1 EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

The safety, pharmacokinetic and antiviral activity reviewed in this NDA support the approval of Emtriva® (emtricitabine, FTC) Oral Solution. Specifically, the Applicant submitted adequate data characterizing the pharmacokinetics of Emtriva Oral Solution in pediatric patients that supports a dose of 6 mg/kg/day (maximum 240 mg/day). Further, the application contained safety, pharmacokinetic and antiviral activity data from 169 HIV-1 infected pediatric patients aged 3 months to 17 years treated with Emtriva® Oral Solution or Emtriva® Capsules in combination with other antiretroviral agents for at least 48 weeks. The data demonstrate comparable exposures (e.g., AUC), safety and efficacy (proportion with HIV RNA <400 c/mL and increases in CD4 cell counts) in pediatric compared to adult patients. Of note, hyperpigmentation manifested as skin discoloration on the palms and soles, occurred substantially more frequently in pediatric patients compared to adults (32% versus 13%); although the etiology remains under investigation, all cases appeared mild with most resolving upon discontinuation of emtricitabine. Finally, the oral solution provides an opportunity for improved dosing in patients with renal impairment; once daily dosing from once every two to four days based on creatinine clearance.

1.2 Recommendation on Postmarketing Actions

1.2.1 Risk Management Activity

Emtriva Capsules have been marketed in the US since September 2004 with a patient package insert. No post-marketing concerns have emerged. As such, no new risk management activity is required.

1.2.2 Required Phase 4 Commitments

- The Applicant is continuing to assess the mechanism of action and clinical significance of hyperpigmentation.
- To address the requirements of PREA, the Applicant has committed to submit the results of an ongoing study of the pharmacokinetics, safety and antiviral activity of emtricitabine in patients 0 (birth) to 3 months of age; a study report is due in March 2006.

1.2.3 Other Phase 4 Requests

There are no new Phase 4 requests for Emtriva Oral Solution.

1.3 Summary of Clinical Findings

1.3.1 Brief Overview of Clinical Program

Emtriva (emtricitabine) Capsules is a member of the class of anti-HIV-1 nucleoside reverse transcriptase inhibitors used in combination with other antiretroviral agents for the treatment of HIV-1 infection in patients >18 years of age.

The clinical program to support approval of Emtriva Oral Solution and Capsules in patients <18 years of age included three clinical studies in which 169 HIV-1 infected pediatric patients (3 months to 21 years of age) received emtricitabine (122 as oral solution and 47 as capsules) in combination with at least two other antiretroviral agents for at least one year (48 weeks). In addition, data were submitted from three clinical pharmacology studies that assessed bioavailability, food effect, and dose-ranging of emtricitabine administered as the oral solution and capsule.

1.3.2 Efficacy

Overall, 83% of pediatric patients achieved and maintained HIV RNA <400 c/mL through 48 weeks of therapy with 73% achieving HIV RNA <50 c/mL. Across all study participants, the median viral load reduction was -3.25 $\log_{10}$ c/mL, the median increase in CD4 cell counts was +198/mm^3 and there were few progressions to advanced CDC stage of disease. These results compare favorably with the efficacy of emtricitabine-containing regimens in adults. However, since emtricitabine was a component of triple drug regimens, and no comparator arms were utilized in any of the clinical trials, the absolute contribution of emtricitabine to efficacy could not be specifically determined.

There were no significant differences in outcomes based on age, degree of antiretroviral experience, or formulation of emtricitabine (Capsules or Oral Solution) used.

1.3.3 Safety

Emtriva® is an approved product with a well characterized safety profile. There was no data in this NDA to suggest that there is a substantial difference in either the types or frequencies of treatment-related adverse events, with the exception of hyperpigmentation, between adult and pediatric patients.

Based on data from previously reviewed trials in HIV-1 infected adults, the common adverse events related to emtricitabine included: headache, nausea, vomiting, diarrhea, rash, skin discoloration (primarily amongst non-Caucasians), elevated ALT and AST levels and neutropenia. The pattern of adverse events was similar between pediatric and adult patients. Headache and nausea occurred less frequently in pediatric patients, while pediatric patients experienced more vomiting, gastroenteritis, fever and infections than adult patients. The higher frequency of vomiting and gastroenteritis may be attributable to the prevalence of gastrointestinal diseases in developing countries as well as the concomitant administration of protease inhibitors.

Of note, there was a case of angioedema associated with rash; as a result, angioedema will be added to the product label.

Hyperpigmentation was reported in 32% (42/132) of pediatric patients compared to 13% in adults. The pattern of skin discoloration was similar to adults, affecting feet and or hands, rarely the tongue, nails and lips. All but one case was considered mild severity and

all but one affected patient was of black African descent. No patient discontinued study medications due to skin discoloration, and 16 (38%) experienced resolution. The mechanism and clinical significance of skin discoloration remains unknown, and the Emtriva labeling includes this information. The applicant is evaluating the nature of these lesions as part of a post-marketing commitment.

1.3.4 Dosing Regimen and Administration

The dose of 6 mg/kg/day (to a maximum of 240 mg) was based on the results of Phase 1 clinical pharmacology studies. The adult dose of emtricitabine, 200 mg QD, was identified in Phase 1/2 trials as being the dose which produced acceptable antiviral activity when given for 14 days of monotherapy and was used in Phase 3 studies of the capsule formulation. In a Phase 1 single-dose trial (Study FTC-105), pharmacokinetic data demonstrated that emtricitabine exposure, expressed as AUC_{tau}, achieved in children receiving a dose of 6 mg/kg QD up to 200 mg, was comparable to the exposure achieved in adults receiving a dose of 200 mg QD, but the oral solution was approximately 20% less bioavailable compared to the capsule formulation. Taking into account the lower bioavailability of the oral solution, the initial dosing recommendation of a maximum of 200 mg/day was modified to allow the emtricitabine oral solution to be administered to a maximum dose of 240 mg. Pharmacokinetic data from patients in the three clinical trials confirmed that the 6 mg/kg/day (to a maximum of 240 mg/day) achieved the targeted AUCs.

1.3.5 Drug-Drug Interactions

Drug-drug interaction studies were conducted during development of the capsule formulation of emtricitabine. Relevant drug-drug interaction information, including recommendations for dose adjustments of emtricitabine or other agents, is included in the Emtriva Capsule label; these will also be included in the Emtriva® Oral Solution label.

1.3.6 Special Populations

In addition to pediatric patients, Emtriva Oral Solution could be used by adults who cannot take or tolerate capsules and by patients with renal and/or hepatic insufficiency. Pharmacokinetic data included in this NDA led to calculations that would allow emtricitabine oral solution to be administered to adult patients with renal impairment once daily based on creatinine clearance versus every two to four days for the capsule formulation. There are no data to support dose adjustments for pediatric patients with renal impairment. It would be extremely difficult for a sponsor to identify sufficient pediatric patients with HIV-1 infection and renal impairment to conduct such a study in that population. However, based on the adult data, it is likely that clinicians could use a similar dosing regimen in pediatric patients with renal impairment.

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