FDA Advisory Committee Briefing Document
Viread™ (Tenofovir DF)
NDA 21-356

Errata

Page 13

3.4 Mitochondrial toxicity

In vivo, no evidence of mitochondrial-related hepatic, hematologic, cardiac, pancreatic, or skeletal muscle toxicity was detected in chronic toxicity studies (42-weeks) in rats and dogs. *An in vivo study to further evaluate potential mitochondrial effects is ongoing in woodchucks.*

3.5 Nonclinical Pharmacology and Toxicology

The nonclinical safety profile of ~~adefovir dipivoxil~~ *tenofovir DF* has been extensively evaluated in pharmacokinetic/ADME, pharmacology, and toxicology studies using test systems and protocols accepted by the ICH and international health authorities.

Page 14

3.5.1 Safety Pharmacology

An assessment of effects on renal function demonstrated ~~increased~~ *decreased* urinary electrolyte excretion and urine volume in rats administered tenofovir DF 500 mg/kg; no effect was observed at 50 mg/kg.

Page 15

3.5.3.1 Gastrointestinal toxicity

No GI toxicity occurred in monkeys administered tenofovir DF for 56 days at doses up to ~~50 mg/kg/day~~ *250 mg/kg/day*.

Page 16

3.5.3.3 Bone

Monkeys treated chronically with tenofovir (sc) 10 mg/kg/day (~~AUC - 8X humans~~) *(AUC - 4X humans)*, had no clinical or radiographic evidence of bone toxicity, and animals who were dose-reduced from 30 mg/kg/day to 10 mg/kg/day showed improvement in bone parameters.

Page 17

3.5.4 Genetic and Reproductive Toxicity

In a study of effects on peri- and postnatal development in rats, reduced survival in the F1 generation was observed and was considered to be due to maternal toxicity *with resultant lack of adequate maternal care* at doses of 450and 600 mg/kg/day.