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APPLICATION NUMBER:

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PHARMACOLOGY REVIEW(S)

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

PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND EVALUATION

Application number:	NDA#22-577
Supporting document/s:	SD#1 and 15
Sponsor's letter date:	June 16, 2011 and November 23, 2011
CDER stamp date:	June 9, 2010
Product:	Viread® (tenofovir disoproxil fumarate) Oral Powder
Indication:	HIV in patients from 2 to 12 years of age
Sponsor:	Gilead Sciences, Inc.
Review Division:	DAVP
Reviewer:	Mark W. Powley, Ph.D.
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1 Executive Summary

1.1 Introduction

Tenofovir disoproxil fumarate is an HIV-1 reverse transcriptase inhibitor marketed for treatment of HIV-1 infection in adults and pediatric patients ≥ 12 years of age. This NDA was submitted to support marketing approval for a pediatric population (i.e., 2 to 12 years of age). To accommodate this population, the drug was reformulated as a powder containing up to (b) (4) *g/day of ethylcellulose.*

This review addresses the safety of ethylcellulose.

1.2 Summary of Available Data

Ethylcellulose is a modified cellulose excipient proposed for use in an oral powder formulation of Viread. The maximum proposed oral dose contains (b) (4) *g/day of ethylcellulose for patients* (b) (4) *kg body weight. While this level exceeds the maximum dose of ethylcellulose in marketed oral products (i.e., 308.8 mg per the FDA Inactive Ingredient Database), there appears to be evidence to support the safe use of this excipient.*

Because modified cellulose/cellulose derivatives are not readily absorbed or degraded, effects of ingestion will likely be limited to local toxicity. The World Health Organization reports laxative effects in humans at 5 g modified cellulose/day while constipation and diarrhea were reported at higher doses (WHO, 1990). As such, modified celluloses as a class were given the designation "ADI unspecified" (i.e., food additive with very low toxicity not expected to represent a hazard to health). In addition, the FDA previously granted GRAS status to ethylcellulose as a substance migrating to food from paper and paperboard products (21 CFR 182.90).

Summaries of publications describing non-clinical studies with test-articles containing ethylcellulose are provided below. Although it is not clear that these studies would be acceptable for regulatory submission, the lack of substantial toxicity provides further evidence to support the safety of ethylcellulose.

> *DeMerlis et al. (2005) – A 3 month general toxicity study in rats as well as genotoxicity studies were conducted with Surelease® Aqueous Ethylcellulose Dispersion. This product contains purified water, ethylcellulose, ammonium hydroxide, medium chain triglycerides, and oleic acid. Adverse effects were not reported in rats following administration of ≤ 5000 mg/kg/day for 3 months. In addition, the product was found to lack genotoxic potential in the bacterial reverse-mutation assay, mouse lymphoma assay, and in vivo mouse micronucleus assay.*
>
> *Palmieri et al. (2000) – An embryofetal development study in rats was conducted with Aquacoat® ECD, a dispersion containing ethylcellulose polymer, cetyl alcohol, and sodium lauryl sulfate in water. Statistically significant increases in the litter incidence of incompletely ossified or wavy ribs were detected in offspring from dams administered 4515 mg/kg/day. In addition, a statistically significant increase in the litter incidence of*

thickened ribs was observed at 2709 and 4515 mg/kg/day. These effects were described as reversible development delays and, in absence of other findings, were not considered biologically significant. The authors conclude that the NOAEL was ≥ 4515 mg/kg/day.

Kotkoskie and Freeman (1998) – A 90 day general toxicology study in rats was conducted with Aquacoat® ECD, a dispersion containing ethylcellulose polymer, cetyl alcohol, and sodium lauryl sulfate in water. Test article-related effects were limited to minor increases in ALT and AST with decreased total protein and globulin in males at 2709 and/or 4515 mg/kg/day. The authors conclude that the NOAEL was ≥ 4515 mg/kg/day in females compared to 903 mg/kg/day in males.

1.3 Conclusion

Non-clinical and clinical studies of ethylcellulose are limited. However, it is reasonable to assume this excipient will behave similar to other modified cellulose products. Due to the lack of bioavailability, the primary effects of these molecules are limited to the GI tract. Because the GI tract is considered functionally mature by ~ 2 years of age (Walthall et al., 2005), effects in pediatric and adult patients are unlikely to differ.

While the potential for GI effects (e.g., laxative effects, etc.) must be considered, the available data suggest minimal risk associated with oral administration of high doses of ethylcellulose.

1.4 References

DeMerlis CC, Schoneker DR, Borzelleca JF (2005) A subchronic study in rats and genotoxicity tests with an aqueous ethylcellulose dispersion. *Food Chem. Toxicol.* 43:1355-1364

Kotkoskie LA, Freeman C (1998) Subchronic oral toxicity study of Aquacoat ECD ethylcellulose aqueous dispersion in the rat. *Food Chem. Toxicol*. 36:705-709

Palmieri MA, Freeman C, Kotkoskie LA (2000) Developmental toxicity study of Aquacoat ECD ethylcellulose aqueous dispersion administered orally to rats. *Food Chem. Toxicol.* 38:71-74

Walthall K, Cappon GD, Hurtt ME, Zoetis T (2005) Postnatal development of the gastrointestinal system: a species comparison. *Birth Defects Res.Part B* 74:132-156

World Health Organization (1990) JEFCA Monograph - modified celluloses. *WHO Food Additives Series* 26

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/s/

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12/01/2011

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