CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

203100Orig1s000

ENVIRONMENTAL ASSESSMENT

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Pharmaceutical Science/Immediate Office

Memorandum

Date: May 02, 2012

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Subject: NDA 203-100: Elvitegravir/Cobicistat/Emtricitabine/Tenofovir Disoproxil Fumarate (EVG/COBI/FTC/TDF) 150/150/200/300 mg Single Tablet Regimen (STR)

Submission Date: November 27, 2011

Gilead Sciences, Inc.
333 Lakeside Drive
Foster City, CA 94404

Background

Gilead Sciences, Inc. has filed NDA application 203-100, a fixed combination of elvitegravir, cobicistat, emtricitabine, and tenofovir disoproxil fumarate, for treatment of HIV infection in adults aged 18 years and older. Gilead Sciences, Inc. has submitted claims of categorical exclusion for elvitegravir, cobicistat, and emtricitabine under 21 CFR 25.15(d) and 21 CFR 25.31(b) and an environmental assessment (EA) for tenofovir disoproxil fumarate by cross-reference to NDA 21-356/S-038.

Review of the Current Submission

The current submission, NDA application 203-100, is for treatment of HIV infection in adults aged 18 years and older using a fixed combination of elvitegravir, cobicistat, emtricitabine, and tenofovir disoproxil fumarate.

The categorical exclusions are based on an expected introduction concentration (EIC) at the point of entry into the aquatic environment of less than 1 part per billion for elvitegravir,

cobicistat, and emtricitabine. The EIC for elvitegravir is [redacted] based on an estimated annual production of [redacted]/year. The EIC for emtricitabine is [redacted] based on an estimated annual production of [redacted] year. The EIC for cobicistat is [redacted] based on an estimated annual production of [redacted]/year. Additionally, in compliance with 21 CFR 25.15 (a), Gilead Sciences, Inc. states, "To the best of Gilead's knowledge, no extraordinary circumstances exist with this filing." A categorical exclusion is acceptable for elvitegravir, cobicistat, and emtricitabine.

For the fourth active ingredient, tenofovir disoproxil fumarate, the applicant references NDA 21-356, Section 1.12.14 Environmental Assessment that was submitted in a Prior Approval Supplement (PAS), SN 0640, dated June 16, 2011. A FONSI was issued for this application on November 8, 2011. Nomenclature, physical-chemical information, environmental fate, and environmental effects data were previously submitted for tenofovir disoproxil fumarate in the cross-referenced EA. No new information, except for a change in estimated predicted sales of tenofovir disoproxil fumarate and the related EIC, is provided. This is basically the same information as was submitted under NDA 21-356 / S-038.

The sponsor estimates that in the first five years of predicted sales of all the applicant's dosage forms and strengths, the highest yearly quantity of tenofovir disoproxil fumarate marketed in the United States, for, will be [redacted] an increase of [redacted] from the last approval. Using this information and the algorithm described in the FDA EA 'Guidance for Industry' document, the updated EIC of tenofovir disoproxil fumarate into the aquatic environment is estimated to be [redacted] This value is an increase from the [redacted] value provided in the June 16, 2011, EA.

Environmental effects data (EC_{50}, LC_{50}, and NOEC) include toxicological studies in *Pseudokirchneriella subcapitata*, *Daphnia magna*, *Oncorhynchus mykiss* and *Pimephales promelas*. A respiration inhibition study was also conducted. For all species, the LOEC or EC_{50}/MEEC ratios were greater than [redacted]. LOEC or EC_{50}/MEEC ratios were recalculated using an EIC of [redacted] and all ratios were still greater than [redacted] greater than the minimum application factor of 100 as specified in the FDA EA guidance document. Additional studies are not required.

Comments and Conclusions

Based on an evaluation of the information provided in this EA and previous EAs, on FDA Guidance, no significant adverse environmental impacts are expected from the approval of this application. A Finding of No Significant Impact (FONSI) is recommended for this application.

Elvitegravir, cobicistat, and emtricitabine qualify for a categorical exclusion under 21 CFR 25.31 (b).

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/s/

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05/03/2012

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05/03/2012