyte excretion, or gastrointestinal motility.

- FTC was not mutagenic, and had a negative micronucleus assay.

- Results of reproductive and developmental toxicology studies demonstrated no adverse effects on male or female fertility, reproductive performance, sperm count (male rats), mortality or developmental toxicity. There are no adequate and well-controlled studies in pregnant women, therefore Emtriva will be classified as Category B.

2.3 Microbiology

For a detailed discussion, please see Dr. Batulla’s review.

The presumed mechanism of action of nucleoside analogues is that they are initially metabolized to their respective 5'-triphosphates (dNTPs) by cellular nucleoside and nucleotide kinases. Accordingly, the prodrug, FTC, inside cells is converted into the active drug form, FTC-triphosphosphate (TP), by sequential phosphorylations with cellular enzymes. The active form, FTC-TP, competes with natural (physiological) nucleoside triphosphates for the nucleotide-binding site on the viral reverse transcriptase. This competition is believed to inhibit the rate of HIV DNA synthesis (both RNA-directed and DNA-directed DNA polymerase activities of RT) by decreasing the incorporation of the natural deoxyribonucleotides. In addition, FTC-TP also serves as an alternate substrate thereby incorporated into the growing DNA chain of the HIV DNA. Since the incorporated FTC-MP nucleotide lacks the 3'-hydroxyl group, no phosphodiester bond formation can occur with the next incoming nucleotide; consequently, the DNA chain growth stops. Thus, the full-length proviral DNA synthesis that is required for viral DNA integration and establishment of viral infection is prevented.
In vitro and in vivo analyses demonstrated:

- FTC is active against various strains of HIV-1, HIV-2, and HBV.
- FTC has a 50% inhibitory concentration (IC₅₀) between 0.001-0.50 μM.
- FTC is more potent than lamivudine, IC₅₀=0.01-0.09 μM versus IC₅₀=0.07-3.2 μM.
- FTC exhibited additive to synergistic activity when combined with delavirdine, efavirenz, nevirapine, abacavir, didanosine, lamivudine, stavudine, zalcitabine, zidovudine, amprenavir, indinavir, nelfinavir, and ritonavir.
- FTC is a weak inhibitor of mammalian DNA polymerase α, β, and ε, and mitochondrial DNA polymerase γ.
- Resistance to FTC develops quickly (within 2-4 passages) and is manifested by a change at codon 184 of the reverse transcriptase with methionine being replaced by valine or isoleucine (M184V/I).

III. Human Pharmacokinetics and Pharmacodynamics

For a detailed discussion, please see Dr. DiGiacinto’s Clinical Pharmacology review.

A. Pharmacokinetics

For a detailed discussion, please see Dr. Jennifer DiGiacinto’s Biopharmaceutics review. The applicant conducted an extensive development program. Included in the NDA are data from 18 studies that assessed single and multiple-dose pharmacokinetics, effects of dose, repeated administration, formulation, co-administration of food, renal impairment, and interactions with various medications that could be taken by HIV-infected patients.

Relevant findings and issues raised by pharmacokinetic studies that are applicable to the indication include:

- FTC is rapidly and well absorbed following oral administration with a T_max of 1.5-2 hours.
- Plasma FTC concentrations achieved levels above the in vitro IC₉₀ (0.014 μg/mL) over a 24 hour period.
- FTC is eliminated primarily unchanged in the urine. Sixty to 70% of an oral dose is absorbed and recovered in urine. FTC is actively secreted by renal tubules. Emtriva is dialyzable, as creatinine clearance decreases Emtriva exposures increase. Hemodialysis treatment removes approximately 30% of an emtricitabine dose over a 3-hour dialysis period starting within 1.5 hours of emtricitabine dosing (blood flow rate of 400 mL/min and a dialysate flow rate of 600 mL/min). It is not known whether emtricitabine can be removed by peritoneal dialysis.
• The elimination half-life is approximately 9 hours, which supports QD dosing.

• The rate of absorption is decreased but exposure was not affected following a standard high-fat meal. Therefore, FTC can be administered with or without food.

• FTC is approximately 4% protein bound.

• No clinically significant interactions with famciclovir, stavudine, tenofovir, or indinavir were identified in drug-drug interaction studies.

• A single dose of FTC increased the AUC and C\text{max} of zidovudine by 26% and 66%, respectively.

B. Pharmacodynamics

The applicant conducted two studies to assess the multiple dose pharmacokinetics and antiviral activity of FTC. These data supported the antiviral activity at the selected 200 mg QD dose.

In study FTC-101, 45 HIV-infected subjects were randomized to receive FTC 25 mg QD, 100 mg QD, 100 mg BID, 200 mg QD or 200 mg BID for 14 days. Pharmacokinetic assessment demonstrated that FTC plasma concentrations increased in a dose proportional manner, FTC triphosphate (FTC-TP) concentrations peaked approximately 6 hours post dose, and FTC-TP concentrations in peripheral blood mononuclear cells also increased in a dose proportional manner. Following 14 days of FTC monotherapy, the median decrease in HIV-1 RNA was -1.4, -1.8, -1.7, -1.9, and -1.8 log_{10} c/mL for the 25 mg BID, 100 mg QD, 100 mg BID, 200 mg QD and 200 mg BID groups, respectively.

Study FTC-102 compared the antiviral activity of three doses of FTC to 3TC administered for 10 days. Eighty HIV-infected subjects were randomized to FTC 25 mg QD, 100 mg QD, or 200 mg QD to 3TC 150 mg BID. The mean change from baseline in log_{10} c/mL HIV-1 RNA were -1.43 for the 25 mg QD dose, -1.52 for the 100 mg QD, and -1.69 for the 200 mg QD doses of FTC compared to -1.5 for 3TC. The applicant concluded that these findings suggested that in large clinical studies FTC-based regimens would provide more robust antiviral responses compared to 3TC-based regimens (see Description of Clinical Studies).

IV. Description of Clinical Data and Sources

A. Overall Data

The data to support Emtriva’s safety and efficacy for treatment of adults with HIV-1 infection were derived primarily from clinical studies conducted by the applicant. Supportive studies conducted by the French Agence Nationale de Recherches sur le SIDA (ANRS) and the AIDS Clinical Trial Group (ACTG) of US National Institutes of Health were also submitted and reviewed.
B. Tables Listing the Clinical Trials

Table 2 presents a schematic overview of all completed and ongoing clinical studies submitted to support the safety and efficacy of Emtriva.
<table>
<thead>
<tr>
<th>Protocol No.</th>
<th>Population Countries</th>
<th>Start Date End Date</th>
<th>Design</th>
<th>Treatment Dose Frequency Duration</th>
<th>No. Patients Treated</th>
</tr>
</thead>
<tbody>
<tr>
<td>FTC-201 (ANRS-091, Montana)</td>
<td>Treatment naïve HIV-1 infected adults France</td>
<td>February 1999 Ongoing</td>
<td>Open-label, single-arm</td>
<td>FTC/ddI/EFV 48 weeks</td>
<td>FTC: 40</td>
</tr>
<tr>
<td>FTC-301</td>
<td>Treatment naïve HIV-1 infected adults U.S. and Chile</td>
<td>August 1999 November 2000</td>
<td>Randomized, open-label, superiority comparison of FTC to abacavir (ABC)</td>
<td>FTC/d4T/EFV or ABC/d4T/EFV 48 weeks</td>
<td>FTC: 18 ABC: 19</td>
</tr>
<tr>
<td>FTC-301A</td>
<td>Treatment naïve HIV-1 infected adults U.S., Canada, Mexico, Chile, Brazil, Argentina, UK, France, Germany</td>
<td>August 2000 September 2002</td>
<td>Randomized, double-blind, equivalence comparison of FTC to d4T</td>
<td>FTC/ddI/EFV or d4T/ddI/EFV 48 weeks</td>
<td>FTC: 286 d4T: 285</td>
</tr>
<tr>
<td>FTC-302</td>
<td>Treatment naïve HIV-1 infected adults South Africa</td>
<td>August 1999 Trial terminated early by RSA MCC and placed on CLINICAL HOLD by DAVDP</td>
<td>Randomized, double-blind comparison of FTC to 3TC</td>
<td>FTC/d4T/NVP or EFV or 3TC/d4T/NVP or EFV 48 weeks</td>
<td>FTC: 234 3TC: 234</td>
</tr>
<tr>
<td>FTC-303</td>
<td>Treatment naïve HIV-1 infected adults U.S.</td>
<td>September 1998 June 2000</td>
<td>Randomized, open-label equivalence of FTC to 3TC</td>
<td>FTC 200 and current background or Continue 3TC containing regimen</td>
<td>FTC: 294 3TC: 146</td>
</tr>
<tr>
<td>FTC-304 (ANRS-099, ALIZE)</td>
<td>Treatment experienced HIV-1 infected adults with stable HIV RNA France</td>
<td>June 2000 Ongoing</td>
<td>Open-label switch versus maintenance</td>
<td>Switch: FTC/ddI/EFV Maintenance: continuation of 1 or 2 PI's plus 2 NRTIs 48 weeks</td>
<td>Switch: 177 Maintenance:177</td>
</tr>
<tr>
<td><strong>FTC-350</strong></td>
<td>September 1999 Ongoing</td>
<td>Open-label rollover</td>
<td>FTC plus prescribed ART regimen Access until virologic failure or FTC commercially available</td>
<td>FTC: 289</td>
<td></td>
</tr>
<tr>
<td>-------------</td>
<td>------------------------</td>
<td>------------------</td>
<td>-------------------------------------------------</td>
<td>---------</td>
<td></td>
</tr>
<tr>
<td>Treatment (3TC) experienced (virologic success) from FTC-303</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>U.S.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>MKC-401</strong></th>
<th>August 1999 March 2002</th>
<th>Randomized, open-label comparison of emivirine (MKC) and ABC</th>
<th>Arm 1: FTC/d4T/MKC or Arm 2: FTC/d4T/ABC 48 weeks</th>
<th>Arm 1: 376 Arm 2: 188</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment naïve HIV-1 infected adults</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>U.S., South Africa</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>ACTG 5015</strong></th>
<th>October 2000 Ongoing</th>
<th>Open-label age differentiated cohort study</th>
<th>FTC/d4T/Kaletra 48 weeks</th>
<th>FTC: 92</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment naïve HIV-1 infected adults</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>U.S.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Denotes pivotal study.

C. Postmarketing Experience

There has been no postmarketing experience with Emtriva® because it is not marketed in any country, nor has a marketing application been submitted to any regulatory agency, other than the FDA.

D. Literature Review

The applicant submitted a comprehensive review of the current state of HIV therapy, articles related to pre-clinical and clinical investigations for Emtriva, and copies of scientific meeting abstracts and posters.
V. Clinical Review Methods
A. How the Review was Conducted

The clinical review of NDA 21-500 (Emtriva® Capsules) was conducted using volumes 1.133-1.150 (ISE and ISS), 1.151 through 1.553 (clinical study reports) and electronic SAS transport files of the NDA submission.

The current indication being considered for this product is treatment of HIV-1 infection in adults >18 years of age. As noted in Table 2 above, the development program to support the safety and efficacy of Emtriva consisted of two pivotal and several supportive studies. Study reports, line listings, and Case Report Forms were reviewed for all efficacy endpoints and demographic subgroups. The safety review also consisted of a review of all adverse events by summary tables and line listings, along with review of physical examination line listings. ‘Clinically significant’ laboratory abnormalities were defined as falling outside the ‘normal’ range values for the parameter by a specified amount defined in the study reports.

An update containing additional safety information (cut off September 1, 2002) and the 48-week results of study FTC-301A were submitted during the review period, as were individual Serious Adverse Event reports from ongoing studies.

Studies to establish pharmacokinetics, safety, and efficacy of Emtriva in HIV exposed patients are ongoing and will be discussed below.

Pertinent positive and negative safety and efficacy findings are discussed in the clinical study reviews. Additional human safety information derived from pharmacokinetics studies and from other specific safety-related investigations is discussed in the integrated summary of safety section. The medical reviewer’s recommendations for approval are summarized in the Conclusions and Recommendations section.

B. Overview of Materials Consulted in Review

The primary materials consulted included the entire NDA and IND, protocols and reports of studies conducted by the ACTG and the French ANRS that included Emtriva, and responses to requests for additional information to the NDA. The NDA and responses to requests for additional information were submitted in both hard copy and to the electronic document room.

C. Overview of Methods Used to Evaluate Data Quality and Integrity
- FTC-301A and FTC-303

The Division of Scientific Investigations (DSI) audited four investigators that participated in the two pivotal FTC studies: Drs. Vilma Vega, David Hass, Robert Wallace, and Larry Bush.
Dr. Hass received a four item 483: one SAE was reported 6 months after the investigator became aware of it, not all adverse events mentioned in the progress notes were transcribed to the adverse event section of the CRF, and two instances of nonadherence to the protocol were detailed.

The DSI audit found no deficiencies at Drs. Vega, Wallace and Bush’s sites that could compromise the integrity of the data. DSI concluded that all three investigators adhered to pertinent federal regulations and/or good clinical practices, and all three received NAI letters.

In summary, DSI concluded that no major deficiencies were noted at the sites that could compromise the integrity of the data, and no subsequent actions or follow-up inspections should be undertaken.

D. Were Trials Conducted in Accordance with Accepted Ethical Standards

Study FTC-302 was terminated early by the Medicines Control Council (MCC) of the Republic of South Africa for patient mismanagement and failure to adhere to good clinical practices. The study was subsequently placed on clinical hold by DAVDP, and the applicant was informed that FTC-302 could not be used as a pivotal efficacy trial. The following is a chronology of important telecoms, meetings, and interactions between DAVDP and Triangle Pharmaceuticals.

In January 2000, DAVDP contacted the Medicines Control Council (MCC) of the Republic of South Africa to inform them of three deaths due to hepatotoxicity and other serious adverse events that had occurred in study FTC-302. On February 2, 2000, representatives of the MCC and FDA discussed the serious nature of the adverse events occurring in FTC-302 in a teleconference. FDA provided the MCC with our response to these events as well as agreements made by Triangle to improve the safe management of patients in the study. The MCC informed us that they would be meeting with the sponsor and the CRO responsible for oversight of the conduct of study FTC-302.

On March 8, 2000, the MCC informed DAVDP that the sponsor agreed to amend the protocol to improve safety monitoring, especially for possible hepatotoxicity. Triangle also agreed to provide patients with a telephone card to facilitate contact with study sites; to arrange for home visits if a patient could not come to clinic; and to submit the CV’s of all investigators. Finally, maximum allowable elevations in hepatic enzymes would be reduced, but no specifics were provided.

Of note, at the meeting between the MCC and Triangle, Triangle was asked about progress in investigating the hepatotoxicity seen in FTC-302, as requested by FDA. The response provided from Triangle to investigators in a letter dated February 22, 2000 stated: “we have assured ourselves that the liver toxicity grade III and IV events were probably related to Nevirapine and remotely related to a drug interaction with the blinded study drugs FTC and lamivudine.” No supporting data for this conclusion was provided to the MCC.
At the same time, DAVDP was made aware that Triangle granted 350 protocol exemptions. The main reasons included lower than allowed CD4 cell counts, prolonged time between screening and baseline visits, and various exceptions for out of range laboratory parameters.

On April 6, 2000, the MCC issued a letter to Triangle stating that because of numerous serious protocol violations that compromised the scientific integrity of study FTC-302, the study should be terminated. Triangle was asked to submit a plan to unwind the study within 7 days. Triangle responded that they would enroll no additional patients into the study, but that they preferred to continue the study in a controlled clinical research setting.

The study was placed on CLINICAL HOLD because of questions about the appropriateness of medical management of subjects who experienced adverse events; the inadequacy of investigations and reporting of adverse events; issues with the capacity of the medical infrastructure in South Africa to support the conduct of such a study; the inadequacy of communication between Triangle and the MCC; and the lack of a DSMB or other oversight group to review safety data and make recommendations regarding human subject protection. In order to remove the hold, we requested that Triangle provide documentation of all findings and deliberations of the MCC’s review of this trial; documentation of an MCC decision to allow the study to continue; satisfactory inspection of clinical trial sites audited by the MCC and the FDA, along with resolution of any unacceptable findings; and establishment of an independent data safety monitoring board (DMSB).

On April 14, 2000, the MCC again informed Triangle that the study was terminated, pointing out that there had been “poor adherence to GCP” and “protocol violations regarding patient recruitment.” Further, the MCC requested that patients who had virologic response defined as HIV RNA <2,000 c/mL continue their present regimen on compassionate grounds. Again it was Triangle’s position that the safest and most appropriate course of action would be to maintain the blinded therapy.

There were apparently no communications between the MCC and Triangle until June 29, 2000, when Triangle met with the MCC and again requested that the trial continue in a blinded manner.

On August 7, 2000 Triangle was informed by the MCC that the trial had been terminated and the data generated by FTC-302 could not be utilized to support a future registration application, and that the compassionate use recommended by the MCC implied that the study be unblinded.

On September 8, 2000, Triangle submitted a compassionate use protocol. According to Triangle, no response was received from the MCC, and in December 2000, the study was completed in a blinded manner.

On January 15, 2001, Triangle submitted a response to the CLINICAL HOLD letter. The CLINICAL HOLD was maintained because the MCC had not reversed their decision to terminate FTC-302. Therefore, the stipulation to document the MCC’s decision to allow FTC-302 to continue was not met. In addition, Triangle had contracted with an independent consulting group specializing in Good Clinical Practice audits and evaluations to audit FTC-302. The audit identified a number of deviations from acceptable
standards: the process and documentation of Informed Consent; enrollment of several unsuitable subjects; discrepancies in compliance and drug accountability; unacceptable management and reporting of Serious Adverse Events in several instances; and backlogs of CRF reviews that were “insufficient to maintain currency with study data and developments.”

Finally, DAVDP did not agree that the Clinical Steering Committee (CSC) that Triangle had formed was an adequate response to the request that an independent DSMB be established. Specifically, the CSC included both Triangle employees and the principal investigator of the study, which called into question the independence of this committee.

DAVDP also recommended that Triangle withdraw study FTC-302 from their US IND.

DAVDP met with Triangle on April 18 and on June 5, 2001. Triangle maintained they did not interpret “terminated” to mean that the study had to be completely stopped and unblinded until the August 7, 2000 communication from the MCC. Regardless of their interpretation of the communications from the MCC, it was Triangle’s position that their study qualifies as an adequate and well-controlled study that would support a marketing application for FTC. DAVDP stated it would be difficult to accept the study as adequate and well controlled to support an NDA since regulatory authorities had terminated the study in the country in which it had been conducted.

Following the April 18, 2001 meeting, DAVDP contacted the Office for Human Research Protection to obtain an opinion on the acceptability of FTC-302 as a pivotal trial in an NDA for FTC. The opinion was that under 21 CFR 312.120(c)(1) and (2), consideration of study FTC-302 as a pivotal trial would not be justified because it did not conform to the foreign country’s standards.

On July 13, 2001, Triangle submitted a legal brief prepared by describing how the clinical efficacy data from study FTC-302 can be used to support an NDA for FTC. The brief and other documents were reviewed upheld, based on 21 CFR 312.120, that the conditions for lifting the CLINICAL HOLD were not met and that the efficacy data could not be used to support an application for FTC.

Study FTC-302 was reviewed for its contribution to the assessment of Emtriva’s safety. No unexpected adverse events related to Emtriva were identified, and the data did not change the overall assessment of Emtriva’s safety.

The two pivotal studies, FTC-301A and FTC-303, appear to have been conducted in accordance with accepted ethical standards.

E. Evaluation of Financial Disclosure

Pursuant to 21 CFR 54.2(e) the financial certification statement provided by the applicant was reviewed. The applicant requested that all investigators and sub-investigators from any studies contained in the NDA that contributed to the assessment of safety and efficacy (covered studies) disclose proprietary interest or significant equity as defined in the regulations. The applicant has
included a list of all investigators and sub-investigators who responded to their request on form 3454.

The applicant disclosed significant financial interests and arrangements for four investigators:

- 
- 
- 
- 

The applicant stated that each of the above individuals were sub-investigators in large double-blind, placebo-controlled multi-center studies, none enrolled sufficient numbers of patients to affect the results of the study, and none was involved in the analysis of the study data. Therefore, the applicant concluded that there was no evidence that these sub-investigators impacted the results of the studies.

Comment: This reviewer concurs that the above financial disclosures did not appear to have impacted outcome of any particular study.

VI. Integrated Review of Efficacy
A. Brief Statement of Conclusions

FTC is an active antiretroviral agent, and the results of studies FTC-301A and FTC-303 demonstrate that regimens containing Emtriva administered once daily produced antiviral and immunologic activity in adult patients with HIV-1 infection comparable to other three drug NRTI-based regimens.

However, Emtriva failed to demonstrate a greater antiviral or immunological response when directly compared to 3TC. The results of study FTC-303, in which Emtriva was substituted for 3TC in patients with suppressed HIV RNA, demonstrated no apparent advantage to substituting 3TC for Emtriva. Although it could not be considered a pivotal study, FTC-302 provided a supportive direct comparison of Emtriva to 3TC in treatment naive patients; the results suggested that Emtriva did not provide a more robust antiviral response as suggested by the applicant based on the results of a dose-ranging study (Study FTC-102).
The results of study FTC-303 suggest no therapeutic advantage for Emtriva® over 3TC in patients who are virologically suppressed a 3TC-containing regimen. In study FTC-303, discontinuations due to adverse events were more common amongst patients who switched to Emtriva. A possibility for the poorer results in two comparative studies is the presence of a fluorine moiety on the FTC molecule. This fluorine moiety is negatively charged, as are viral DNA strands, Emtriva may not have interacted as well with viral DNA further leading to less chain termination potency.

Study 301A demonstrated that the regimen of Emtriva+ddI+EFV was active and better tolerated than the comparator regimen of d4T+ddI+EFV. This was quite consistent with other studies that showed that regimens containing lamivudine and efavirenz are extremely effective and that ddI+d4T is a more toxic backbone and when combined with efavirenz, is associated with worse virologic outcomes.

B. General Approach to Review of the Efficacy of the Drug

The principal focus of review was the two pivotal studies, FTC-301A and FTC-303. Supportive controlled and uncontrolled studies were evaluated for any usable efficacy information.

C. Detailed Review of Trials by Indication

Treatment of HIV-infected adults is the only indication being sought in the current application. The two pivotal efficacy studies (FTC-301A and FTC-303) submitted in support of this indication are reviewed in detail. Brief reviews of additional controlled and uncontrolled supportive efficacy studies are also presented below.

C.1 Review of Pivotal Efficacy Studies
C.1.a Study FTC-303

“A Randomized, Open-Label Equivalence Study of FTC Versus Lamivudine in Patients on a Stable Triple Antiretroviral Therapy Regimen Containing Lamivudine, Stavudine or Zidovudine, and a Protease Inhibitor or Non-Nucleoside Reverse Transcriptase Inhibitor.”

FTC-303 was conducted between September 1998 and May 2000, in 43 sites in the US.

- Objectives

The primary objectives were to compare: (1) plasma HIV RNA AAUCMB between treatment arms after 24 weeks of treatment; (2) the proportion of subjects in each treatment arm who maintained virologic success at week 48 (defined as continued suppression of HIV RNA to <400 copies/mL); and, (3) the proportion of subjects who discontinued therapy over 48 weeks.

Secondary objectives included comparisons of: (1) time to virologic failure; (2) time to effectiveness failure; (3) the proportion of effectiveness failures; (4) the proportion whose HIV RNA remained <50 copies/mL; (5) the proportion who remained on the randomized treatment arm; (6) AAUCMB between FTC and 3TC; (7) CD4 and CD8 cell counts; (8) the percentage
increase above baseline; (9) population pharmacokinetics; and, (10) reverse transcriptase genotype of isolates from virologic failures.

- **Design**

FTC-303 was a phase 3 open-label, multi-center, randomized, equivalence study. Patients were to be on a stable triple antiretroviral background therapy consisting of lamivudine (3TC) with zidovudine (ZDV) or stavudine (d4T) and a protease inhibitor (PI) for ≥12 weeks or a nonnucleoside reverse transcriptase inhibitor (NNRTI) for ≥8 weeks, with HIV RNA <400 c/mL. Following screening, patients were randomized 2:1 to replace 3TC with Emtriva or remain on 3TC as described below:

Arm 1: switch 3TC to Emtriva 200 mg qd with current background regimen.
Arm 2: continue on current 3TC 150 mg bid containing regimen.

Randomization was stratified based on HIV RNA levels and concomitant antiretroviral therapy: <50 copies/mL + PI, <50 copies/mL + NNRTI, 50-400 copies/mL + PI, and 50-400 copies/mL + NNRTI. The duration of dosing was 48 weeks with comparisons of virologic outcomes at weeks 24 and 48.

- **Demographics and Disposition**

The applicant enrolled 459 HIV-1 infected male and female patients 18 years of age and older with plasma HIV RNA of <400 copies/mL on stable antiretroviral therapy containing 3TC plus d4T or ZDV, and a PI or NNRTI were enrolled: 307 to Emtriva and 152 to continued 3TC. Of the 459, 440 (294 Emtriva and 146 3TC) received at least one dose of study medication.

At study entry, 86% were male, 64% were Caucasian, 21% were black, and 13% were Hispanic. The mean age of study patients was 42 years (range 22-80). Patients entered with a median duration of prior antiretroviral therapy of 37.3 months in the Emtriva arm and 31.3 months in the 3TC arm. The mean baseline CD4 cell count was 527 cells/mm³ (range 37-1909 cells/mm³). At randomization, 86% had HIV RNA <50 c/mL and 14% were between 50 and 400 c/mL.

Twenty-nine and 23% had a history of a CDC class C AIDS-defining event at baseline in the Emtriva and 3TC arms, respectively.

Approximately 70% of patients in both treatment arms had been on antiretroviral regimens prior to their current stable 3TC-containing regimen. More patients in the Emtriva arm had received prior ddi (25%) and nelfinavir (8%) compared to those in the 3TC arm, 15% and 3%, respectively. The arms were well balanced with respect to other PIs and NNRTIs.

**Comment**: The two arms were similar in baseline demographic and disease characteristics, and represented a population of relatively healthy HIV-infected individuals. It does not appear that the applicant could support an argument that the longer duration of previous antiretroviral therapy contributed to higher rates of virologic failure in the Emtriva arm because the overall virologic failure rates were comparable (see below). Further, although
for a high proportion of patients the entry regimen was not their first regimen, there was
no data submitted as to the reasons for changes in the previous regimen(s), i.e., changes due
to virologic failure or adverse events. Thus, it is difficult to reach a firm conclusion that
these patients represent a more advanced population of HIV infected patients.

Overall compliance with study medication, as assessed by investigators was high, median 98% in
both treatment arms. When assessed by drug accountability records, compliance was again
similar between treatment arms, median 90%.

Patient disposition is described in Table 3.

**Table 3. Patient disposition through 48 weeks**

<table>
<thead>
<tr>
<th></th>
<th>Emtriva®</th>
<th>3TC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Randomized</td>
<td>307</td>
<td>152</td>
</tr>
<tr>
<td>Received at least one dose</td>
<td>294</td>
<td>146</td>
</tr>
<tr>
<td>Completed 48 weeks</td>
<td>227 (77%)</td>
<td>119 (82%)</td>
</tr>
<tr>
<td>Discontinued</td>
<td>67</td>
<td>26</td>
</tr>
<tr>
<td>Adverse event</td>
<td>14 (5%)</td>
<td>0</td>
</tr>
<tr>
<td>Non-compliance</td>
<td>4 (1%)</td>
<td>0</td>
</tr>
<tr>
<td>Virologic failure</td>
<td>20 (7%)</td>
<td>11 (8%)</td>
</tr>
<tr>
<td>Protocol violation</td>
<td>5 (2%)</td>
<td>4 (3%)</td>
</tr>
<tr>
<td>Withdrawal request</td>
<td>15 (5%)</td>
<td>9 (6%)</td>
</tr>
<tr>
<td>Death</td>
<td>0</td>
<td>1 (1%)</td>
</tr>
<tr>
<td>Other</td>
<td>8 (3%)</td>
<td>2 (1%)</td>
</tr>
</tbody>
</table>

Comment: The reasons for premature discontinuation were comparable between treatment
arms. More patients discontinued Emtriva due to adverse events. A few discontinuations
warrant mention. In two cases, patients discontinued Emtriva due to gastrointestinal
events that resolved following replacement of Emtriva with 3TC. In one case, a patient
discontinued Emtriva due to anemia, despite having received ZDV (known to cause
anemia) for over 2 years.

There may have been bias against Emtriva due to the open-label design; e.g., patients were
more likely to discontinue Emtriva because of the impression that new adverse events may
be related to the introduction of this new drug. Further, patients who would not tolerate
3TC would have discontinued use of 3TC prior to entry into this study, again introducing
bias against the new regimen.

- **Outcome Assessments and Results**

For a detailed review of all efficacy parameters, please see Dr. Zhou’s statistical review.

The intent-to-treat population was to have HIV RNA <400 c/mL at baseline. The primary
endpoint was a comparison of the stratum adjusted proportion of subjects with continued
suppression of HIV RNA <400 c/mL at week 48. The study was powered to provide 80% power
to reject the null hypothesis that the difference in 48 week virologic response would be >12.5%
in favor of 3TC.
The major secondary endpoints included the proportion with HIV RNA <50 c/mL, virologic failure (defined as HIV-1 RNA >400 c/mL on two consecutive evaluations), efficacy failure (defined as virologic failure, CDC Class C progression, death, or lost to follow-up), effectiveness failure (defined as virologic failure, tolerability failure, CDC Class C progression, or lost to follow-up), and mean change from baseline of CD4+ cells. Table 4 presents the 48-week efficacy results for the groups whom switched to Emtriva® or remained on their 3TC-containing regimen.

Table 4. Outcomes of randomized treatment at Week 48.

<table>
<thead>
<tr>
<th></th>
<th>Emtriva+ZDV/d4T+NNRTI/PI (n=294)</th>
<th>Epivir®+ZDV/d4T+NNRTI/PI (n=146)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV RNA&lt;400 c/mL</td>
<td>77%</td>
<td>82%</td>
</tr>
<tr>
<td>HIV RNA&lt;50 c/mL</td>
<td>67%</td>
<td>72%</td>
</tr>
<tr>
<td>Virologic failure</td>
<td>7%</td>
<td>8%</td>
</tr>
<tr>
<td>Death</td>
<td>0%</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>DC due to adverse events</td>
<td>4%</td>
<td>0%</td>
</tr>
<tr>
<td>DC due to other reasons</td>
<td>12%</td>
<td>10%</td>
</tr>
</tbody>
</table>

1. Patients achieved and maintained confirmed HIV RNA <400 c/mL through Week 48.
2. Patients achieved and maintained confirmed HIV RNA <50 c/mL through Week 48.
3. Includes patients who failed to achieve virologic suppression or rebounded after achieving virologic suppression.
4. Includes lost to follow-up, consent withdrawal, non-compliance, protocol violations, and other reasons.

The stratum-adjusted difference between the Emtriva and Epivir arms was -4.8% with a 95% confidence interval of -12.8% to 3.3%, numerically favoring remaining on 3TC.

Disease Progression

New CDC Class C events were considered evidence of disease progression. There was no difference between treatment arms with respect to the occurrence of new Class C events. Five patients experienced a new Class C event: two received Emtriva (Kaposi’s sarcoma and mycobacterium infection) and three received 3TC (pneumocystis pneumonia, cervical cancer, and cytomegalovirus disease).

Thirteen Emtriva and 6 3TC-treated patients experienced new CDC Class B events. The events in the Emtriva arm included: seborrhea, tinea cruris, molluscum contagiosum, herpes zoster, herpes simplex (2), hairy leukoplakia (2), community acquired pneumonia (2), and peripheral neuropathy. The events in the 3TC arm included: seborrhea (2), herpes zoster, hairy leukoplakia, psoriasis, wasting syndrome, and oral thrush.

Virologic failure

The frequency of virologic failure, defined as HIV RNA >400 c/mL on two consecutive assessments, was comparable between treatment arms (see Table 4). Longitudinal comparisons of Kaplan-Meier curves for loss of virologic response (LOVR) demonstrated that a history of Combivir® (fixed dose ZDV+3TC) use and baseline HIV RNA >50 c/mL were associated with a greater risk of LOVR. No association between LOVR and other risk factors was identified.
Thirty-four patients experienced virologic failure (23 in Emtriva arm and 11 in 3TC arm). Genotypic analyses demonstrated a higher proportion of Emtriva-treated patients having evidence of a new M184V/I mutation, 17/19 (90%) versus 3/4 (75%) in 3TC failures. The numbers are small and do not include samples on all patients.

**Immunologic Outcomes**

At study entry, the mean baseline CD4 cell count was approximately 530 cells/mm³ in both arms. Patients who remained on their 3TC-containing regimen experienced greater increases in absolute CD4 cell counts over the duration of the study, +61 cells/mm³ compared to +29 cells/mm³ in the Emtriva arm. The median percent change in CD4 cells was +1.7% and +2.5% in the Emtriva and 3TC arms, respectively.

**Proportion who remained on randomized therapy**

A total of 23 (8%) Emtriva and 7 (5%) 3TC patients had at least one change of their study medication; the reasons for switching were similar between arms.

**Assessment of Outcomes by Gender, Age and Ethnicity**

Treatment by gender and treatment differences were observed with regard to LOVR. When stratified by treatment arm, male patients who switched to Emtriva had better virologic responses than female patients who switched. These findings may be accounted for by the higher frequency of discontinuations among female patients, 38% versus 19%. No gender difference was observed in the 3TC arm, and no treatment differences were observed in male patients in either treatment arm.

The statistical reviewer used a median age of 41 to categorize patients as younger (≤42) or older (>42). Overall, age >42 was associated with greater LOVR in both treatment arms. Younger patients in the 3TC treatment arm did better with respect to LOVR than those in the Emtriva treatment arm. No treatment difference was found for the older subjects.

Patients in three ethnic categories Caucasian, Black and Hispanic constituted 98% of the ITT study population. Overall, there were no significant treatment differences in LOVR between racial groups.

- **Overall Assessment of Study FTC-303**

Previous studies suggest that when 3TC is used as a component of triple antiretroviral therapy, 70% efficacy (HIV RNA <400 c/mL through 48 weeks) can be anticipated. In study FTC-303, this threshold was exceeded by nearly 10% in patients who mostly received over 2 years of 3TC-based therapy. Although patients who switched to Emtriva® also had better than 70% success, the immunologic results suggest that numerical efficacy was less than continued 3TC, although new CDC class B and C events were comparable. In addition, secondary endpoints such as effectiveness failure and mean change in CD4 cell counts demonstrated an advantage in favor of patients remaining on 3TC-based therapy.
Although the numbers of patients on whom samples were tested was small, genotypic analysis of patients who experienced rebound of viral load identified no difference in the frequency of the M184V/I mutation between Emtriva and 3TC.

The reason for the differential efficacy results may be related to the higher frequency of discontinuations from the Emtriva arm due to adverse events (patients may have been more likely to discontinue because of the impression that new adverse events may be related to the new drug), or possibly because of a desire of open label subjects not to be on a perceived inferior arm. Alternatively, some patients may have lost Emtriva potency because the molecule contains a negatively charged fluorine moiety that may have interacted less well with viral DNA than 3TC.

Compliance with study medication was comparable between treatment groups. At the time the study was initiated, it was theorized that Emtriva would provide a compliance advantage over 3TC because it would be administered once daily compared to twice daily for 3TC. Since the study was conducted, 3TC has been approved for once daily administration, thus eliminating any perceived dose frequency advantage for Emtriva.

C.1.b Study FTC-301A

“A Randomized, Double-Blind, Equivalence Trial Comparing Emtricitabine to Stavudine within a Triple Combination Containing Didanosine Plus Efavirenz in Antiretroviral-Drug Naïve HIV-1 Infected Patients.”

This study was conducted between August 2000 and May 2002 in 101 centers in North America, Latin America, South America, and Europe.

- Objectives

The primary objective was to assess the safety and efficacy of Emtriva compared to stavudine (d4T) when used within a regimen containing didanosine (ddI) and efavirenz (EFV).

Secondary objectives included comparisons of (1) time to virologic failure; (2) time to effectiveness failure; (3) time to plasma HIV-1 RNA nadir; (4) change from baseline values in HIV-1 RNA. Other secondary objectives included a determination of the magnitude of CD4 cell count changes and percent increase above baseline and characterization of the reverse-transcriptase genotype from virologic failures.

- Design

FTC-301A was a phase 3, randomized, double blind, double-dummy, multi-center study to evaluate the equivalence of Emtriva to d4T when combined with ddI and EFV. The study was to

---

1 In May 1999, the applicant submitted the original protocol for study FTC-301, which proposed an open-label, randomized, multi-center study to determine superiority for FTC compared to abacavir (ABC) when combined with EFV and d4T in antiretroviral-naïve HIV-infected subjects. The Division provided a significant number of recommendations related to the design and analysis of the study (see Medical and Statistical reviews for IND: Serial 056, July 15, 1999). The applicant addressed a number of the minor recommendations but did not address the major study design deficiencies. The applicant subsequently initiated the study and enrolled approximately 40 patients. In January 2000, the
enroll 350 antiretroviral-naïve HIV-1 infected patients 18 years of age or older with baseline HIV RNA >5,000 c/mL and a CD4 cell count ≥200 cells/mm³. Patients were randomized 1:1 to:

Arm 1: FTC (200 mg QD)+d4T placebo (BID)+ddI (400 mg QD)+EFV (600 mg QD)³
Arm 2: FTC placebo (QD)+d4T (40 mg BID)+ddI (400 mg QD)+EFV (600 mg QD)³

Randomization was stratified based on screening plasma HIV RNA, and previous participation in study FTC-301 as follows:

Stratum 1: antiretroviral-naïve with HIV RNA 5,000-100,000 c/mL
Stratum 2: antiretroviral-naïve with HIV RNA >100,000 c/mL
Stratum 3: patients previously enrolled in FTC-301 (n=27)

The study will continue until the last randomized patient completes 48 weeks of treatment. Patients whose viral load was <400 c/mL through the end of the study will be offered an open-label triple combination regimen containing Emtriva (study FTC-350).

Comment: At the time the study was designed, ddI+d4T was a commonly used first-line NRTI combination. Since then, the utility of this combination has waned because of an association with a high frequency of adverse events, which has led to lower than expected efficacy due to frequent discontinuations.

- Demographics and Disposition

A total 584 treatment-naïve HIV-1 infected male and female patients 18 years of age and older were enrolled: 294 to Emtriva and to 290 d4T. Of these, 286 and 285 received at least one dose of Emtriva or d4T, respectively.

The baseline characteristics demonstrated the study population to be 85% male, 52% Caucasian, 16% black, and 25% hispanic. The mean age was 36 years (range 18-69). The mean baseline HIV-RNA was 4.8 log₁₀ c/mL (range 2.6-7.0 log₁₀ c/mL), with 56% of patients having HIV RNA <100,000 c/mL. The mean CD4 cell count was 318 cells/mm³ (range 5-1317 cells/mm³). Eighteen percent and 3% had a history of a CDC class B or C AIDS-defining event at baseline.

Comment: The treatment arms were well balanced and represented a reasonably healthy population of treatment naïve patients.

Patient disposition is described in Table 5.

---

³ Subjects weighing <60 kg received d4T 30 mg bid and ddI 250 mg QD.
Table 5. Patient disposition through 48 weeks.

<table>
<thead>
<tr>
<th></th>
<th>Emtriva®</th>
<th>d4T</th>
</tr>
</thead>
<tbody>
<tr>
<td>Randomized</td>
<td>294</td>
<td>290</td>
</tr>
<tr>
<td>Received at least one dose*</td>
<td>286</td>
<td>285</td>
</tr>
<tr>
<td>Completed 48 weeks</td>
<td>237 (83%)</td>
<td>207 (73%)</td>
</tr>
<tr>
<td>Discontinued</td>
<td>49</td>
<td>78</td>
</tr>
<tr>
<td>Adverse event</td>
<td>16 (6%)</td>
<td>33 (12%)</td>
</tr>
<tr>
<td>Lost to follow-up</td>
<td>9 (3%)</td>
<td>12 (4%)</td>
</tr>
<tr>
<td>Non-compliance</td>
<td>2 (&lt;1%)</td>
<td>3 (1%)</td>
</tr>
<tr>
<td>Virologic failure</td>
<td>8 (2%)</td>
<td>22 (8%)</td>
</tr>
<tr>
<td>Protocol violation</td>
<td>7 (2%)</td>
<td>4 (&lt;1%)</td>
</tr>
<tr>
<td>Request withdrawal</td>
<td>5 (2%)</td>
<td>2 (&lt;1%)</td>
</tr>
<tr>
<td>Death</td>
<td>0</td>
<td>2 (&lt;1%)</td>
</tr>
<tr>
<td>Other</td>
<td>2 (&lt;1%)</td>
<td>2 (&lt;1%)</td>
</tr>
</tbody>
</table>

*5 patients in each treatment group failed to return following their baseline visit.

Significantly more patients discontinued the d4T+ddI regimen due to adverse events; a finding that was not unexpected as this is a combination that is associated with clinically significant adverse effects.

- **Outcome Assessments and Results**

The primary endpoint was the proportion of patients with HIV RNA ≤400 c/mL at 48 weeks using a non-completer equals failure analysis.

The trial was powered to demonstrate that FTC would be equivalent to d4T. According to the sponsor, with a minimum sample size of 175 patients per arm there would be 80% power to detect a 10% difference in the proportion of patients with HIV RNA ≤50 c/mL between FTC and d4T at 24 and 48 weeks. Patients in Stratum 3 were analyzed separately.

Table 6 presents the 48-week results for the intent-to-treat population.

Table 6. Outcomes of randomized treatment at Week 48.

<table>
<thead>
<tr>
<th></th>
<th>Emtriva+ddI+EFV (n=294)</th>
<th>Zerit®+ddI+EFV (n=290)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV RNA&lt;400 c/mL</td>
<td>81%</td>
<td>68%</td>
</tr>
<tr>
<td>HIV RNA&lt;50 c/mL</td>
<td>78%</td>
<td>59%</td>
</tr>
<tr>
<td>Virologic failure</td>
<td>3%</td>
<td>11%</td>
</tr>
<tr>
<td>Death</td>
<td>0%</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>DC due to adverse events</td>
<td>7%</td>
<td>13%</td>
</tr>
<tr>
<td>DC due to other reasons</td>
<td>9%</td>
<td>8%</td>
</tr>
</tbody>
</table>

1. Patients achieved and maintained confirmed HIV RNA <400 c/mL through Week 48.
2. Patients achieved and maintained confirmed HIV RNA <50 c/mL through Week 48.
3. Includes patients who failed to achieve virologic suppression or rebounded after achieving virologic suppression.
4. Includes lost to follow-up, consent withdrawal, non-compliance, protocol violations, and other reasons.
Immunologic Outcomes

Patients in the Emtriva arm experienced greater increases in absolute CD4 cell counts (+163 cells/mm³ versus +139 cells/mm³) and CD4% (+10% versus +6%).

Disease Progression

Occurrence of a new CDC Class C event was considered evidence of HIV disease progression. There were no significant differences between treatment groups. Five patients in the Emtriva arm (1.7%) and nine in the d4T arm (3.1%) had a new CDC Class C event on study. The events in the Emtriva arm included Kaposi's sarcoma (1), diarrhea due to Isospora belli (1), Mycobacterium tuberculosis (1), esophageal candidiasis (1), and herpes simplex virus (1).

In the d4T arm, the events included: pneumocystis carinii pneumonia with herpes simplex proctitis (1), wasting syndrome (4), diarrhea due to Cryptosporidium (1), esophageal candidiasis (1), and Kaposi's sarcoma (2).

Virologic Failure

As presented in Table 6, more patients experienced virologic failures in the d4T arm compared to the Emtriva arm. Through 48 weeks, 58 patients had confirmed virologic failure, 17 in the Emtriva group and 41 in the d4T group. Six Emtriva failures had evidence of the M184V/I mutation compared to none in the d4T arm, an expected finding. More patients in the d4T group had evidence of resistance to EFV and thymidine analogue mutations. Genotypic mutations suggesting resistance to ddi was similar between treatment arms.

Assessment of Outcomes by Gender, Age and Ethnicity

Gender and treatment differences in the LOVR analysis were identified. Overall, males had better virologic responses than females. Further, females in the d4T treatment arm had lower virologic response than females in the Emtriva treatment arm. No significant treatment difference was observed in male subjects between the two treatment arms. Since overall only 15% of study participants were female, no additional conclusions could be reached.

Patients 35 years and older in the d4T treatment arm had worse virologic response than older patients in the Emtriva arm. No significant treatment effect in LOVR was observed among patients age < 35 years. Stratified by treatment arm, increased age was not associated with higher LOVR.

Stratified by treatment arm, Caucasians had the lowest LOVR, followed by Hispanics, and Blacks in the d4T treatment arm, but no difference was observed in the Emtriva arm. Stratified by race, Hispanics in the d4T treatment arm had greater LOVR compared to Hispanics in the Emtriva treatment arm.

Additionally, significant racial differences in LOVR were seen in patients with screening HIV RNA < 100,000 c/mL in the d4T treatment arm favoring Caucasians. Conversely, Hispanics with
screening HIV RNA < 100,000 c/mL had the best virologic outcomes in the Emtriva arm.

Assessment of study FTC-301A

The results of study FTC-301A demonstrate: (1) the virologic response was similar for the Emtriva arm and equivalent to the d4T reference arm; (2) the virologic response was sustained over 48 weeks; and (3) the virologic response was associated with a significant rise in CD4+ cell counts and CD4%. Discontinuations due to adverse events (patients were classified as treatment failures in the efficacy analyses) and more virologic failures from the d4T arm accounted for the differences in efficacy.

The results of study FTC-301A support a conclusion that an initial regimen in treatment naïve patients that includes Emtriva rather than the combination of d4T+ddI may be more tolerable and result in greater virologic success. These findings support the conclusion of other studies showing that regimens containing both lamivudine and efavirenz are extremely effective and that ddI+d4T is a more toxic nucleoside backbone and when combined with efavirenz, is associated with worse virologic outcomes (preliminary results of ACTG 384). Given the similarity between Emtriva and lamivudine, it is not unreasonable that these conclusions would apply to regimens containing Emtriva and efavirenz.

C.2 Review of Supportive Efficacy Studies-Controlled Studies

FTC-304 (ANRS 099, ALIZE,) is an ongoing open-label, randomized study comparing the efficacy and tolerability of maintaining a protease inhibitor (PI) containing regimen (maintenance) versus changing to the once-daily combination of Emtriva+ddI+EFV (switch) in patients with undetectable HIV RNA. The study has enrolled 355 patients, 177 in the maintenance arm and 178 in the switch arm. The study is to continue until all patients have completed 48-weeks of dosing. As of May 2002, 176 patients had at least 48 weeks of exposure in the switch arm. The study is being conducted by the French ANRS. The applicant did not submit efficacy data in this application. However, the ANRS presented results of the study at a recent international conference. According to the ANRS, 95% of patients in the switch group compared to 87% of maintenance patients had HIV RNA <50 c/mL at 48 weeks. Mean increase in CD4 cells and rates of treatment discontinuation were similar between treatment groups (Poster 551, 10th CROI, Boston, February 2003).

Comment: These results could not be confirmed since the data were not submitted as part of this NDA. If confirmed, they suggest that the Emtriva+ddI+EFV regimen is active and may represent an option for constructing a protease-inhibitor-sparing regimen.

ACTG-5015 is an ongoing study of the once-daily regimen of Emtriva+d4T+Kaletra® (lopinavir/ritonavir) in two age differentiated cohorts (13-30 years and ≥45 years) to evaluate the effect of age on immune reconstitution. The study is being conducted by the Division of AIDS of the NIH under US IND(____). The total duration of dosing is to be 48 weeks. As of September 2002, 91 patients had been enrolled, and 84 were on treatment. Through 24 weeks, the overall proportion of patients with HIV RNA ≤200 c/mL was reported to be 66% and ≤50 c/mL was 82%. No efficacy data was submitted.
Comment: Preliminary data suggest that the regimen is active, as would be expected from a Kaletra-based regimen. Since there is no control arm, it is not possible to determine the contribution of Emtriva to the 24-week efficacy results.

MKC-401 was a phase 3 study designed to evaluate the safety and efficacy of emivirine (MKC-442) a non-nucleoside reverse transcriptase inhibitor (NNRTI), compared to abacavir (ABC). In this study, 564 antiretroviral naïve patients with HIV RNA ≥1000 and <100,000 c/mL and CD4+ cell count >200 cells/mm³ were randomized to receive MKC+Emtriva+d4T (n=376) or Emtriva+ABC+d4T (n=188). The study was designed as a 48-week equivalence study but was terminated early because of inferior antiviral activity in the MKC-442 arm. Since Emtriva was a component of both treatment arms, and the study was terminated early, no contribution of Emtriva to efficacy could be assessed.

C.3 Review of Supportive Efficacy Studies-Uncontrolled Studies

FTC-201 (ANRS-091/MONTANA) is an ongoing phase 2, open-label, non-randomized study evaluating the once-daily regimen of Emtriva+d4T+EFV. The study is being conducted in France. Forty treatment naive patients with HIV RNA ≥5000 c/mL, CD4+ cell count ≥100 cells/mm³, and Karnofsky score ≥60% were enrolled. After 96 weeks of treatment, the proportion with HIV RNA reported to be ≤400 c/mL and ≤50 c/mL was 83% and 80%, respectively. The mean increase in CD4+ cell count from baseline is 259 cells/mm³. The study is being conducted by the French ANRS. It remains ongoing and has been extended to 192 weeks (4 years).

FTC-350 is the rollover protocol for patients who completed study FTC-303 with HIV RNA <400 c/mL at 48 weeks. All patients were offered open-label access to Emtriva in addition to their current antiretroviral regimen until Emtriva becomes commercially available. A total of 289 patients entered study FTC-350. As of September 2002, 106 patients (37%) have discontinued the study for the following reasons: site closing (n=36), withdrawal of consent (n=28), virologic failure (n=15), adverse events (n=14), lost to follow-up (n=5), protocol violations (n=3), death (n=3), and non-compliance (n=2). The Kaplan-Meier probability of virologic failure, defined as HIV RNA >400 c/mL on two occasions 4 weeks apart, was reported to be 13.5%.

C.4 Review of Studies for Indications Not Included in the NDA
D. Efficacy Conclusions

The results from two adequate and well-controlled studies and other comparative and non-comparative studies demonstrate that regimens containing Emtriva impart potent antiviral and
immunologic activity. However, no additional immunologic or virologic benefit was identified compared to 3TC when Emtriva® was used in either a first-line regimen or among patients who had virologic suppression on a 3TC-containing regimen. Compared to the regimen of d4T+ddI, the regimen containing Emtriva appeared more tolerable resulting in fewer discontinuations and less virologic failures; this finding is consistent with previous studies that reported similar findings for regimens containing 3TC.
VII. Integrated Review of Safety

A. 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 Emtriva, however, the safety review benefits from the availability of adverse events from studies in which Emtriva is being or was administered as a monotherapy to patients with chronic HBV infection. In these studies, abdominal pain, asthenia, headache, malaise, pain, diarrhea, dyspepsia, nausea, arthralgia, dizziness, insomnia, paresthesia, increased cough, pharyngitis, rhinitis, pruritis, and rash were reported in ≥3% of patients.

Across the HIV-1 studies included in the NDA, the most common clinical adverse events included those listed above as occurring in HBV studies, as well as myalgia, bronchitis and sinusitis, depressive disorders, neuropathy, and vomiting. In the two comparative 3TC HIV studies, the types, frequency, and severity of adverse events were comparable between Emtriva arms and 3TC arms.

The Emtriva-based regimen used in study FTC-301A caused less adverse events than the d4T-based regimen. This finding is consistent with a significant body of evidence that the combination of d4T+ddI is more difficult to tolerate than 3TC-based regimens.

Grade 3 and 4 liver function abnormalities (elevated AST and ALT) occurred in approximately 5% of Emtriva-treated patients. The frequency was similar among patients in control groups, but led to more study medication discontinuations from Emtriva in study FTC-303. Excessive, but comparable hepatotoxicity occurred in study FTC-302, which was likely due to dose escalation of nevirapine (see Adverse Events of Special Interest).

Other nucleoside analogue related toxicities (e.g., pancreatitis, lactic acidosis, rash, and peripheral neuropathy) occurred with comparable frequency and severity compared to 3TC, but less than with d4T+ddI.

B. Description of Patient Exposure

Development of Emtriva® for treatment of adults with HIV infection has involved administration of the drug to over 2500 individuals: approximately 130 non-infected subjects in single and multiple dose studies and >2400 HIV-infected and HBV-infected patients in clinical trials. Long-term exposure/safety data was derived from approximately 1400 HIV infected adults who received Emtriva at the proposed marketing dose of 200 mg QD for ≥48 weeks. These data represent an estimated 3100 subject-years of exposure to Emtriva. These numbers represent patients who received at least one dose of medication.

Most patients enrolled in the controlled Emtriva clinical trials were male (66% versus 34%), with a mean age of 38 (range 18 to 70) years of age, and similar proportions of Caucasians and Africans, 42% and 45%, respectively. The Emtriva development program was international in scope with a significant number of patients being enrolled in clinical trials from Europe, South
America, and South Africa, which may have contributed to the ethnic distribution described herein.

C. Methods and Specific Findings of Safety Review

The safety review is based on review of phase 1 healthy volunteer, phase 2-3 adult controlled and uncontrolled HIV studies, and phase 2-3 HBV studies.

C.1. Deaths

Twenty deaths among patients treated with Emtriva were reported in the NDA (<1% of all patients): 19 in HIV studies and 1 in a HBV study.

All causes of deaths, regardless of relationship to Emtriva, included: hepatic failure (2), pneumonia (1), pulmonary edema (1), cerebral vascular accident (1), gastrointestinal bleeding due to renal failure (1), hyperkalemia due to renal failure (1), carcinoma of the liver (2), carcinoma (2), cardiac arrest due to a fire (1), lymphoma-like reaction (1), sudden cardiac death (1), accidental overdose (1), lactic acidosis (2), sepsis (1), meningitis (1), embolism (1), accidental injury (1). The relationship of Emtriva in the deaths due to hyperkalemia, the two cases of hepatic failure, the two cases lactic acidosis could not be completely ruled out.

In comparison, eight deaths were reported in patients not receiving Emtriva. The events in this population included: an apparent heart attack, ketosis, lymphoma-like reaction, meningitis, hepatic failure, sudden death possibly related to alcohol abuse, acute kidney failure, and an intentional overdose.

Comment: No specific patterns of toxicities leading to death were identified, and the causes were similar among patients not exposed to Emtriva. It was difficult to assess direct relationship to Emtriva because all patients were on multiple drugs. Pre-clinical testing did not identify specific events likely to cause death.

C.2. Serious and Severe Adverse Events

Serious adverse events (SAEs) were reported in 15% (236/1582) of patients treated with Emtriva in the HIV-1 studies. The most frequent SAEs reported included: hepatic-related events (hepatic failure, acute hepatitis, increased ALT and AST) observed most often in study FTC-302, accidental injury, infections, pneumonia, CNS events, rash events, lactic acidosis, gastrointestinal events (nausea, vomiting, diarrhea, and gastroenteritis), and abortion. The frequencies of these events were approximately 1-2% in each study. In trials in which there was a comparator arm, the types and frequencies of SAEs were generally similar between Emtriva and non-Emtriva containing arms.

Severe or life-threatening adverse events reported in clinical studies included elevated ALT and AST, rash events, increased amylase levels, CNS events, and headache. Again, the frequency of these events was comparable between Emtriva and control arms.
In HBV studies, SAEs were reported in approximately 12% of patients. The most common SAE was exacerbation of hepatitis B following cessation of therapy (which is important for labeling). Other SAEs included: headache, on-treatment hepatitis, threatened abortion, lung cancer, liver cancer, post liver biopsy pain and bleeding, nausea, vomiting, cerebral infarct, and accidental injury; each event occurring in <1% of cases.

C.3. Discontinuations due to Adverse Events

Approximately 9% of patients discontinued Emtriva® across all clinical trials. In controlled HIV studies, hepatic-related events (hepatic failure, hepatitis, abnormal liver function, unspecified hepatic toxicity, and increased AST/ALT) accounted for the majority of discontinuations. Other adverse events that led to discontinuations were diverse and infrequent, and included anemia possibly related to zidovudine, depression, anger, suicidal ideation, peripheral neuropathy. In uncontrolled studies, allergic reactions, lactic acidosis, liver function abnormalities, hepatic-related events, myalgia, pruritis, and rash appeared frequent reasons for discontinuation of treatment arms that contained Emtriva.

In studies FTC-302 and FTC-303 where Emtriva and 3TC were directly compared, more patients discontinued Emtriva for abnormal liver function (elevated AST and ALT), and increased amylase and lipase, than discontinued 3TC.

Discontinuations in the HBV studies were rare (2%), with the most common reasons being headache and digestive disorders.

C.4. General Clinical and Laboratory Adverse Events

The review of clinical and laboratory adverse events was conducted in the following manner:

1. The safety of Emtriva in Phase 1 studies was reviewed. The most common adverse events reported included headache, diarrhea, nausea, dizziness, drowsiness, and rhinitis.

2. In vivo Emtriva undergoes phosphorylation to 3TC monophosphate (which is subsequently converted to the active triphosphate). Therefore, it was reasonable to directly compare the types and frequencies of adverse events in the two studies in which Emtriva and 3TC were directly compared (studies FTC-302 and FTC-303). Selected events that occurred at ≥5% were compared between Emtriva and 3TC, and, where available, further compared to the most common clinical and laboratory adverse events listed in the Epivir® (3TC) label (see Table 7). For some events, the frequency was <5%, but they are included in the table to complete the comparison to historical data.

3. The types and frequencies of adverse events in study FTC-301A were reviewed to determine if there were any observable difference in the safety profiles of Emtriva and d4T (see Table 9).

4. Supportive controlled and uncontrolled HIV and HBV studies were reviewed to determine the frequency of events among patients taking Emtriva, and if any of these events had not previously been observed for 3TC.
C.4.1 General Clinical Adverse Events

Table 7 presents a comparison of adverse events (regardless of severity or relationship to drug) reported in the two 3TC comparative studies (FTC-302 and FTC-303), with a comparison to available historical 3TC adverse event rates as listed in the currently approved Epivir® label.
Table 7. Adverse events occurring in >5% of patients in studies in studies FTC 303 and FTC-302 with comparison to historical rates.

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>FTC-303 QD (n=294)</th>
<th>FTC-303 BID (n=146)</th>
<th>FTC-302 QD (n=234)</th>
<th>FTC-302 BID (n=234)</th>
<th>3TC Historical*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Body as a whole</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>13%</td>
<td>6%</td>
<td>35%</td>
<td>38%</td>
<td>5%</td>
</tr>
<tr>
<td>Pain</td>
<td>15%</td>
<td>12%</td>
<td>16%</td>
<td>15%</td>
<td></td>
</tr>
<tr>
<td>Asthenia</td>
<td>16%</td>
<td>10%</td>
<td>15%</td>
<td>14%</td>
<td></td>
</tr>
<tr>
<td>Fever or chills</td>
<td>9%</td>
<td>6%</td>
<td>4%</td>
<td>7%</td>
<td>10%</td>
</tr>
<tr>
<td><strong>Digestive</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>8%</td>
<td>11%</td>
<td>19%</td>
<td>20%</td>
<td>9%</td>
</tr>
<tr>
<td>Nausea</td>
<td>18%</td>
<td>12%</td>
<td>22%</td>
<td>21%</td>
<td>33%</td>
</tr>
<tr>
<td>Vomiting</td>
<td>9%</td>
<td>7%</td>
<td>17%</td>
<td>16%</td>
<td>13%</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>23%</td>
<td>18%</td>
<td>22%</td>
<td>27%</td>
<td>18%</td>
</tr>
<tr>
<td>Anorexia</td>
<td>5%</td>
<td>2%</td>
<td>6%</td>
<td>6%</td>
<td>10%</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>4%</td>
<td>5%</td>
<td>6%</td>
<td>6%</td>
<td>5%</td>
</tr>
<tr>
<td><strong>Hemic and Lymphatic</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lymphadenopathy</td>
<td>11%</td>
<td>6%</td>
<td>10%</td>
<td>11%</td>
<td></td>
</tr>
<tr>
<td><strong>Nervous system</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neuropathy</td>
<td>4%</td>
<td>3%</td>
<td>6%</td>
<td>5%</td>
<td>12%</td>
</tr>
<tr>
<td>Insomnia</td>
<td>7%</td>
<td>3%</td>
<td>3%</td>
<td>5%</td>
<td></td>
</tr>
<tr>
<td>Dizziness</td>
<td>4%</td>
<td>5%</td>
<td>7%</td>
<td>14%</td>
<td>11%</td>
</tr>
<tr>
<td>Depressive disorders</td>
<td>6%</td>
<td>10%</td>
<td>4%</td>
<td>7%</td>
<td>10%</td>
</tr>
<tr>
<td><strong>Respiratory</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rhinitis</td>
<td>18%</td>
<td>12%</td>
<td>11%</td>
<td>10%</td>
<td>20%</td>
</tr>
<tr>
<td>Increased cough</td>
<td>14%</td>
<td>11%</td>
<td>13%</td>
<td>13%</td>
<td>18%</td>
</tr>
<tr>
<td>Pharyngitis</td>
<td>11%</td>
<td>12%</td>
<td>15%</td>
<td>15%</td>
<td></td>
</tr>
<tr>
<td>Bronchitis</td>
<td>5%</td>
<td>8%</td>
<td>8%</td>
<td>12%</td>
<td></td>
</tr>
<tr>
<td>Sinusitis</td>
<td>6%</td>
<td>7%</td>
<td>4%</td>
<td>4%</td>
<td></td>
</tr>
<tr>
<td><strong>Skin</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rash event^1</td>
<td>17%</td>
<td>14%</td>
<td>23/33%</td>
<td>21/29%</td>
<td>9%</td>
</tr>
<tr>
<td>Herpes simplex</td>
<td>6%</td>
<td>4%</td>
<td>5%</td>
<td>6%</td>
<td></td>
</tr>
<tr>
<td><strong>Metabolic</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lipodystrophy</td>
<td>9%</td>
<td>6%</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td><strong>Musculoskeletal</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Myalgia</td>
<td>4%</td>
<td>4%</td>
<td>6%</td>
<td>4%</td>
<td>8%</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>3%</td>
<td>4%</td>
<td>5%</td>
<td>4%</td>
<td>5%</td>
</tr>
</tbody>
</table>

Source: NDA reports for studies FTC-302 (Table 31, Volume 5.21) and FTC-303 (Table 21, Volume 5.3).

* Rash event includes rash, pruritis, maculopapular rash, urticaria, vesiculobullosus rash, and pustular rash.

Approximately 16% of patients in each treatment arm of study FTC-302 required a dose modification or interruption of the study regimen. The reasons for dose modification or interruption were similar between treatment arms with the most common being headache, nausea, vomiting, rash, and increased AST and ALT.
Table 8 presents the most frequently (>5%) reported treatment-emergent adverse events reported in study FTC-301A, all grades, and regardless of relationship to study drug.

Table 8. Clinical Adverse Events in Study FTC-301A

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Emtriva® (n=286)</th>
<th>Zerit® (n=285)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body as a Whole</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>22%</td>
<td>25%</td>
</tr>
<tr>
<td>Pain</td>
<td>18%</td>
<td>20%</td>
</tr>
<tr>
<td>Asthenia</td>
<td>12%</td>
<td>17%</td>
</tr>
<tr>
<td>Fever or chills</td>
<td>7%</td>
<td>8%</td>
</tr>
<tr>
<td>Digestive</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>23%</td>
<td>32%</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>14%</td>
<td>17%</td>
</tr>
<tr>
<td>Nausea</td>
<td>13%</td>
<td>23%</td>
</tr>
<tr>
<td>Vomiting</td>
<td>9%</td>
<td>12%</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>8%</td>
<td>12%</td>
</tr>
<tr>
<td>Anorexia</td>
<td>3%</td>
<td>6%</td>
</tr>
<tr>
<td>Musculoskeletal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arthralgia</td>
<td>5%</td>
<td>6%</td>
</tr>
<tr>
<td>Myalgia</td>
<td>6%</td>
<td>3%</td>
</tr>
<tr>
<td>Nervous system</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dizziness</td>
<td>25%</td>
<td>26%</td>
</tr>
<tr>
<td>Insomnia and other sleep disorders</td>
<td>16%</td>
<td>21%</td>
</tr>
<tr>
<td>Abnormal dreams</td>
<td>11%</td>
<td>19%</td>
</tr>
<tr>
<td>Depressive disorders</td>
<td>9%</td>
<td>13%</td>
</tr>
<tr>
<td>Neuropathy</td>
<td>4%</td>
<td>13%</td>
</tr>
<tr>
<td>Respiratory</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pharyngitis</td>
<td>12%</td>
<td>10%</td>
</tr>
<tr>
<td>Bronchitis</td>
<td>13%</td>
<td>16%</td>
</tr>
<tr>
<td>Rhinitis</td>
<td>14%</td>
<td>10%</td>
</tr>
<tr>
<td>Increased cough</td>
<td>14%</td>
<td>8%</td>
</tr>
<tr>
<td>Sinusitis</td>
<td>8%</td>
<td>10%</td>
</tr>
<tr>
<td>Skin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rash event*</td>
<td>30%</td>
<td>33%</td>
</tr>
<tr>
<td>Herpes simplex</td>
<td>12%</td>
<td>9%</td>
</tr>
</tbody>
</table>

Source: NDA report for study FTC-301A (Table 22, Volume 5.2). Safety update submitted December 27, 2002.
* Rash event includes rash, pruritis, maculopapular rash, urticaria, vesiculobullous rash, and pustular rash.

The combination of d4T+ddl has an established toxicity profile that is well characterized and is associated with poor tolerability of the regimen. Expected adverse events related to ddl+d4T include peripheral neuropathy, asthenia, diarrhea, nausea, pancreatitis, lactic acidosis, hepatic steatosis and hepatic failure. In study FTC-301A, these events led to the higher rate of discontinuations from the d4T+ddl arm, and likely led to the efficacy difference between treatment arms.

Insomnia, sleep disorders, and abnormal dreams have occasionally been reported among patients receiving 3TC, and were occasionally reported in patients taking Emtriva. In study FTC-301A, all patients received efavirenz, which is known to frequently cause these types of events. Therefore, since the frequency of these events were low in studies FTC-302 and FTC-303 in
which very few patients received efavirenz, it is likely efavirenz was the reason for the higher frequency observed in study FTC-301A.

In a single dose study (study FTC-103), Emtriva increased the AUC₀-∞ and Cₘₐₓ of ZDV by 26% and 66%, respectively. In study FTC-303, approximately 150 patients received concomitant Emtriva and ZDV for up to 48 weeks. The frequency and severity of anemia, the primary dose limiting toxicity of ZDV, was comparable between groups who received ZDV with Emtriva or 3TC. Thus, the increases in certain ZDV pharmacokinetic parameters did not appear to impact its clinical safety.

C.4.2 Laboratory Abnormalities

A comparison of laboratory abnormalities was also conducted. There were no observable differences between Emtriva and 3TC with respect to severe (Grade 3 or 4) laboratory abnormalities. Comparisons to historical 3TC rates were not included because there were very few laboratory events listed in the 3TC label and the grading system using in the 3TC label was different from the system used in the FTC studies.

Between 30-40% of patients in studies FTC-301A, FTC-302, and FTC-303 experienced Grade 3 or 4 laboratory abnormalities (see Tables 9 and 10).
Table 9. Laboratory Abnormalities in Studies FTC-303 and FTC-302

<table>
<thead>
<tr>
<th></th>
<th>FTC-303</th>
<th>FTC-302</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Emtriva (n=294)</td>
<td>Epivir (n=146)</td>
</tr>
<tr>
<td>% with Grade 3 or 4 abnormality</td>
<td>40%</td>
<td>38%</td>
</tr>
<tr>
<td>AST</td>
<td></td>
<td></td>
</tr>
<tr>
<td>All Grades</td>
<td>28%</td>
<td>27%</td>
</tr>
<tr>
<td>Grade 3-4</td>
<td>3%</td>
<td>1%</td>
</tr>
<tr>
<td>(&gt;5 x ULN)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ALT</td>
<td></td>
<td></td>
</tr>
<tr>
<td>All Grades</td>
<td>26%</td>
<td>25%</td>
</tr>
<tr>
<td>Grade 3-4</td>
<td>2%</td>
<td>1%</td>
</tr>
<tr>
<td>(&gt;5 x ULN)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bilirubin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>All Grades</td>
<td>17%</td>
<td>19%</td>
</tr>
<tr>
<td>Grade 3-4</td>
<td>1%</td>
<td>2%</td>
</tr>
<tr>
<td>(&gt;5 x ULN)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serum lipase</td>
<td></td>
<td></td>
</tr>
<tr>
<td>All Grades</td>
<td>1%</td>
<td>2%</td>
</tr>
<tr>
<td>Grade 3-4</td>
<td>1%</td>
<td>1%</td>
</tr>
<tr>
<td>(&gt;2 x ULN)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serum amylase</td>
<td></td>
<td></td>
</tr>
<tr>
<td>All Grades</td>
<td>14%</td>
<td>16%</td>
</tr>
<tr>
<td>Grade 3-4</td>
<td>2%</td>
<td>2%</td>
</tr>
<tr>
<td>(&gt;2 x ULN)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Creatine kinase</td>
<td></td>
<td></td>
</tr>
<tr>
<td>All Grades</td>
<td>41%</td>
<td>52%</td>
</tr>
<tr>
<td>Grade 3-4</td>
<td>11%</td>
<td>14%</td>
</tr>
<tr>
<td>(&gt;4 x ULN)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glucose</td>
<td></td>
<td></td>
</tr>
<tr>
<td>All Grades</td>
<td>52%</td>
<td>54%</td>
</tr>
<tr>
<td>Grade 3-4</td>
<td>3%</td>
<td>3%</td>
</tr>
<tr>
<td>(&gt;250 mg/dL)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Triglycerides</td>
<td></td>
<td></td>
</tr>
<tr>
<td>All Grades</td>
<td>22%</td>
<td>28%</td>
</tr>
<tr>
<td>Grade 3-4</td>
<td>10%</td>
<td>8%</td>
</tr>
<tr>
<td>(&gt;750 mg/dL)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neutrophils</td>
<td></td>
<td></td>
</tr>
<tr>
<td>All Grades</td>
<td>25%</td>
<td>14%</td>
</tr>
<tr>
<td>Grade 3-4</td>
<td>5%</td>
<td>3%</td>
</tr>
<tr>
<td>(&lt;750/mm³)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

ULN = Upper Limit of Normal
Source: NDA reports for studies FTC-302 (Table 35, Volume 5.21) and FTC-303 (Table 27, Volume 5.3).
Table 10. Laboratory Abnormalities in Study FTC-301A

<table>
<thead>
<tr>
<th></th>
<th>Emtriva (n=286)</th>
<th>Zerit (n=285)</th>
</tr>
</thead>
<tbody>
<tr>
<td>% with Grade 3 or 4 abnormality</td>
<td>29%</td>
<td>36%</td>
</tr>
<tr>
<td>AST</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- All Grades</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Grade 3-4 (&gt;5 x ULN)</td>
<td>27%</td>
<td>51%</td>
</tr>
<tr>
<td>- Grade 3-4 (&gt;2 x ULN)</td>
<td>6%</td>
<td>9%</td>
</tr>
<tr>
<td>ALT</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- All Grades</td>
<td>27%</td>
<td>51%</td>
</tr>
<tr>
<td>- Grade 3-4 (&gt;5 x ULN)</td>
<td>5%</td>
<td>6%</td>
</tr>
<tr>
<td>Bilirubin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- All Grades</td>
<td>2%</td>
<td>5%</td>
</tr>
<tr>
<td>- Grade 3-4 (&gt;2 x ULN)</td>
<td>&lt;1%</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>Creatine kinase</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- All Grades</td>
<td>40%</td>
<td>42%</td>
</tr>
<tr>
<td>- Grade 3-4 (&gt;4 x ULN)</td>
<td>10%</td>
<td>10%</td>
</tr>
<tr>
<td>Serum lipase</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- All Grades</td>
<td>4%</td>
<td>4%</td>
</tr>
<tr>
<td>- Grade 3-4 (&gt;2 x ULN)</td>
<td>1%</td>
<td>2%</td>
</tr>
<tr>
<td>Serum amylase</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- All Grades</td>
<td>36%</td>
<td>46%</td>
</tr>
<tr>
<td>- Grade 3-4 (&gt;2 x ULN)</td>
<td>5%</td>
<td>10%</td>
</tr>
<tr>
<td>Pancreatic amylase</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- All Grades</td>
<td>4%</td>
<td>7%</td>
</tr>
<tr>
<td>- Grade 3-4 (&gt;2 x ULN)</td>
<td>&lt;1%</td>
<td>1%</td>
</tr>
<tr>
<td>Glucose</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- All Grades</td>
<td>42%</td>
<td>42%</td>
</tr>
<tr>
<td>- Grade 3-4 (&gt;250 mg/dL)</td>
<td>2%</td>
<td>3%</td>
</tr>
<tr>
<td>Triglycerides</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- All Grades</td>
<td>20%</td>
<td>18%</td>
</tr>
<tr>
<td>- Grade 3-4 (&gt;750 mg/dL)</td>
<td>9%</td>
<td>6%</td>
</tr>
<tr>
<td>Neutrophils</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- All Grades</td>
<td>25%</td>
<td>22%</td>
</tr>
<tr>
<td>- Grade 3-4 (&lt;750/mm³)</td>
<td>5%</td>
<td>7%</td>
</tr>
</tbody>
</table>

ULN= Upper Limit of Normal
Source: NDA report for study FTC-301A (Table 33, Volume 5.9).

Although more patients discontinued Emtriva, the overall frequency of AST, ALT, and bilirubin elevations were comparable between the Emtriva arms in studies FTC-301A and FTC-303. The LFT abnormalities in study FTC-302 were associated with higher rates of clinical hepatotoxicity, which was likely due to the use of nevirapine in the study (see below). Compared to d4T, the frequency of Grade 3 or 4 LFT abnormalities was similar.

The longer duration of therapy with protease inhibitors in study FTC-303 may have led to the higher rates of triglyceride elevations.

Review of data from other controlled and uncontrolled supportive HIV studies yielded no new specific safety concerns.

In HBV studies, Emtriva is being or was administered as monotherapy, thus providing a reasonably good assessment of events directly related to Emtriva. The most common adverse events include headache, flu syndrome, gastrointestinal events (diarrhea and abdominal pain)
malaise, asthenia, and rash. Abnormalities of liver function, specifically elevations in transaminase levels, occurred in 6-10% of patients. Of note, a number of patients experienced flares of liver function (i.e., Grade 3-4 elevations of AST and ALT) following cessation of Emtriva therapy. This phenomenon has been described in patient treated with 3TC and is thought to be related to exacerbation of hepatitis following removal of anti-HBV drug pressure.

Comment: The types and frequencies of adverse events observed in HBV studies were generally comparable to those observed in the HIV studies.

C.5. Adverse Events of Special Interest

Hepatotoxicity, lactic acidosis/hyperlactacidemia, pancreatitis, and rash are well-described adverse events associated with nucleoside analogues used for treatment of HIV, and may be a possible consequence of drug-induced mitochondrial toxicity. Pre-clinical testing suggested that Emtriva® did not have strong affinity for mitochondrial enzymes. However, since Emtriva is a nucleoside analogue, it was prudent that these events be reviewed and discussed to ensure that a potential signal would not be missed.

Emtriva was administered with at least 2 other antiretroviral agents, which also cause adverse events and could confound an accurate assessment of events directly related to Emtriva. Emtriva is being administered as a single agent compared to placebo to patients with chronic HBV infection. Therefore, these patients provide a less biased opportunity to assess Emtriva-related events.

Some HIV-infected women become pregnant in the clinical trials. Although the studies precluded enrollment of pregnant women, required women of childbearing age to practice birth control, and monitored for the occurrence of pregnancy, some women did become pregnant. According to the applicant, antiretroviral therapy was interrupted in all cases of pregnancy. Pregnancy is not a specific contraindication to antiretroviral therapy, and preclinical data suggested that Emtriva did not pose an undue risk to the developing fetus. Therefore, the occurrence and outcomes of pregnancies that occurred in clinical studies were evaluated in an attempt to determine if the preclinical data was, in fact, predictive of clinical outcomes.

An interesting finding of skin discoloration occurring more frequently in non-Caucasians was identified during review of the NDA.

C.5.1 Hepatotoxicity

Early in the conduct of study FTC-302, significant hepatotoxicity, defined grade 3 and 4 elevations of liver function tests (bilirubin, alkaline phosphatase, ALT, and AST) was reported, and there were three deaths secondary to liver failure. Although hepatotoxicity has been reported to occur with all NRTI (there is hepatotoxicity-related class labeling), the Division was concerned that FTC’s additional fluoride residue may have caused the hepatotoxicity to be more severe, as the pattern was similar to that observed with another fluorinated nucleoside analogue: FIAU. FIAU was being investigated for the treatment of HBV in HIV-1 infected patients. During clinical trials, significant numbers of patients experienced moderate AST and ALT
elevations, and two patients experienced fulminant hepatic failure that required liver transplantation; deaths due to liver failure were also reported. Development of FIAU was subsequently discontinued due to these events.

In study FTC-302, patients with baseline HIV RNA <100,000 c/mL received nevirapine (an NNRTI) and d4T (an NRTI) as unblinded background antiretroviral therapy. Nevirapine is administered as one 200 mg tablet once-daily for 14 days and then one 200 mg tablet twice daily. All patients with HIV RNA >100,000 c/mL received efavirenz instead of nevirapine.

A total of 66 patients (29 Emtriva and 37 3TC) experienced at least one Grade 3 or 4 hepatotoxic event during the study, all of which occurred among patients who received nevirapine. The majority of patients also experienced signs/symptoms of hepatitis (nausea, vomiting, rash, jaundice, liver or abdominal tenderness). All cases occurred in patients receiving nevirapine.

Review of demographic characteristics of patients experiencing hepatotoxicity revealed that they were more often female (46 versus 20) with a mean baseline CD4 cell count of 444 cells/mm³ (range 177-930 cells/mm³). Four patients were HbsAg positive and two had serologic evidence of hepatitis C virus infection at screening.

There was a pattern of hepatotoxicity observed in FTC-302. Typically patients began to experience clinical signs and symptoms shortly after escalation of their nevirapine dose from 200 mg once daily to 200 mg twice daily during week 2 of the study. Then, at the next scheduled visit (approximately study week 4) the patient was found to have clinical signs and symptoms of hepatotoxicity. Of the 66 patients, 18 were treated through the hepatotoxicity without sequelae and 17 had medications temporarily interrupted and reintroduced after toxicity resolved. Twenty-one patients (32%) permanently discontinued study medications. Eight patients were switched from nevirapine to efavirenz after their toxicity resolved.

Two patients died, one in each treatment group. Both were black females. Both experienced Grade 4 ALT and AST elevations within 4 weeks of study entry (two weeks following escalation of nevirapine from once to twice daily, and both died within one week of discontinuation of study medication.

In summary, the hepatotoxicity observed in study FTC-302 followed closely the pattern (following escalation of nevirapine from 200 mg once daily to 200 mg twice daily) and the at-risk population (females) described in the nevirapine labeling.

An additional death due to hepatotoxicity was reported in a 22-year old black female who received Emtriva+d4T+MKC-442 (a NNRTI) in study MKC-401. On study day 14, the dose of MKC-442 was increased from 1000 mg/day to 1500 mg/day. On day 23 she was noted to have a rash, on day 29 she had Grade 4 elevations of her AST and ALT, on day 57 she was hospitalized, and on day 65 she died as a result of hepatitis.

In studies FTC-301A and FTC-303, approximately 9% of patients were co-infected with HBV or HCV. In general, the frequency of Grade 3 and 4 transaminitis in the Emtriva arms was similar to the comparator arms.
In study FTC-301A, Emtriva-treated patients experienced seven hepatotoxic events: hepatomegaly (3), hepatitis (1), reactivation of hepatitis B (2), and jaundice (1).

In HBV trials, on treatment transaminitis were reported in 15% of patients treated with Emtriva; approximately 7% of these events were considered Grade 3 or 4. More commonly, however, patients experienced post-treatment exacerbation of hepatitis B days to weeks following cessation of treatment as evidenced by significant transaminitis and hyperbilirubinemia.

C.5.2. Pancreatitis

Emtriva, like 3TC, was not expected to cause significant cases of pancreatitis. Only six cases of pancreatitis were reported in the over 2000 patients contained in the safety database who were treated with Emtriva; five were adults and one was a pediatric patient. None died, and four were receiving concomitant d4T at the time pancreatitis was diagnosed.

C.5.3. Symptomatic hyperlactatemia/lactic acidosis

In studies FTC-301A, FTC-302 and FTC-303, there were no cases of symptomatic hyperlactatemia/lactic acidosis reported in the Emtriva arms. In study FTC-301A, there were seven patients who experienced symptomatic hyperlactatemia/lactic acidosis in the d4T arm; two also had hepatic steatosis, one also had pancreatitis, and one had peripheral neuropathy. Two of the cases were judged to be life threatening, and one was considered severe; two of these patients had resolution following study drug discontinuation, and for one the outcome is unknown because he was lost to follow-up.

C.5.4. Peripheral Neuropathy

Peripheral neuropathy was reported in <10% of Emtriva patients, which was comparable to 3TC, but lower than in patients in study FTC-301A who received d4T+ddl. The majority of cases were mild to moderate, no cases were life-threatening, and no patients discontinued Emtriva due to peripheral neuropathy.

C.5.6. Rash

Nucleoside analogues are known to cause rashes. The applicant defined a “rash event” as allergic reaction, angioedema, erythema multiforme, maculopapular rash, pruritis, pustular rash, urticaria, or vesiculobullous rash. A rash event was reported by approximately 27% of patients who received Emtriva. The majority of rash events were mild to moderate in severity. There were 2 cases of Stevens-Johnson syndrome reported in FTC-302, both patients were receiving Emtriva and nevirapine.

Overall, rash events were reported with similar frequency between patients treated with Emtriva compared to 3TC and d4T (see Tables 7 and 8, above).
The majority of significant rash events occurred in study FTC-302, and appeared temporally related to the increase of nevirapine from 200 mg QD to 200 mg BID.

Rash and pruritis were the most commonly reported skin-related events in the ongoing HBV studies; the frequency was approximately 5% for both.

C.5.7. Pregnancy

Female patients of childbearing potential were required to have evidence of a negative pregnancy test prior to entry. In addition, they were instructed to practice birth control, and were to undergo pregnancy testing every three months. Despite these efforts, 53 women exposed to Emtriva became pregnant. Twenty-nine were terminated by medical abortion, six spontaneous abortions were reported, and there were 19 live births.

At the time pregnancy was reported, study medications were interrupted. Five women were allowed to restart therapy if they had been off study medications for less than 30 days and if they were beyond the first trimester; all five gave birth to healthy babies.

C.5.8 Skin Discoloration

Skin discoloration was reported to occur in 13% (176/1348) of patients in the applicant's largest HIV studies: FTC-301A, FTC-302, FTC-303, and MKC-401. The skin discoloration was described as hyperpigmentation on the palms and soles, and it predominantly occurred in black patients. In the majority of cases, investigators assessed the severity as mild, and no patients discontinued HIV studies due to this event. However, two patients in a HBV study (FTCB-301) discontinued due to skin discoloration.

The Division of Dermatologic and Dental Drug Products (HFD-540) was consulted for an opinion on the potential clinical significance of skin discoloration, and for recommendations for labeling and postmarketing studies.

The Dermatology reviewer found that hyperpigmentation has been noted in patients with HIV infection and is well documented in the literature. Many of the cases may be associated with anti-retroviral therapy, and/or due to concomitant medications such as Bactrim. For example, proliferation or accentuation of palmar/plantar hyperpigmented macules due to zidovudine has been noted in one publication (Bendick, Rasokat, and Steigleder, Arch. Dermatol., 1989). This type of drug induced hyperpigmentation is especially common in African-American patients. The hyperpigmentation has been described as being more prominent in the sun-exposed areas of the skin (e.g. greater darkening of the face than the covered torso). Mucosal and non-sun-exposed surfaces have also been noted to be involved. Accentuation of palmar/plantar and non-palmar/plantar hyperpigmented macules can be seen in patients on various chemotherapeutic agents, such as doxorubicin, adriamycin, bleomycin.

The differential diagnosis of new onset palmar/plantar hyperpigmented macules includes secondary syphilis. This should be given high consideration due to the population being studied (HIV positive patients). Long-standing, single hyperpigmented macules on the palms and soles
in African Americans that are changing (e.g., becoming more accentuated) should give rise to concern about acral lentiginous melanoma. However, this could be ruled out by examination of the lesions by a dermatologist and from history.

In summary, the mechanism and clinical significance of skin discoloration remains unknown, and the labeling will include this information. A post-marketing commitment to evaluate further the nature of these lesions will be obtained. Subjects should have pigmented lesions further assessed. Additional assessment should include screening for RPR and evaluation of concomitant medications. Close-up photographs could help in the documentation and evaluation of these lesions, and biopsies should only be obtained when clinically indicated.

D. Adequacy of Safety Testing

The safety database is robust and contains short and long-term exposure data on >2000 HIV-1-infected and >500 HBV-infected patients exposed to Emtriva® in clinical studies.

E. Summary of Critical Safety Findings and Limitations of Data

Emtriva® exhibited a clinical and laboratory adverse event profile comparable to 3TC. Adverse events occurred with similar frequency in patients treated with Emtriva and 3TC, and occurred with generally less frequency than reported in historical data.

The most common adverse clinical events and laboratory abnormalities include: headache, pain, asthenia, fever/chills, abdominal pain, nausea, vomiting, diarrhea, rhinitis, increased cough, pharyngitis, rash, and increased AST and ALT; these events will be listed in the label.

The safety data reviewed in this NDA demonstrates that Emtriva and 3TC have a comparable safety profile. Compared to d4T, there was a clear difference in adverse events with d4T-treated patients experiencing more gastrointestinal, hepatic, and peripheral neurological events; events that have been well characterized among patients receiving d4T alone and in combination with ddI. These toxicities have led to recommendations that use of d4T+ddI be curtailed, at least as a first-line NRTI regimen.

When adverse events reported in patients treated with Emtriva in studies FTC-301A, FTC-302, and FTC-303 were compared, the rates were generally similar across all Emtriva-containing arms.

The excess frequency of rash (which occurred similarly in both arms) and hepatotoxicity in study FTC-302 was likely due to nevirapine.

The concern that hepatotoxicity observed in patients treated with Emtriva was more severe than that observed with other NRTIs was not borne out. Although several patients experienced significant hepatotoxicity, the frequency and severity were similar amongst patients treated with Emtriva and other NRTIs. There was no hepatic toxicity noted in preclinical toxicity studies. The Emtriva label will, however, contain the same class warning related to hepatotoxicity that is included in other nucleoside labels. In addition, there is a concern, as with other medications
with activity against both HIV and HBV that post treatment exacerbation of hepatitis may occur once therapy is withdrawn. There were cases of this phenomena identified in the NDA. Therefore, the label will include a warning to clinicians about this potential risk.

With respect to other nucleoside analogue-related toxicities (rash, pancreatitis, hyperlactatemia/lactic acidosis, and peripheral neuropathy), the frequency and severity were comparable to 3TC. Pancreatitis, hyperlactatemia/lactic acidosis, and peripheral neuropathy occurred more often among patients who received d4T+ddl, as expected.

Review of the outcomes of pregnancies reported among women exposed to Emtriva did not suggest an increased risk to the health of the woman or the developing fetus. However, adequate and well-controlled studies have not been conducted, so it is unknown if Emtriva may have contributed to the spontaneous abortions. Therefore, given the preclinical and clinical data reviewed herein, Emtriva will be labeled Category B.

The safety data from study FTC-302 was reviewed in order to create a more robust database and provide additional patients for comparisons. No new Emtriva-related adverse events were identified, and as mentioned above, the frequency and severity of adverse events between Emtriva and 3TC were generally comparable. However, because of the problems with its conduct, because it remains on Clinical Hold, and because there were no new findings with regard to Emtriva, the labeling will not contain any reference to study FTC-302.

VIII. Dosing, Regimen, and Administration Issues

The adult dose of Emtriva is one-200 mg capsule daily administered without regard to food. The dose is based on the results of 2 phase 1 studies (FTC-101 and FTC-102) in which escalating doses of FTC were administered for 14 days. Early in development, the Division expressed concerns about the utility of the database from the phase 1 studies as the basis for selection of the dose for phase 3 studies and potential risks to the applicant associated with such a selection. Concerns were raised about the small number of subjects enrolled, the limited duration of dosing (it was not possible to extend dosing beyond 2 weeks for fear of resistance), and whether the data on reductions in HIV RNA demonstrated meaningful differences among the doses studied in FTC-101 and FTC-102. It was suggested that additional dose finding studies be conducted that the clinical trials be modified to include additional doses of FTC for comparisons. The sponsor was encouraged to propose additional dose finding studies, taking into account trial design issues, practicality, and any ethical considerations associated with the conduct of such trials. The applicant chose to initiate all clinical trials using the 200 mg dose. In summary, the 200 mg QD dose appears active, and although it may not be optimal, provides reasonable antiviral benefit and safety margins.

Dosing for patients with renal insufficiency (CrCl <50 mg/mL) will be every 48-96 hour based on CrCl.
IX. Use in Special Populations
A. Evaluation of Gender Effects Analyses and Adequacy of Investigation

Gender

Males and females accounted for 58% and 42% of HIV-1 clinical trial enrollees. There did not appear to be any significant safety differences between males and females. The types of adverse events were similar. Males reported headache, constipation, pruritis, rash, and skin discoloration more frequently and females reported urogenital events more often. The frequency and severity of other adverse events were comparable.

With respect to efficacy outcomes, it appeared that males had better virologic responses than females. In study FTC-303 this may have been due to higher discontinuations among females due to adverse events, and in study FTC-301A only 15% of study participants were female.

B. Evaluation of Evidence for Age, Race, or Ethnicity Effects on Safety or Efficacy

Ethnicity/Race

Approximately 72% of patients enrolled in Emtriva HIV-1 studies were Caucasian.

Racial or ethnic differences did not appear to impact overall response to Emtriva treatment.

Non-Caucasians experienced higher rates of headache, increased AST and ALT, dizziness and skin discoloration. Conversely, Caucasians reported more insomnia and elevated triglyceride levels. The higher rates of increased AST and ALT among non-Caucasians was likely influenced by the overall high frequency of these events in study FTC-302 where >95% of the study population was non-Caucasian. The primarily Caucasian population in study FTC-303, the majority of whom were receiving protease inhibitors, appeared to account for the higher frequency of elevated triglycerides.

Age

In study FTC-301A, the median age of patients was 31 years compared to 41 years in study FTC-303. In general, older patients had lower virologic responses and higher LOVR compared to younger patients.

Patients ≥65 years of age accounted for <1% of HIV-1 trial participants; thus, it was not possible to reach any conclusions about safety or efficacy in this subgroup. Also, there are insufficient pharmacokinetic data in this age group. Although the numbers of elderly patients with HIV-1 infection is overall relatively small, there do not appear from preclinical or clinical studies, any overt contraindications to using Emtriva in this age group. Caution should be exercised, however, in elderly patients who often have decreased renal function; Emtriva should not be administered to patients with a CrCl <50 mg/mL. Additional safety, pharmacokinetic, and efficacy data in this population would be helpful; the applicant will be asked to supply these data as a Phase 4 commitment.
Redacted

pages of trade secret and/or confidential commercial information
X. Conclusions and Recommendations
A. Conclusions

The efficacy data demonstrate that antiretroviral drug regimens including Emtriva® plus two other agents are virologically and immunologically active and produce activity, as measured by suppression of HIV-1 RNA and increases in CD4 cell counts, generally comparable to other triple drug regimens. Thus, Emtriva administered once daily, as part of a multiple drug regimen, represents an additional option for patients who might benefit from a once daily antiretroviral regimen.

Despite in vitro data suggesting greater activity of Emtriva compared to 3TC, there was no immunologic or antiviral advantage in favor of Emtriva over 3TC demonstrated in two clinical studies. At the time the phase 3 studies were initiated, Epivir® was approved only for twice daily administration. Since then, Epivir has been approved for once-daily administration. Therefore, any potential advantage for Emtriva with respect to compliance due to once daily frequency of dosing is limited. A regimen that contains Emtriva appear better tolerated than regimens containing d4T+ddl; a conclusion that has also been reached for regimens containing 3TC.

In HIV trials adverse event data were collected on the entire study drug regimen, which can make it difficult to specify an individual study drug as being related to a particular adverse event. Based on the review of the safety database, Emtriva was generally well tolerated with a safety profile comparable to Epivir. The most common adverse events related to Emtriva included: headache, nausea, vomiting, diarrhea, rash, skin discoloration (primarily amongst non-Caucasians which will be described in the label), and elevated ALT and AST.

Specific nucleoside-related toxicities (i.e., hepatotoxicity, lactic acidosis, rash) also occurred with comparable frequency and severity as 3TC. However, more patients discontinued from the d4T+ddl arm of FTC-301A due to pancreatitis and peripheral neuropathy, which likely led to the differential efficacy results.

Post treatment exacerbation of hepatitis was noted in HBV studies. Although FTC will not be indicated for HBV, a number of HIV infected patients are co-infected with HBV. Thus, some patients with HBV may actually receive FTC. In these cases, there is a potential concern that should a patient discontinue FTC (as anti-HIV therapy) they could experience an exacerbation of hepatitis. The labeling will carry a WARNING to alert clinicians to this possibility.
Resistance to Emtriva emerges rapidly both in vitro by a few passages of the virus in cells and in vivo by a few weeks of monotherapy. The pattern of resistance is similar to lamivudine and is typically manifested by a change at codon 184 of the reverse transcriptase with methionine being substituted with valine or isoleucine (M184V/I). The need for clinicians to assess susceptibility to Emtriva in treatment experienced will be highlighted in the label, as these patients may be less likely to respond to Emtriva if they have previously received 3TC and harbor the M184V/I mutation.

B. Recommendations

Based on the review of the clinical safety and efficacy data submitted in NDA 21-500, this reviewer recommends the Emtriva® application be approved.
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/
----------------------
Russell Fleischer
7/2/03 12:34:02 PM
MEDICAL OFFICER

Jeffrey Murray
7/2/03 03:04:21 PM
MEDICAL OFFICER