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Committee for Medicinal Products for Human Use (CHMP)

Assessment report

VIREAD

International non-proprietary name: TENOFOVIR DISOPROXIL FUMARATE

Procedure No. EMEA/H/C/000419/II/0119

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

AE	adverse event
ALT	alanine aminotransferase
ARV	antiretroviral
AST	aspartate aminotransferase
BL	baseline
BMD	bone mineral density
BMI	body mass index
CCDS	Company Core Data Sheet
CFR	Code of Federal Regulations
CHB	chronic hepatitis B
CHMP	Committee for Medicinal Products for Human Use
CSR	Clinical Study Report
DB	double-blind
DBEE	double-blind efficacy evaluation
DEXA	dual-energy x-ray absorptiometry
DNA	deoxyribonucleic acid
EMEA	European Medicines Evaluation Agency
EU	European Union
FAS	Full Analysis Set
GCP	Good Clinical Practice
GSI	Gilead Sciences, Inc.
HBeAg	hepatitis B early antigen
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCC	hepatocellular carcinoma
HCV	Hepatitis C virus
HDV	Hepatitis D virus
HIV	human immunodeficiency virus
HIV-1	human immunodeficiency virus type 1
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IRB	Institutional Review Board
IVRS	interactive voice response system
LLoQ	lower limits of quantitation
MAH	Marketing Authorisation Holder
NtRTI	nucleotide reverse transcriptase inhibitor
OL	open-label
PDCO	Paediatric Committee
PIP	paediatric investigation plan
PK	pharmacokinetics
PLB	placebo
pol	polymerase
PRT	proximal renal tubulopathy

RAT	randomized and treated
RDA	recommended daily allowance
RT	reverse transcriptase
RSI	Request for supplementary information
SAE	serious adverse event
SD	standard deviation
SmPC	Summary of Product Characteristics
SOC	system organ class
TDF	tenofovir disoproxil fumarate
TFV	tenofovir
ULN	upper limit of the normal range
US	United States

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1. Scientific discussion

1.1. Introduction

This Type II variation for Viread 245 mg film-coated tablets seeks to extend the indication for the treatment of HIV-1 to include treatment-experienced adolescents 12 to < 18 years of age.

This procedure in parallel with application EMEA/H/X/105G will cover the HIV paediatric population aged 2 to < 18 years.

This Type II variation provides data related to treatment-experienced adolescents 12 to < 18 years old, combined with the limited treatment options and limitations of other drugs in the nucleoside reverse transcriptase inhibitor (NRTI) class to support the extension of use of Viread to include HIV-1 infected treatment-experienced adolescents 12 to < 18 years of age.

The MAH also provided a clinical overview that refers to the studies that comprise the ongoing clinical development programs for TDF both in HIV-1 and HBV infected paediatric subjects.

Efficacy and safety data in HIV-1 infected adolescents are supported by the comprehensive adult data, and by clinical study data in younger HIV-1 infected subjects and in HBV infected adolescents. In addition, existing post-marketing data show the profile of AEs with a possible association to TDF in paediatric cases to be consistent with that observed in adults.

The clinical studies referred to in the Clinical overview have been previously submitted for this product.

- GS-US-104-0321 (pivotal phase III study in HIV-infected adolescents)
- GS-US-104-0352 (pivotal phase III study in HIV-infected subjects aged 2 to <12 years of age)
- GS-01-926 (phase I study in HIV-1 infected paediatric subjects)
- GS-01-927 (phase I/II study in HIV-infected paediatric subjects)
- GS-US-174-0115 (pivotal phase III study in TDF-naive adolescents 12 to < 18 years old with CHB)

This assessment report summarises the most relevant aspects of study GS-US-104-0321 in support of the extension of indication for the treatment of adolescents infected with HIV. Detailed data is included in the CHMP assessment report of the procedure EMEA/H/C/419/II/98 where this study has also been submitted.

About the product

Tenofovir disoproxil fumarate (tenofovir DF, TDF) is a nucleotide reverse transcriptase inhibitor (NtRTI).

Viread tablets (containing 245 mg of tenofovir disoproxil as fumarate, equivalent to 300 mg tenofovir DF or 136 mg of tenofovir) was first approved in US (26 October 2001), EU (5 February 2002), and other countries worldwide for the treatment of human immunodeficiency virus type 1 (HIV-1) in combination with other antiretroviral (ARV) medicinal products in infected adults aged 18 years and older.

Viread was subsequently approved for the treatment of chronic hepatitis B in EU (23 April 2008) and US.

Following approval for use in adults, clinical development programs are being undertaken in HIV-1 and HBV infected paediatric subjects. In the EU, a paediatric investigation plan (PIP) for Viread was agreed on 08 February 2010 (EMEA-000533-PIP01-08, Decision Ref. EMA/63121/2010 P/18/2010).

In the United States (US), Viread tablets were approved for the treatment of HIV-1 infected subjects 12 to < 18 years of age and with body weight ≥ 35 kg on 25 March 2010.

In the European Union, the MAH has submitted in June 2010 a type II variation EMEA/H/C/419/II/98 to extend the therapeutic indication to treatment-experienced adolescents 12 to < 18 years of age and with body weight ≥ 35 kg. Following major objections raised by the CHMP, mainly driven by the lack of reassurance on the renal and bone toxicity of the drug in this population together with inadequate efficacy demonstration, the indication was not extended to include treatment-experienced adolescents 12 to < 18 years of age and with body weight ≥ 35 kg.

1.2. Non-clinical aspects

1.2.1. Ecotoxicity/environmental risk assessment

An ERA has been submitted in accordance with Article 8(3) of Directive 2001/83 requirements.

Table 1. Summary of main study results

Substance (INN/Invented Name): tenofovir disoproxil fumarate				
CAS-number (if available):				
PBT screening		**Result**		**Conclusion**
Bioaccumulation potential- log K_{ow}	OECD107	0.992 at pH 4 1.18 at pH 7 could not be determined at pH 10 due to the instability of TDF in the buffer phase		Potential PBT: no
Phase I				
Calculation	**Value**	**Unit**		**Conclusion**
PEC $_{surfacewater}$, default or refined (e.g. prevalence, literature)	1.5	μg/L		> 0.01 threshold
Phase II Physical-chemical properties and fate				
Study type	**Test protocol**	**Results**		
Adsorption-Desorption	OECD 121	K_{oc} = 18 L/kg		
Ready Biodegradability Test	OECD 301	Not readily biodegradable		
Aerobic and Anaerobic Transformation in Aquatic Sediment systems	OECD 308	TDF rapidly underwent primary degradation converting to several degradation products		
Phase IIa Effect studies				
Study type	**Test protocol**	**Endpoint**	**value**	**Unit**
Algae, Growth Inhibition *Pseudokirchneriella subcapitata*	OECD 201	NOEC EC_{50}	14 47	mg/L mg/L
Daphnia, acute immobilisation test / Daphna magnia	OECD 202	NOEC EC_{50}	98 ≥ 98	mg/L mg/L
Fish Acute Toxicity Test Rainbow trout, *Oncorhynchus mykiss*	OECD 203	NOEC LC_{50}	92 >92	mg/L mg/L
Daphnia sp. Reproduction Test *Water fleas*	OECD 211	NOEC EC_{50}	13 21	mg/L mg/L

Fish, Early Life Stage Toxicity Test/ Fathead Minnow, *Pimephales promelas*	OECD 210	NOEC LOEC	1.9 >1.9	mg/L mg/L
Activated Sludge, Respiration Inhibition Test	OECD 209	NOEC EC_{50}	600 940	mg/L* mg/L*
Phase IIb Studies				
Sediment dwelling organism *Chironomus riparius*	OECD 218	NOEC	100	mg/kg

* active ingredient

It is considered by the CHMP that Viread is unlikely to represent a risk to the aquatic environment, to micro-organisms, or to sediment dwelling organisms.

1.3. Clinical aspects

Pharmacokinetics

Available PK data in paediatric patients from initial studies

Initial clinical studies were undertaken using an oral suspension formulation (GS-02-983 in HIV-1 infected subjects 2 to 8 years of age) and 75-mg tablets of tenofovir DF (GS-01-926 and GS-01-927 in HIV-1 infected subjects 6 to 16 years of age). Each of these studies included pharmacokinetic assessments for all subjects. Based on data from these studies, the dose of tenofovir DF selected for investigation in subsequent studies was 8 mg/kg of actual body weight to a maximum of 300 mg/day (≥ 35 kg).

Table 2. Pharmacokinetic Evaluations in HIV-1 Infected Pediatric Subjects

Study	Study Design	Age Group (years)	Number of Subjects Evaluated
GS-US-104-0321	Multidose, Phase 3	12 – < 18	8
GS-01-926	Multidose, Phase 1	6 – 16 inclusive	18
GS-01-927	Multidose, Phase 1/2	9 – 16 inclusive	7
GS-02-983	Single-dose, Phase 1	2 – 8 inclusive	12

In adolescents, the efficacy and safety of TDF is being evaluated in an ongoing Phase 3 study (GS-US-104-0321) of HIV-1 infected, treatment-experienced adolescents (12 to 18 years of age and with a body weight ≥ 35 kg) who were failing to achieve virologic suppression on their existing antiretroviral regimen. In this pivotal study, TFV pharmacokinetics were examined in 8 HIV-1 infected adolescent subjects receiving the TDF 300-mg tablet once daily plus a background antiretroviral regimen for at least 4 weeks. Steady-state TFV exposures achieved in these subjects (AUCtau 3390.6 ng·h/mL, Cmax 377.5 ng/mL, and Tmax 1.98 hours) were similar to those observed in HIV-1 infected adults receiving TDF 300 mg/day.

Pharmacokinetic data are also available from 7 HIV-1 infected subjects 12 to < 18 years of age who received multiple doses of TDF 300 mg once daily (4 × 75 mg tablets) in earlier Phase 1/2 Studies GS-01-926 and GS-01-927 (combined data). Tenofovir was rapidly absorbed with a median Tmax of 2.08 hours and mean Cmax of 268.3 ng/mL. A mean AUCtau of 3007.8 ng•h/mL and a median T½ of 13.99 hours were achieved.

The overall PK data available, including the PK data in adolescent from the study -321, show an almost similar exposure in adolescents and adults dosed with the 300mg tablet, supporting the use of a

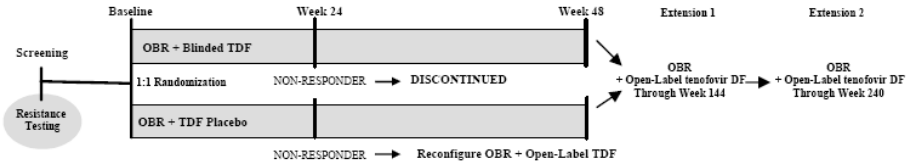
300mg dose (equivalent to a 8mg/kg dose for patient with 37.5kg weight) in adolescents aged 12 to <18 years and weighting ≥ 35kg.

1.4. Clinical efficacy

Study design

Design aspects for study GS-US-104-0321 are summarized below:

Title of the study	A Phase 3, double-blind, randomized, placebo-controlled study of the Safety and Efficacy of Tenofovir DF as Part of an Optimized Antiretroviral Regimen in HIV-1 Infected Adolescents
Study Centers	18 study centers: 17 in Brazil and 1 in Panama (US sites were initiated but did not enroll any subjects)
Study Period:	13 June 2006 (first subject screened) 09 March 2009 (last subject observation for this report) Anticipated date for completion (last patient, last visit): By March 2013
Objectives	The primary objective of this study was as follows: • To assess the efficacy of tenofovir DF plus a genotype-guided optimized background regimen (OBR) compared to placebo plus OBR in the treatment of HIV-1 infected antiretroviral treatment-experienced adolescents with plasma HIV-1 RNA levels ≥ 1000 copies/mL through 24 weeks of drug exposure. The secondary objectives of this study (Weeks 0–48) were as follows: • To assess the efficacy of tenofovir DF plus a genotype-guided OBR compared to placebo plus OBR in the treatment of HIV-1 infected antiretroviral treatment-experienced adolescents with plasma HIV-1 RNA levels ≥ 1000 copies/mL through 48 weeks of drug exposure. • To evaluate the safety and tolerability of tenofovir DF plus OBR compared to placebo plus OBR. • To measure changes in bone mineral density (BMD) in the two treatment groups. A secondary objective that will be evaluated beyond Week 48 (Weeks 0–240) is as follows: • To evaluate the long-term efficacy, safety, and tolerability of treatment with tenofovir DF through up to 240 weeks of drug exposure.
Population and main inclusion criteria	HIV-1 infected male and female subjects, 12 to < 18 years of age, with plasma HIV-1 RNA ≥ 1000 copies/mL and weight ≥ 35 kg. Subjects were naive to tenofovir DF and had no K65R mutation on genotypic testing, had prior treatment experience with at least two antiretroviral drug classes, and were receiving combination antiretroviral therapy for at least 12 weeks at the time of study entry. Subjects also had to have adequate hematologic, renal and hepatic functions, and based upon resistance testing, were able to receive an OBR not containing didanosine. Patients with history of significant renal or bone disease were excluded.
Number of subjects	Planned: 100 evaluable (50 in each treatment group) Randomized and treated (RAT): 87 (tenofovir DF 45, placebo 42; All TDF 81 [double-blind and extension phase data for subjects who received tenofovir DF in the study])
Study duration	240 weeks
Criteria for	Efficacy: The primary efficacy endpoint was time-weighted average change from baseline through Week 24 (DAVG24) in plasma HIV-1 RNA.

evaluation	Among secondary endpoints: DAVG48, change from baseline in log10 HIV-1 RNA at Weeks 24 and 48, change from baseline in CD4 cell count and CD4% at Weeks 24 and 48, proportion of subjects with HIV-1 RNA < 400 copies/mL and < 50 copies/mL at Weeks 24 and 48, time to virologic failure Safety: Safety data were collected for the following parameters: adverse events (AEs); clinical laboratory tests; spine and total body BMD (assessed using DEXA); bone biochemical markers; height; weight; vital signs; and physical examinations (complete or symptom-directed).
Dosing regimen	Adolescent (weighing ≥ 35 kg) received the 300mg dose of TDF (i.e. approved adult dose). All subjects were instructed to take their assigned tenofovir DF dose orally, once daily, without regard to meals. The tenofovir DF tablets were film-coated to mask taste.
Study design	This was a 48-week, randomized, double-blind, placebo-controlled, multi-center study of the safety and efficacy of tenofovir DF as part of an optimized antiretroviral regimen in HIV-1 infected adolescents (12 years to < 18 years of age) who were failing their current antiretroviral regimen and had HIV-1 RNA levels ≥ 1000 copies/mL at screening. Two consecutive 96-week study extensions (ongoing) will evaluate the long-term efficacy, safety, and tolerability of open-label tenofovir DF as part of an optimized antiviral regimen, providing data for up to 240 weeks of total drug exposure.  Pretreatment: HIV-1 genotyping was performed as part of the screening assessments to assist in the construction of an OBR, defined as at least 3, but no more than 5 antiretroviral agents, not including tenofovir DF or placebo. Baseline–Week 48: Subjects were randomized in a 1:1 ratio to receive either tenofovir DF + OBR or placebo + OBR. Stopping rules: At Week 24, subjects who were adherent to study drug (in the opinion of the investigator), but did not demonstrate a ≥ 0.5 log10 copies/mL decrease from baseline in HIV-1 RNA, were considered to be nonresponders and were unblinded. Nonresponders randomized to the placebo group were given the option to continue on study and receive open-label tenofovir DF with an appropriate background regimen determined by the investigator. Nonresponders randomized to the tenofovir DF treatment group were discontinued from the study. The majority of efficacy and safety assessments were performed at each clinic visit (Weeks 4, 8, 16, 24, 32, 40, and 48). Bone biochemical markers were assessed at baseline, and at Weeks 4, 16, 24, 32, and 48. Dual energy x-ray absorptiometry (DEXA) scans to assess spine and total body BMD and body fat (including limb fat) were performed at baseline, Week 24, and Week 48.

Main efficacy results

Table 3. The primary efficacy endpoint was time-weighted average change from baseline through Week 24 ($DAVG_{24}$) in plasma HIV-1 RNA (log10 copies/mL).

Time-Weighted Average Change in HIV-1 RNA (log_{10} copies/mL) from Baseline through Week 24 ($DAVG_{24}$)[a, b, c]	Tenofovir DF (N = 44)	Placebo (N = 41)	p-value[d]
DAVG Through Week 24			
N	44	41	0.55
Mean (SD)	−1.246 (1.1160)	−1.346 (1.2449)	
Median	−1.580	−1.549	
Q1, Q3	−2.15, −0.27	−2.36, −0.34	
Min, Max	−2.81, 0.89	−3.09, 0.88	

a DAVG through time X is the time weighted average between the first postbaseline value through the last value up to week X minus the baseline value.

b HIV-1 RNA analyzed using Roche PCR Ultrasensitive assay (range 50 to 100,000 copies/mL); or PCR COBAS as a reflex test.

c HIV-1 RNA collected after first dose of open-label tenofovir DF or after last randomized dose date + 2 days (if terminated) for double-blind groups was excluded.

d p-value is from a Van Elteren test stratified by baseline genotypic sensitivity score (GSS) (without tenofovir DF) <= or > median [median GSS is 2].

Both treatment groups exhibited clinically relevant decreases from baseline in plasma HIV-1 RNA; the median DAVG24 in plasma HIV-1 RNA was −1.580 log10 copies/mL in the tenofovir DF group (n = 44) and −1.549 log10 copies/mL in the placebo group (n = 41) (p = 0.55, Van Elteren test). However, there were no statistically significant differences between treatment groups in the DAVG24 in plasma HIV-1 RNA or for any of the secondary efficacy endpoints at any of the timepoints analysed.

Summary of main study results

Table 4. Summary of Efficacy for trial GS-US-104-0321

Title: A Phase 3, Randomized, Double-Blind, Placebo-Controlled Study of the Safety and Efficacy of Tenofovir DF as Part of an Optimized Antiretroviral Regimen in HIV-1 Infected Adolescents	
Study identifier	Gilead protocol number: GS-US-104-0321 EudraCT number: 2007-003418-32
Design	This was a 48-week, randomized, double-blind, placebo-controlled, multicenter study of the safety and efficacy of tenofovir DF as part of an optimized antiretroviral regimen in HIV-1 infected adolescents (12 years to < 18 years of age) who were failing their current antiretroviral regimen and had HIV-1 RNA levels >= 1000 copies/mL at screening. Data from three consecutive 96-week study extensions (ongoing) have been used to evaluate the long-term efficacy, safety, and tolerability of open-label tenofovir DF as part of an antiviral regimen, providing data for up to 336 weeks of total drug exposure. Pretreatment: HIV-1 genotyping was performed as part of the screening assessments to assist in the construction of an OBR, defined as at least 3, but no more than 5 antiretroviral agents, not including tenofovir DF or placebo. Randomized Phase: Participants were randomized in a 1:1 ratio to receive either tenofovir DF + OBR or placebo

	+ OBR. The majority of efficacy and safety assessments were performed at each clinic visit (Weeks 4, 8, 16, 24, 32, 40, and 48). At Week 24, participants who were adherent to study drug (in the opinion of the investigator), but did not demonstrate a >= 0.5 log10 copies/mL decrease from baseline in HIV-1 RNA, were considered to be nonresponders and were unblinded. Nonresponders randomized to the placebo group were given the option to continue on study and receive open-label tenofovir DF with an appropriate background regimen determined by the investigator. Nonresponders randomized to the tenofovir DF treatment group were discontinued from the study. Extension Phases: After completing 48 weeks of double-blind treatment with tenofovir DF or placebo, participants who had not reached 18 years of age, and who, in the opinion of the investigator, would derive clinical benefit from the use of open-label tenofovir DF, were given the option to continue (or initiate) treatment with open-label tenofovir DF in the first of three 96 week study extension periods. Nonresponders who received open-label tenofovir DF after Week 24 were also considered eligible for the first study extension if they met the above criteria at Week 48. After completing the first (or second) 96 week study extension, participants who had not reached 18 years of age, and who had shown ongoing clinical benefit from tenofovir DF, were given the option to continue receiving open-label tenofovir DF for an additional 96 weeks or until tenofovir DF became commercially available in the country where the participants were enrolled, whichever occurred first.		
	Duration of main phase:		48 weeks
	Duration of Run-in phase:		Not applicable
	Duration of Extension phase:		Up to 288 weeks (total duration up to 336 weeks including main phase of 48 weeks)
Hypothesis	Superiority		
Treatments groups	Treatment A		Tenofovir DF 300-mg tablets + optimized background regimen (Weeks 0–48) (n=44, ITT analysis set).
	Treatment B		Matching tenofovir DF placebo tablets + optimized background regimen (Weeks 0–48) (n=41, ITT analysis set).
Endpoints and definitions	Primary endpoint	DAVG24	Time-weighted average change from baseline through Week 24 ($DAVG_{24}$) in plasma HIV-1 RNA (log10 copies/mL)
	Secondary endpoint	DAVG48	Time-weighted Average Change from Baseline through Week 48 ($DAVG_{48}$) in Plasma HIV-1 RNA (log10 copies/mL)
	Secondary endpoint	Change from baseline HIV-1 RNA (LOCF)	Change from Baseline in $\log_{10}$ HIV-1 RNA at Week 48 (Last observation carried forward)
	Secondary endpoint	Change from baseline CD4% (M=E)	Change from baseline in CD4 percentage (%) at Week 48 (Missing = Excluded analysis)
	Secondary endpoint	Change from baseline CD4 count (M=E)	Change from baseline in CD4 cell count (cells/mm3) at Week 48 (Missing = Excluded analysis)
	Secondary endpoint	HIV-1 RNA decrease of $\geq$ 1.0 $\log_{10}$ copies/mL (LOCF)	Proportion of subjects achieving a plasma HIV-1 RNA decrease of $\geq$ 1.0 $\log_{10}$ copies/mL from baseline at Weeks 48 (Last observation carried

			forward)
	Secondary endpoint	HIV-1 RNA < 400 copies/mL (M=F)	Proportion of subjects with plasma HIV-1 RNA < 400 copies/mL at Week 48 (Missing = Failure analysis)
	Secondary endpoint	HIV-1 RNA < 50 copies/mL (M=F)	Proportion of subjects with plasma HIV-1 RNA < 50 copies/mL at Week 48 (Missing = Failure analysis)
Database lock	31 March 2009 for the primary efficacy analysis		

Results and Analysis

Analysis description	**Primary Analysis**		
Analysis population and time point description	Intent to treat – 48 weeks.		
Descriptive statistics and estimate variability	Treatment group	Treatment A	Treatment B
	Number of subject	44	41
	DAVG24 Median (Q1, Q3)	-1.58 (-2.15, -0.27)	−1.55 (−2.36, −0.34)
	DAVG48 Median (Q1, Q3)	−1.42 (−2.25, −0.25)	−1.35 (−2.72, −0.53)
	Change from baseline HIV-1 RNA (Week 48; LOCF) Mean (standard deviation)	−1.19 (1.451)	−1.46 (1.460)
	Change from baseline CD4% (Week 48; M=E) Mean (standard deviation)	5.7 (4.47)	5.1 (4.01)
	Change from baseline CD4 count (Week 48; M=E) Mean (standard deviation)	155 (233.0)	182 (190.9)
	HIV-1 RNA decrease of ≥ 1.0 $\log_{10}$ copies/mL (Week 48; LOCF) n (%)	21/44 (47.7%)	22/41 (53.7%)
	HIV-1 RNA < 400 copies/mL (Week 48; M=F) n (%)	15/44 (34.1%)	18/41 (43.9%)
	HIV-1 RNA < 50 copies/mL (Week 48; M=F) n (%)	12/44 (27.3%)	15/41 (36.6%)

Effect estimate per comparison	DAVG24	Comparison groups	Treatment A versus Treatment B
		Difference between groups	Not calculated -
		95% Confidence Interval	Not calculated -
		P-value (Van Elteren test stratified by baseline genotypic sensitivity score (GSS) (without tenofovir DF) <= or> median [median GSS is 2])	0.55

	DAVG48	Comparison groups	Treatment A versus Treatment B
		Difference between groups	Not calculated -
		95% Confidence Interval	Not calculated -
		P-value (Van Elteren test stratified by baseline genotypic sensitivity score (GSS) (without tenofovir DF) <= or> median [median GSS is 2])	0.40
	Change from baseline HIV-1 RNA (LOCF)	Comparison groups	Treatment A versus Treatment B
		Difference between groups	Not calculated -
		95% Confidence Interval	Not calculated -
		P-value (Van Elteren test stratified by baseline genotypic sensitivity score (GSS) (without tenofovir DF) <= or> median [median GSS is 2])	0.37
	Change from baseline CD4%	Comparison groups	Treatment A versus Treatment B
		Difference between groups	Not calculated
		95% Confidence Interval	Not calculated
		P-value (Van Elteren test stratified by baseline genotypic sensitivity score (GSS) (without tenofovir DF) <= or > median [median GSS is 2].)	0.63
	Change from baseline CD4 count	Comparison groups	Treatment A versus Treatment B
		Difference between groups	Not calculated -
		95% Confidence Interval	Not calculated -
		P-value (Van Elteren test stratified by baseline genotypic sensitivity score (GSS) (without tenofovir DF) <= or > median [median GSS is 2])	0.47

	HIV-1 RNA decrease of ≥ 1.0 log_{10} copies/mL	Comparison groups	Treatment A versus Treatment B
		Difference between groups	Not calculated -
		95% Confidence Interval	Not calculated -
		P-value (Fisher's exact test)	0.67
	HIV-1 RNA < 400 copies/mL (M=F)	Comparison groups	Treatment A versus Treatment B
		Difference between groups	Not calculated -
		95% Confidence Interval	Not calculated -
		P-value (Fisher's exact test)	0.38
	HIV-1 RNA < 50 copies/mL (M=F)	Comparison groups	Treatment A versus Treatment B
		Difference between groups	Not calculated -
		95% Confidence Interval	Not calculated -
		P-value (Fisher's exact test)	0.48
Notes	-		

1.5. Clinical safety

Main safety results

Summary of adverse events

Table 5. Summary of adverse events

	Tenofovir DF (N=45)	Placebo (N=42)
Patients with any AE	45 (100%)	40 (95.2%)
Patients with grade>=3 AE	4 (10,1%)	1 (2.4%)
Patients with any serious AE	10 (22,2%)	3 (7,2%)
Patients with any AE leading to discontinuation	1 (2%)	0 (0%)
AE related to study drug	12	6
Death	0	0

Renal events

One case of hypophosphatemia grade 1 was reported in tenofovir group occurring only once during the therapy. Estimated Creatinine Clearance decreased during the blinding period in both groups but more significantly in tenofovir group (-11 mL/min/1.73 vs -5,35 mL/min/1.73).

Seven cases of grade 1 proteinuria have been reported in the tenofovir group compared to 2 cases in the placebo group.

Bone parameters

Spine Bone Mineral Density

In the double-blind treatment period, differences between groups in the percentage change from baseline in spine BMD were not statistically significant; as expected for this adolescent population, increases from baseline in spine BMD were seen for both groups at Weeks 24 and 48.

In the All TDF group, increases from baseline in spine BMD were seen at all time points. Spine BMD Z-score was low at baseline (median −0.912) and 48% of subjects [39/81] had abnormal spine BMD at baseline (Z-scores ≤ −1). No clinically relevant change was seen at any time point. There were no marked shifts from baseline in the clinical status of spine BMD Z-scores.

Total Body Bone Mineral Density

In the double-blind treatment period, differences between groups in the percentage change from baseline in total body BMD were not statistically significant; increases from baseline in total body BMD were seen in both groups at Weeks 24 and 48.

In the All TDF group, increases from baseline in total body BMD were seen at all time points. Total body BMD Z-score was low at baseline (median −0.758) and 44% of subjects (36/81) had abnormal total body BMD at baseline (Z-scores ≤ −1). No clinically relevant changes were seen at any time point in total body BMD Z-score, and no clinically relevant shifts from baseline were seen in the clinical status of total body BMD Z-scores.

There is nevertheless a trend for a lower increase of total BMD in the tenofovir group compared to the placebo group. Moreover, osteopenia was reported as an AE for 3 subjects in the tenofovir DF group and 2 subjects in the placebo group in the double-blind treatment period. Even though no AE of osteopenia was serious, it is to be noted that osteopenia AEs were considered related to study drug for the 3 subjects in the tenofovir DF group and 1 subject in the placebo group. One of them with low BMD Z-score at baseline had further reduction of BMD during treatment and experienced fracture (ankle fracture).

Overall discussion

1.6. Pharmacovigilance system

Risk management plan

The MAH submitted an updated Risk Management Plan which included a risk minimisation plan. The RMP was updated to address the safety concerns identified for tenofovir..

Risk minimisation plan

The MAH proposed a HIV paediatric educational brochure for children and adolescents aged 2 to <18 years to address renal and bone toxicity and to include dosing recommendations on this population, in addition to the educational brochure for adults. The CHMP recognises the need of this educational material and formalised the ongoing activities in Annex II of the product information. The key messages are reflected in Annex II of the product information. The CHMP requested the review the HIV educational brochure for children and adolescents aged 2 to <18 years.

Table 6. Summary of the risk management plan (including the changes related to the application presented highlighted)

Safety Concern	Proposed Pharmacovigilance Activities (routine and additional)	Proposed Risk Minimization Activities (routine and additional)
Important Identified Risks		
Renal Toxicity	Routine pharmacovigilance activities including a renal tubulopathy targeted follow-up questionnaire for postmarketing reports Observational study (GS-US-104-0353) Cumulative review of reversibility of renal tubulopathy in HIV-1 and HBV infected adult patients Monitoring of renal parameters in HIV-1 and HBV infected adult and pediatric subjects in clinical studies who discontinue tenofovir DF due to renal tubulopathy Post-authorization safety study of HIV-1 and HBV infected pediatric patients Drug Utilization Study in HIV-1 and HBV infected pediatric patients	Routine Risk Minimization Activities Current approved Viread SmPC text is as follows: Statements in Section 4.2 of the Viread SmPC: *Tenofovir is eliminated by renal excretion and the exposure to tenofovir increases in patients with renal dysfunction. There are limited data on the safety and efficacy of tenofovir disoproxil fumarate in patients with moderate and severe renal impairment (creatinine clearance < 50 ml/min) and long term safety data has not been evaluated for mild renal impairment (creatinine clearance 50-80 ml/min). Therefore, in patients with renal impairment tenofovir disoproxil fumarate should only be used if the potential benefits of treatment are considered to outweigh the potential risks. Dose interval adjustments are recommended for patients with creatinine clearance < 50 ml/min.* *Mild renal impairment (creatinine clearance 50–80 ml/min): Limited data from clinical studies support once daily dosing of tenofovir disoproxil fumarate in patients with mild renal impairment.* *Moderate renal impairment (creatinine clearance 30–49 ml/min): Administration of 245 mg tenofovir disoproxil (as fumarate) every 48 hours is recommended based on modeling of single-dose pharmacokinetic data in HIV negative and non-HBV infected subjects with varying degrees of renal impairment, including end-stage renal disease requiring haemodialysis, but has not been confirmed in clinical studies. Therefore, clinical response to treatment and renal function should be closely monitored in these patients.* *Severe renal impairment (creatinine clearance < 30 ml/min) and haemodialysis patients: Adequate dose adjustments cannot be applied due to lack of alternative tablet strengths, therefore use in this group of patients is not recommended. If no alternative treatment is available, prolonged dose intervals may be used as follows:* *Severe renal impairment: 245 mg tenofovir disoproxil (as fumarate) may be administered every 72–96 hours (dosing twice a week).* *Haemodialysis patients: 245 mg tenofovir disoproxil (as fumarate) may be administered every 7 days following completion of a haemodialysis session*.* *These dose adjustments have not been confirmed in clinical studies. Simulations suggest that the prolonged dose interval is not optimal and could result in increased toxicity and possibly inadequate response. Therefore clinical response to treatment and renal function should be closely monitored.* ** Generally, once weekly dosing assuming three haemodialysis sessions per week, each of approximately 4 hours duration or after 12 hours cumulative haemodialysis.* *No dosing recommendations can be given for non-haemodialysis patients with creatinine clearance < 10 ml/min.* Warnings in Section 4.4 of the Viread SmPC: *Co-administration of other medicinal products: Viread should not be administered concomitantly with other medicinal products containing tenofovir disoproxil fumarate.* *Renal function: Renal safety with tenofovir has only been studied to a very limited degree in patients with impaired renal function (creatinine clearance < 80 ml/min).* *It is recommended that creatinine clearance is calculated in all patients prior to initiating therapy with tenofovir disoproxil fumarate and renal function (creatinine clearance and serum phosphate) is also monitored every four weeks during the first year, and then every three months. In patients at risk for renal impairment, including patients who have previously experienced renal events while receiving adefovir dipivoxil, consideration should be given to more frequent monitoring of renal function.* *Patients with creatinine clearance < 50 ml/min, including haemodialysis patients: There are limited data on the safety and efficacy of tenofovir disoproxil fumarate in patients with impaired renal function. Therefore, tenofovir disoproxil fumarate should only be used if the potential benefits of treatment are considered to outweigh the potential risks. In patients with severe renal impairment (creatinine clearance < 30 ml/min) and in patients who require haemodialysis use of tenofovir is not recommended. If no alternative treatment is available, the dosing interval must be adjusted and renal function should be closely monitored.* *If serum phosphate is < 1.5 mg/dl (0.48 mmol/l) or creatinine clearance is decreased to < 50 ml/min in any patient receiving tenofovir disoproxil fumarate, renal function should*

		be re-evaluated within one week, including measurements of blood glucose, blood potassium and urine glucose concentrations. Consideration should also be given to interrupting treatment with tenofovir disoproxil fumarate in patients with creatinine clearance decreased to < 50 ml/min or decreases in serum phosphate to < 1.0 mg/dl (0.32 mmol/l). *Use of tenofovir disoproxil fumarate should be avoided with concurrent or recent use of a nephrotoxic medicinal product (e.g. aminoglycosides, amphotericin B, foscarnet, ganciclovir, pentamidine, vancomycin, cidofovir or interleukin-2). If concomitant use of tenofovir disoproxil fumarate and nephrotoxic agents is unavoidable, renal function should be monitored weekly.* *Tenofovir disoproxil fumarate has not been clinically evaluated in patients receiving medicinal products which are secreted by the same renal pathway, including the transport proteins human organic anion transporter (hOAT) 1 and 3 or MRP 4 (e.g. cidofovir, a known nephrotoxic medicinal product). These renal transporter proteins may be responsible for tubular secretion and in part, renal elimination of tenofovir and cidofovir. Consequently, the pharmacokinetics of these medicinal products which are secreted by the same renal pathway including transport proteins hOAT 1 and 3 or MRP 4 might be modified if they are co-administered. Unless clearly necessary, concomitant use of these medicinal products which are secreted by the same renal pathway is not recommended, but if such use is unavoidable, renal function should be monitored weekly.* *Bone abnormalities (infrequently contributing to fractures) may be associated with proximal renal tubulopathy. If bone abnormalities are suspected then appropriate consultation should be obtained.* Statements in Section 4.8 of the Viread SmPC: *a. Summary of the safety profile* *HIV-1 and hepatitis B: In patients receiving tenofovir disoproxil fumarate, rare events of renal impairment, renal failure and proximal renal tubulopathy (including Fanconi syndrome) sometimes leading to bone abnormalities (infrequently contributing to fractures) have been reported. Monitoring of renal function is recommended for patients receiving Viread (see section 4.4).* *c. Description of selected adverse reactions* *HIV-1 and hepatitis B:* *Renal impairment: As Viread may cause renal damage monitoring of renal function is recommended (see sections 4.4 and 4.8a).* *e. Other special population(s)* *Patients with renal impairment: Since tenofovir disoproxil fumarate can cause renal toxicity, close monitoring of renal function is recommended in any patient with renal impairment treated with Viread (see sections 4.2, 4.4 and 5.2).* Adverse reactions in Section 4.8b of the Viread SmPC: *Renal and urinary disorders:* *Uncommon: increased creatinine* *Rare: acute renal failure, renal failure, acute tubular necrosis, proximal renal tubulopathy (including Fanconi syndrome), nephritis (including acute interstitial nephritis), nephrogenic diabetes insipidus* *Metabolism and nutrition disorders:* *Very common: hypophosphataemia** *Uncommon: hypokalaemia** *Musculoskeletal and connective tissue disorders:* *Uncommon: rhabdomyolysis*, muscular weakness** *Rare: osteomalacia (manifested as bone pain and infrequently contributing to fractures)*, myopathy** ** This adverse reaction may occur as a consequence of proximal renal tubulopathy. It is not considered to be causally associated with tenofovir disoproxil fumarate in the absence of this condition.* Update of labeling as appropriate Proposed additional Viread SmPC text specific to the treatment of pediatric patients is as follows (based on proposed updates to the Viread 245 mg SmPC): Statement in Section 4.2 of the Viread SmPC: *The use of tenofovir disoproxil fumarate is not recommended in paediatric patients with renal impairment (see section 4.4).* Statements in Section 4.4 of the Viread SmPC: *Renal and bone effects in paediatric population* *There are uncertainties associated with the long term effects of bone and renal toxicity. Moreover, the reversibility of renal toxicity cannot be fully ascertained. Therefore, a multidisciplinary approach is recommended to adequately weigh on a case by case basis the benefit/risk balance of treatment, decide the appropriate monitoring during treatment*

		(including decision for treatment withdrawal) and consider the need for supplementation. *Renal effects* *Renal adverse reactions consistent with proximal renal tubulopathy have been reported in HIV-1 infected paediatric patients aged 2 to <12 years in clinical study GS-US-104-0352 (see sections 4.8 and 5.1).* *Renal monitoring* *Renal function (creatinine clearance and serum phosphate) should be evaluated prior to treatment and monitored during treatment as in adults (see above).* *Renal management* *If serum phosphate is confirmed to be < 3.0 mg/dl (0.96 mmol/l) in any paediatric patient receiving tenofovir disoproxil fumarate, renal function should be re-evaluated within one week, including measurements of blood glucose, blood potassium and urine glucose concentrations (see section 4.8, proximal tubulopathy). If renal abnormalities are suspected or detected then consultation with a nephrologist should be obtained to consider interruption of tenofovir disoproxil fumarate treatment.* *Co-administration and risk of renal toxicity* *The same recommendations apply as in adults (see above).* *Renal impairment* *The use of tenofovir disoproxil fumarate is not recommended in paediatric patients with renal impairment (see section 4.2). Tenofovir disoproxil fumarate should not be initiated in paediatric patients with renal impairment and should be discontinued in paediatric patients who develop renal impairment during tenofovir disoproxil fumarate therapy.* Statement in Section 4.8 of the Viread SmPC: *Paediatric population* *HIV-1* *Of 89 patients (2 to < 12 years) who received tenofovir disoproxil fumarate in study GS-US-104-0352 (median exposure 104 weeks), 4 patients discontinued from the study due to adverse reactions consistent with proximal renal tubulopathy.* Statements in Section 5.1 of the Viread SmPC *Paediatric population:* *HIV-1:* *In study GS-US-104-0352, 4 out of 89 paediatric patients exposed to tenofovir disoproxil fumarate discontinued due to adverse reactions consistent with proximal renal tubulopathy (median tenofovir disoproxil fumarate exposure was 104 weeks).* <u>Additional Risk Minimization Activities</u> Educational initiatives ('HIV and the Kidney' educational program, renal educational program for HBV, educational brochures distributed to prescribers). Update of educational program as appropriate Following the approval of the pediatric applications, renal risk minimization activities will be updated to include information on HIV-1 infected children and adolescents and HBV infected adolescents. Educational brochures specific to the use of Viread in these pediatric populations will be distributed to pediatric prescribers.
Bone events due to proximal renal tubulopathy/loss of bone mineral density	Routine pharmacovigilance activities including monitoring and review in PSURs. Clinical studies (GS-99-903, GS-US-236-0103 GS-US-174-0102, GS-US-174-0103, GS-US-174-0115, GS-US-174-0121, GS-US-104-0321, GS-US-104-0352) Retrospective analyses of pediatric BMD Z-scores adjusted by height (GS-US-174-0115, GS-US-104-0321, GS-US-104-0352) Planned clinical study in HBV infected pediatric patients (GS-US-174-0144)	<u>Routine Risk Minimization Activities</u> Current approved Viread SmPC text is as follows: Statements in Section 4.4 of the Viread SmPC: *Bone effects: In HIV infected patients, in a 144-week controlled clinical study that compared tenofovir disoproxil fumarate with stavudine in combination with lamivudine and efavirenz in antiretroviral-naïve patients, small decreases in bone mineral density of the hip and spine were observed in both treatment groups. Decreases in bone mineral density of spine and changes in bone biomarkers from baseline were significantly greater in the tenofovir disoproxil fumarate treatment group at 144 weeks. Decreases in bone mineral density of hip were significantly greater in this group until 96 weeks. However, there was no increased risk of fractures or evidence for clinically relevant bone abnormalities over 144 weeks.* *Bone abnormalities (infrequently contributing to fractures) may be associated with proximal renal tubulopathy. If bone abnormalities are suspected then appropriate consultation should be obtained.* *Paediatric population: Viread may cause a reduction in BMD. The effects of tenofovir disoproxil fumarate-associated changes in BMD on long-term bone health and future fracture risk are currently unknown (see section 5.1).* Statements in Section 4.8 of the Viread SmPC *a. Summary of the safety profile* *HIV-1 and hepatitis B: In patients receiving tenofovir disoproxil fumarate, rare events of renal impairment, renal failure and proximal renal tubulopathy (including Fanconi syndrome) sometimes leading to bone abnormalities (infrequently contributing to*

	Post-authorization safety study of HIV-1 and HBV infected pediatric patients Drug Utilization Study in HIV-1 and HBV infected pediatric patients Planned cross-sectional study to assess BMD in HIV-1 infected patients of interest who include those over 50 years of age, particularly women, and who have been exposed to tenofovir DF for at least 3 years (GS-US-104-0423).	*fractures) have been reported. Monitoring of renal function is recommended for patients receiving Viread (see section 4.4).* Adverse reactions in Section 4.8b of the Viread SmPC *Musculoskeletal and connective tissue disorders:* *Rare: osteomalacia (manifested as bone pain and infrequently contributing to fractures)*[1,2] [1] *This adverse reaction may occur as a consequence of proximal renal tubulopathy. It is not considered to be causally associated with tenofovir disoproxil fumarate in the absence of this condition.* [2] *This adverse reaction was identified through post-marketing surveillance but not observed in randomized controlled clinical trials or the tenofovir disoproxil fumarate expanded access program. The frequency category was estimated from a statistical calculation based on the total number of patients exposed to tenofovir disoproxil fumarate in randomized clinical trials and the expanded access program (n = 7,319).* Statements in Section 5.1 of the Viread SmPC *Paediatric population:* *HIV-1: In study GS-US-104-0321, 87 HIV-1 infected treatment experienced patients 12 to < 18 years of age were treated with tenofovir disoproxil fumarate (n = 45) or placebo (n = 42) in combination with an optimised background regimen (OBR) for 48 weeks. In patients who received treatment with tenofovir disoproxil fumarate or placebo, mean lumbar spine BMD Z-score was -1.004 and -0.809, and mean total body BMD Z-score was -0.866 and -0.584, respectively, at baseline. Mean changes at week 48 (end of double-blind phase) were -0.215 and -0.165 in lumbar spine BMD Z-score, and -0.254 and -0.179 in total body BMD Z-score for the tenofovir disoproxil fumarate and placebo groups, respectively. The mean rate of BMD gain was less in the tenofovir disoproxil fumarate group compared to the placebo group. At week 48, six adolescents in the tenofovir disoproxil fumarate group and one adolescent in the placebo group had significant lumbar spine BMD loss (defined as > 4% loss). Among 28 patients receiving 96 weeks of treatment with tenofovir disoproxil fumarate, BMD Z-scores declined by -0.341 for lumbar spine and -0.458 for total body.* Update of labeling as appropriate Proposed additional Viread SmPC text specific to the treatment of pediatric patients is as follows: Statements in Section 4.4 of the Viread SmPC: *Renal and bone effects in paediatric population* *There are uncertainties associated with the long term effects of bone and renal toxicity. Moreover, the reversibility of renal toxicity cannot be fully ascertained. Therefore, a multidisciplinary approach is recommended to adequately weigh on a case by case basis the benefit/risk balance of treatment, decide the appropriate monitoring during treatment (including decision for treatment withdrawal) and consider the need for supplementation.* *Bone effects:* *If bone abnormalities are detected or suspected in paediatric patients, consultation with an endocrinologist and/or nephrologist should be obtained.* Statement in Section 4.8 of the Viread SmPC: *Paediatric population* *HIV-1* *Reductions in BMD have been reported in paediatric patients. In HIV-1 infected adolescents, the BMD Z-scores observed in subjects who received tenofovir disoproxil fumarate were lower than those observed in subjects who received placebo. In HIV-1 infected children, the BMD Z-scores observed in subjects who switched to tenofovir disoproxil fumarate were lower than those observed in subjects who remained on their stavudine- or zidovudine-containing regimen (see sections 4.4 and 5.1).* *Chronic hepatitis B* *Reductions in BMD have been observed in HBV-infected adolescents. The BMD Z-scores observed in subjects who received tenofovir disoproxil fumarate were lower than those observed in subjects who received placebo (see sections 4.4 and 5.1).* Statements in Section 5.1 of the Viread SmPC *In study GS-US-104-0352, 97 treatment experienced patients 2 to < 12 years of age with stable, virologic suppression on stavudine- or zidovudine-containing regimens were randomised to either replace stavudine or zidovudine with tenofovir disoproxil fumarate (n = 48) or continue on their original regimen (n = 49) for 48 weeks.* *Reductions in BMD have been reported in paediatric patients. In patients who received treatment with tenofovir disoproxil fumarate, or stavudine or zidovudine, mean lumbar spine BMD Z-score was -1.034 and -0.498, and mean total body BMD Z-score was -0.471 and -0.386, respectively, at baseline. Mean changes at week 48 (end of*

		randomised phase) were 0.032 and 0.087 in lumbar spine BMD Z-score, and -0.184 and -0.027 in total body BMD Z-score for the tenofovir disoproxil fumarate and stavudine or zidovudine groups, respectively. The mean rate of lumbar spine bone gain at week 48 was similar between the tenofovir disoproxil fumarate treatment group and the stavudine or zidovudine treatment group. Total body bone gain was less in the tenofovir disoproxil fumarate treatment group compared to the stavudine or zidovudine treatment group. One tenofovir disoproxil fumarate treated subject and no stavudine or zidovudine treated subjects experienced significant (> 4%) lumbar spine BMD loss at week 48. BMD Z-scores declined by -0.012 for lumbar spine and by -0.338 for total body in the 64 subjects who were treated with tenofovir disoproxil fumarate for 96 weeks. BMD Z-scores were not adjusted for height and weight. *Chronic hepatitis B: In study GS-US-174-0115, 106 HBeAg negative and HBeAg positive patients aged 12 to < 18 years with chronic HBV infection [HBV DNA ≥ 10^5 copies/ml, elevated serum ALT (≥ 2 x ULN) or a history of elevated serum ALT levels in the past 24 months] were treated with tenofovir disoproxil 245 mg (as fumarate) (n = 52) or placebo (n = 54) for 72 weeks.* *No subjects met the primary safety endpoint of a 6% decrease in lumbar spine BMD. In subjects receiving tenofovir disoproxil fumarate or placebo, mean (SD) lumbar spine BMD Z-score was -0.43 (0.764) and -0.28 (0.813), and mean total body BMD Z-score was -0.20 (1.126) and -0.26 (0.878), respectively, at baseline. The mean (SD) change in lumbar spine BMD Z-score from baseline to week 72 in subjects receiving tenofovir disoproxil fumarate was -0.05 (0.310) and 0.07 (0.377) in those receiving placebo. BMD Z-scores were not adjusted for height and weight. The mean change in whole body BMD Z-score in subjects receiving tenofovir disoproxil fumarate was -0.15 (0.379) and 0.06 (0.361) in those receiving placebo. The mean percentage increase in whole body and lumbar spine BMD from baseline to week 72 was 2.84% and 4.95%, respectively, in subjects receiving tenofovir disoproxil fumarate. These mean percentage increases in whole body and lumbar spine BMD were 2.53% and 3.19% less, respectively, when compared to subjects receiving placebo. Three subjects in the tenofovir disoproxil fumarate group and 2 subjects in the placebo group had a decrease of > 4% in spine BMD.*
Post-treatment hepatic flares in HBV monoinfected and HIV/HBV coinfected patients	Routine pharmacovigilance activities	<u>Routine Risk Minimization Activities</u> Statement in Section 4.2 of the Viread SmPC: *If Viread is discontinued in patients with chronic hepatitis B with or without HIV co-infection, these patients should be closely monitored for evidence of exacerbation of hepatitis (see Section 4.4).* Warning in Section 4.4 of the Viread SmPC: *Flares after treatment discontinuation: Acute exacerbation of hepatitis has also been reported in patients who have discontinued hepatitis B therapy. Post-treatment exacerbations are usually associated with rising HBV DNA, and the majority appears to be self-limited. However, severe exacerbations, including fatalities, have been reported. Hepatic function should be monitored at repeated intervals with both clinical and laboratory follow-up for at least 6 months after discontinuation of hepatitis B therapy. If appropriate, resumption of hepatitis B therapy may be warranted. In patients with advanced liver disease or cirrhosis, treatment discontinuation is not recommended since post-treatment exacerbation of hepatitis may lead to hepatic decompensation.* *Liver flares are especially serious, and sometimes fatal in patients with decompensated liver disease.* Statements in Section 4.8 of the Viread SmPC: *a. Summary of the safety profile* *Acute exacerbation of hepatitis has been reported in patients on treatment as well as in patients who have discontinued hepatitis B therapy (see section 4.4).* *c. Description of selected adverse reactions* *Exacerbations of hepatitis after discontinuation of treatment: In HBV infected patients, clinical and laboratory evidence of exacerbations of hepatitis have occurred after discontinuation of HBV therapy (see section 4.4).* Update of labeling as appropriate.
Interaction with didanosine	Routine pharmacovigilance activities	<u>Routine Risk Minimization Activities</u> Warning in Section 4.4 of the Viread SmPC (interaction also described in Section 4.5): *Co-administration of tenofovir disoproxil fumarate and didanosine is not recommended. Co-administration of tenofovir disoproxil fumarate and didanosine results in a 40–60% increase in systemic exposure to didanosine that may increase the risk of didanosine-related adverse reactions. Rarely, pancreatitis and lactic acidosis, sometimes fatal, have been reported. Co-administration of tenofovir disoproxil fumarate and didanosine at a dose of 400 mg daily has been associated with a significant decrease in CD4 cell count, possibly due to an intracellular interaction increasing phosphorylated (i.e. active)*

		didanosine. A decreased dosage of 250 mg didanosine co-administered with tenofovir disoproxil fumarate therapy has been associated with reports of high rates of virological failure within several tested combinations for the treatment of HIV-1 infection. Statements in Section 4.8 of the Viread SmPC: *a. Summary of the safety profile* *Co- administration of Viread and didanosine is not recommended as this may result in an increased risk of adverse reactions (see section 4.5). Rarely, pancreatitis and lactic acidosis, sometimes fatal, have been reported (see section 4.4).* *c. Description of selected adverse reactions* *Interaction with didanosine: Co-administration of tenofovir disoproxil fumarate and didanosine is not recommended as it results in a 40-60% increase in systemic exposure to didanosine that may increase the risk of didanosine-related adverse reactions (see section 4.5). Rarely, pancreatitis and lactic acidosis, sometimes fatal, have been reported.* Update of labeling as appropriate.
Pancreatitis	Routine pharmacovigilance activities	Routine Risk Minimization Activities Pancreatitis is listed in Section 4.8b of the Viread SmPC: *Gastrointestinal disorders:* *Uncommon: pancreatitis* There are also warning statements in Sections 4.4, 4.5 and 4.8 of the Viread SmPC regarding the risk of pancreatitis associated with the interaction with didanosine (see above). Update of labeling as appropriate.
Lactic acidosis and severe hepatomegaly with steatosis	Routine pharmacovigilance activities	Routine Risk Minimization Activities Warning in Section 4.4 of the Viread SmPC: *Lactic acidosis: Lactic acidosis, usually associated with hepatic steatosis, has been reported with the use of nucleoside analogues. The preclinical and clinical data suggest that the risk of occurrence of lactic acidosis, a class effect of nucleoside analogues, is low for tenofovir disoproxil fumarate. However, as tenofovir is structurally related to nucleoside analogues, this risk cannot be excluded. Early symptoms (symptomatic hyperlactataemia) include benign digestive symptoms (nausea, vomiting and abdominal pain), non specific malaise, loss of appetite, weight loss, respiratory symptoms (rapid and/or deep breathing) or neurological symptoms (including motor weakness). Lactic acidosis has a high mortality and may be associated with pancreatitis, liver failure or renal failure. Lactic acidosis generally occurred after a few or several months of treatment.* *Treatment with nucleoside analogues should be discontinued in the setting of symptomatic hyperlactataemia and metabolic/lactic acidosis, progressive hepatomegaly, or rapidly elevating aminotransferase levels.* *Caution should be exercised when administering nucleoside analogues to any patient (particularly obese women) with hepatomegaly, hepatitis or other known risk factors for liver disease and hepatic steatosis (including certain medicinal products and alcohol).* *Patients co-infected with hepatitis C and treated with alpha interferon and ribavirin may constitute a special risk.* *Patients at increased risk should be followed closely.* Statements in Section 4.8 of the Viread SmPC: *a. Summary of the safety profile* *Lactic acidosis, severe hepatomegaly with steatosis and lipodystrophy are associated with tenofovir disoproxil fumarate (see sections 4.4 and 4.8c).* *c. Description of selected adverse reactions* *Lactic acidosis and severe hepatomegaly with steatosis: Lactic acidosis, usually associated with hepatic steatosis, has been reported with the use of nucleoside analogues. Treatment with nucleoside analogues should be discontinued in the setting of symptomatic hyperlactataemia and metabolic/lactic acidosis, progressive hepatomegaly, or rapidly elevating aminotransferase levels (see section 4.4).* Lactic acidosis is listed in Section 4.8b of the Viread SmPC: *Metabolism and nutrition disorders:* *Rare: lactic acidosis* There are also warning statements in Section 4.4, 4.5 and 4.8 of the Viread SmPC regarding the risk of lactic acidosis associated with the interaction with didanosine (see above). Update of labeling as appropriate.
Lipodystrophy	Routine pharmacovigilance activities	Routine Risk Minimization Activities Precautionary statements in Section 4.4 of the Viread SmPC: *Lipodystrophy: Combination antiretroviral therapy has been associated with the redistribution of body fat (lipodystrophy) in HIV patients. The long-term consequences of*

		these events are currently unknown. Knowledge about the mechanism is incomplete. A connection between visceral lipomatosis and protease inhibitors and lipoatrophy and nucleoside reverse transcriptase inhibitors has been hypothesised. A higher risk of lipodystrophy has been associated with individual factors such as older age, and with drug related factors such as longer duration of antiretroviral treatment and associated metabolic disturbances. Clinical examination should include evaluation for physical signs of fat redistribution. Consideration should be given to the measurement of fasting serum lipids and blood glucose. Lipid disorders should be managed as clinically appropriate. *Tenofovir is structurally related to nucleoside analogues hence the risk of lipodystrophy cannot be excluded. However, 144-week clinical data from antiretroviral-naïve HIV infected patients indicate that the risk of lipodystrophy was lower with tenofovir disoproxil fumarate than with stavudine when administered with lamivudine and efavirenz.* Statements in Section 4.8 of the Viread SmPC: *a. Summary of the safety profile* *Lactic acidosis, severe hepatomegaly with steatosis and lipodystrophy are associated with tenofovir disoproxil fumarate (see sections 4.4 and 4.8c).* *c. Description of selected adverse reactions* *Combination antiretroviral therapy has been associated with redistribution of body fat (lipodystrophy) in HIV patients including the loss of peripheral and facial subcutaneous fat, increased intra-abdominal and visceral fat, breast hypertrophy and dorsocervical fat accumulation (buffalo hump).* *In a 144-week controlled clinical study in antiretroviral-naïve patients that compared tenofovir disoproxil fumarate with stavudine in combination with lamivudine and efavirenz, patients who received tenofovir disoproxil had a significantly lower incidence of lipodystrophy compared with patients who received stavudine. The tenofovir disoproxil fumarate arm also had significantly smaller mean increases in fasting triglycerides and total cholesterol than the comparator arm.* Update of labeling as appropriate.
Important Potential Risks		
Development of resistance during long-term exposure in HBV infected patients	Routine pharmacovigilance activities Clinical studies (GS-US-174-0102, GS-US-174-0103, GS-US-174-0121)	<u>Routine Risk Minimization Activities</u> Section 5.1 of the Viread SmPC states the following: *Resistance: No HBV mutations associated with tenofovir disoproxil fumarate resistance have been identified. In cell based assays, HBV strains expressing the rtV173L, rtL180M, and rtM204I/V mutations associated with resistance to lamivudine and telbivudine showed a susceptibility to tenofovir ranging from 0.7- to 3.4-fold that of wild-type virus. HBV strains expressing the rtL180M, rtT184G, rtS202G/I, rtM204V and rtM250V mutations associated with resistance to entecavir showed a susceptibility to tenofovir ranging from 0.6- to 6.9-fold that of wild-type virus. HBV strains expressing the adefovir-associated resistance mutations rtA181V and rtN236T showed a susceptibility to tenofovir ranging from 2.9- to 10-fold that of wild-type virus. Viruses containing the rtA181T mutation remained susceptible to tenofovir with EC_{50} values 1.5-fold that of wild-type virus.* *Clinical resistance: Four hundred and twenty-six HBeAg negative (GS-US-174-0102, n = 250) and HBeAg positive (GS-US-174-0103, n = 176) patients were evaluated for genotypic changes in HBV polymerase from baseline. Genotypic evaluations performed on all patients initially randomised to the tenofovir disoproxil fumarate arm (i.e excluding patients who received double-blind adefovir dipivoxil and then switched to open-label tenofovir disoproxil fumarate) with HBV DNA > 400 copies/ml at week 48 (n = 39), week 96 (n = 24) and week 144 (n = 6) and week 192 (n = 5) on tenofovir disoproxil fumarate monotherapy, showed that no mutations associated with tenofovir disoproxil fumarate resistance have developed.* *In study GS-US-174-0108, 45 patients (including 9 patients with lamivudine and/or adefovir dipivoxil resistance mutations at baseline) received tenofovir disoproxil fumarate for up to 48 weeks. Genotypic data from paired baseline and on treatment HBV isolates were available for 6/8 patients with HBV DNA > 400 copies/ml. No amino acid substitutions associated with resistance to tenofovir disoproxil fumarate were identified in these isolates.* Update of labeling as appropriate.
Important Missing Information		
Safety in children (including long-term safety)	Routine pharmacovigilance activities Clinical studies in HIV-1 infected	<u>Routine Risk Minimization Activities</u> Current approved Viread SmPC text is as follows: Statement in Section 4.2 of the Viread SmPC: *Paediatric population: Viread is not recommended for use in children The clinical data available in HIV-1 infected adolescents are inadequate to support the use of tenofovir*

	children (GS-US-104-0321, GS-US-104-0352) Clinical study in HBV infected adolescents (GS-US-174-0115) Planned clinical study, including a PK substudy, in HBV infected children aged 2 to < 12 years (GS-US-174-0144) Planned PK bioavailability study of TDF oral granules in the fed state Post-authorization safety study of HIV-1 and HBV infected pediatric patients Drug Utilization Study in HIV-1 and HBV infected pediatric patients	*disoproxil fumarate in this population and no data are currently available in younger children.* *No data are currently available in paediatric patients infected with chronic hepatitis B.* Statement in Section 4.4 of the Viread SmPC: *Viread may cause a reduction in BMD. The effects of tenofovir disoproxil fumarate-associated changes in BMD on long-term bone health and future fracture risk are currently unknown.* Statement in Section 4.8 of the Viread SmPC: *d. Paediatric population* *Assessment of adverse reactions is based on one randomised trial (study GS-US-104-0321) in 87 HIV-1 infected adolescent patients (aged 12 to < 18 years) who received treatment with tenofovir disoproxil fumarate (n = 45) or placebo (n = 42) in combination with other antiretroviral agents for 48 weeks.* Statements in Section 5.1 of the Viread SmPC: *Paediatric population:* *HIV-1: In study GS-US-104-0321, 87 HIV-1 infected treatment-experienced patients 12 to < 18 years of age were treated with tenofovir disoproxil fumarate (n = 45) or placebo (n = 42) in combination with an optimised background regimen (OBR) for 48 weeks. In patients who received treatment with tenofovir disoproxil fumarate or placebo, mean lumbar spine BMD Z-score was -1.004 and -0.809, and mean total body BMD Z-score was -0.866 and -0.584, respectively, at baseline. Mean changes at week 48 (end of double-blind phase) were -0.215 and -0.165 in lumbar spine BMD Z-score, and -0.254 and -0.179 in total body BMD Z-score for the tenofovir disoproxil fumarate and placebo groups, respectively. The mean rate of BMD gain was less in the tenofovir disoproxil fumarate group compared to the placebo group. At week 48, six adolescents in the tenofovir disoproxil fumarate group and one adolescent in the placebo group had significant lumbar spine BMD loss (defined as > 4% loss). Among 28 patients receiving 96 weeks of treatment with tenofovir disoproxil fumarate, BMD Z-scores declined by -0.341 for lumbar spine and -0.458 for total body.* *The efficacy and safety data derived from this study do not support the use of Viread in adolescents.* Proposed additional Viread SmPC text specific to the treatment of pediatric patients is as follows (based on proposed updates to the Viread 245 mg SmPC): Statements in Section 4.2 of the Viread SmPC: *Paediatric population* *HIV-1: The safety and efficacy of tenofovir disoproxil fumarate in HIV-1 infected children under 2 years of age have not been established. No data are available.* *Chronic hepatitis B: The safety and efficacy of tenofovir disoproxil fumarate in children with chronic hepatitis B aged 2 to < 12 years or weighing < 35 kg have not been established. No data are available.* *Special populations* *Renal impairment: The use of tenofovir disoproxil fumarate is not recommended in paediatric patients with renal impairment (see section 4.4).* Statements in Section 4.4 of the Viread SmPC: *Renal and bone effects in paediatric population* *There are uncertainties associated with the long term effects of bone and renal toxicity. Moreover, the reversibility of renal toxicity cannot be fully ascertained. Therefore, a multidisciplinary approach is recommended to adequately weigh on a case by case basis the benefit/risk balance of treatment, decide the appropriate monitoring during treatment (including decision for treatment withdrawal) and consider the need for supplementation.* *Renal effects* *Renal adverse reactions consistent with proximal renal tubulopathy have been reported in HIV-1 infected paediatric patients aged 2 to <12 years in clinical study GS-US-104-0352 (see sections 4.8 and 5.1).* *Renal monitoring* *Renal function (creatinine clearance and serum phosphate) should be evaluated prior to treatment and monitored during treatment as in adults (see above).* *Renal management* *If serum phosphate is confirmed to be < 3.0 mg/dl (0.96 mmol/l) in any paediatric patient receiving tenofovir disoproxil fumarate, renal function should be re-evaluated within one week, including measurements of blood glucose, blood potassium and urine glucose concentrations (see section 4.8, proximal tubulopathy). If renal abnormalities are suspected or detected then consultation with a nephrologist should be obtained to*

		consider interruption of tenofovir disoproxil fumarate treatment. *Co-administration and risk of renal toxicity* *The same recommendations apply as in adults (see above).* *Renal impairment* *The use of tenofovir disoproxil fumarate is not recommended in paediatric patients with renal impairment (see section 4.2). Tenofovir disoproxil fumarate should not be initiated in paediatric patients with renal impairment and should be discontinued in paediatric patients who develop renal impairment during tenofovir disoproxil fumarate therapy.* *Bone effects:* *If bone abnormalities are detected or suspected in paediatric patients,, consultation with an endocrinologist and/or nephrologist should be obtained.* Statements in Section 4.8 of the Viread SmPC: *Paediatric population* *HIV-1:* *Assessment of adverse reactions is based on two randomised trials (studies GS-US-104-0321 and GS-US-104-0352) in 184 HIV-1 infected paediatric patients (aged 2 to < 18 years) who received treatment with tenofovir disoproxil fumarate (n = 93) or placebo/active comparator (n = 91) in combination with other antiretroviral agents for 48 weeks (see section 5.1). The adverse reactions observed in paediatric patients who received treatment with tenofovir disoproxil fumarate were consistent with those observed in clinical studies of tenofovir disoproxil fumarate in adults (see section 4.8 Tabulated summary of adverse reactions and 5.1).* *Reductions in BMD have been reported in paediatric patients. In HIV-1 infected adolescents, the BMD Z-scores observed in subjects who received tenofovir disoproxil fumarate were lower than those observed in subjects who received placebo. In HIV-1 infected children, the BMD Z-scores observed in subjects who switched to tenofovir disoproxil fumarate were lower than those observed in subjects who remained on their stavudine- or zidovudine-containing regimen (see sections 4.4 and 5.1).* *Of 89 patients (2 to < 12 years) who received tenofovir disoproxil fumarate in study GS-US-104-0352 (median exposure 104 weeks), 4 patients discontinued from the study due to adverse reactions consistent with proximal renal tubulopathy.* *Chronic hepatitis B:* *Assessment of adverse reactions is based on one randomised study (study GS-US-174-0115) in 106 adolescent patients (12 to < 18 years of age) with chronic hepatitis B receiving treatment with tenofovir disoproxil 245 mg (as fumarate) (n = 52) or placebo (n = 54) for 72 weeks. The adverse reactions observed in adolescent patients who received treatment with tenofovir disoproxil fumarate were consistent with those observed in clinical studies of tenofovir disoproxil fumarate in adults (see section 4.8 Tabulated summary of adverse reactions and 5.1).* *Reductions in BMD have been observed in HBV-infected adolescents. The BMD Z-scores observed in subjects who received tenofovir disoproxil fumarate were lower than those observed in subjects who received placebo (see sections 4.4 and 5.1).* Statements in Section 5.1 of the Viread SmPC *In study GS-US-104-0352, 97 treatment experienced patients 2 to < 12 years of age with stable, virologic suppression on stavudine- or zidovudine-containing regimens were randomised to either replace stavudine or zidovudine with tenofovir disoproxil fumarate (n = 48) or continue on their original regimen (n = 49) for 48 weeks.* *Reductions in BMD have been reported in paediatric patients. In patients who received treatment with tenofovir disoproxil fumarate, or stavudine or zidovudine, mean lumbar spine BMD Z-score was -1.034 and -0.498, and mean total body BMD Z-score was -0.471 and -0.386, respectively, at baseline. Mean changes at week 48 (end of randomised phase) were 0.032 and 0.087 in lumbar spine BMD Z-score, and -0.184 and -0.027 in total body BMD Z-score for the tenofovir disoproxil fumarate and stavudine or zidovudine groups, respectively. The mean rate of lumbar spine bone gain at week 48 was similar between the tenofovir disoproxil fumarate treatment group and the stavudine or zidovudine treatment group. Total body bone gain was less in the tenofovir disoproxil fumarate treatment group compared to the stavudine or zidovudine treatment group.* *One tenofovir disoproxil fumarate treated subject and no stavudine or zidovudine treated subjects experienced significant (> 4%) lumbar spine BMD loss at week 48. BMD Z-scores declined by -0.012 for lumbar spine and by -0.338 for total body in the 64 subjects who were treated with tenofovir disoproxil fumarate for 96 weeks. BMD Z-scores were not adjusted for height and weight.* *In study GS-US-104-0352, 4 out of 89 paediatric patients exposed to tenofovir disoproxil fumarate discontinued due to adverse reactions consistent with proximal renal tubulopathy (median tenofovir disoproxil fumarate exposure was 104 weeks).* *Chronic hepatitis B: In study GS-US-174-0115, 106 HBeAg negative and HBeAg positive*

		patients aged 12 to < 18 years with chronic HBV infection [HBV DNA ≥ 10^5 copies/ml, elevated serum ALT (≥ 2 x ULN) or a history of elevated serum ALT levels in the past 24 months] were treated with tenofovir disoproxil 245 mg (as fumarate) (n = 52) or placebo (n = 54) for 72 weeks. *No subjects met the primary safety endpoint of a 6% decrease in lumbar spine BMD. In subjects receiving tenofovir disoproxil fumarate or placebo, mean (SD) lumbar spine BMD Z-score was -0.43 (0.764) and -0.28 (0.813), and mean total body BMD Z-score was -0.20 (1.126) and -0.26 (0.878), respectively, at baseline. The mean (SD) change in lumbar spine BMD Z-score from baseline to week 72 in subjects receiving tenofovir disoproxil fumarate was -0.05 (0.310) and 0.07 (0.377) in those receiving placebo. The mean change in whole body BMD Z-score in subjects receiving tenofovir disoproxil fumarate was -0.15 (0.379) and 0.06 (0.361) in those receiving placebo. BMD Z-scores were not adjusted for height and weight. The mean percentage increase in whole body and lumbar spine BMD from baseline to week 72 was 2.84% and 4.95%, respectively, in subjects receiving tenofovir disoproxil fumarate. These mean percentage increases in whole body and lumbar spine BMD were 2.53% and 3.19% less, respectively, when compared to subjects receiving placebo. Three subjects in the tenofovir disoproxil fumarate group and 2 subjects in the placebo group had a decrease of > 4% in spine BMD.* The proposed Viread oral granules SmPC also contains statements indicating that limited clinical data are available at the 6.5 mg/kg dose of the oral granules and therefore close monitoring of efficacy and safety is needed, and that investigations are planned to further substantiate the dose in children from 2 years of age. Following the approval of the pediatric applications, renal risk minimization activities will be updated to include information on HIV-1 infected children and adolescents and HBV infected adolescents. Educational brochures specific to the use of Viread in these pediatric populations will be distributed to pediatric prescribers (see Renal Safety Concern).
Safety in pregnancy	Routine pharmacovigilance activities Epidemiological studies (Antiretroviral Pregnancy Registry; Cross-sectional study to assess the risk of mitochondrial disease in children exposed to NRTIs in utero [MITOC group])	<u>Routine Risk Minimization Activities</u> Statements in Section 4.6 of the Viread SmPC: *Pregnancy* *A moderate amount of data on pregnant women (between 300-1,000 pregnancy outcomes) indicate no malformations or foetal/neonatal toxicity associated with tenofovir disoproxil fumarate. Animal studies do not indicate reproductive toxicity (see section 5.3). The use of tenofovir disoproxil fumarate may be considered during pregnancy, if necessary.* Update of labeling as appropriate.
Safety in patients with renal impairment	Routine pharmacovigilance activities Clinical study in HBV infected patients including patients with mild to moderate renal impairment (GS-US-174-0121) Planned clinical study in HBV infected patients with moderate to severe renal impairment (GS-US-174-0127)	<u>Routine Risk Minimization Activities</u> See Renal Safety Concern. A Type II variation application for tenofovir DF 40 mg/g oral granules is planned to be submitted by Q4 2012 to enable adjustment of daily dose as well as dose interval of tenofovir DF in HIV-1 infected and HBV infected adult patients with moderate or severe renal impairment.
Safety in elderly patients	Routine pharmacovigilance activities	<u>Routine Risk Minimization Activities</u> Warning in Section 4.4 of the Viread SmPC (also in section 4.8e): *Elderly; Tenofovir disoproxil fumarate has not been studied in patients over the age of 65. Elderly patients are more likely to have decreased renal function; therefore caution should be exercised when treating elderly patients with tenofovir disoproxil fumarate.* Update of labeling as appropriate.
Safety in lactation	Routine pharmacovigilance activities	<u>Routine Risk Minimization Activities</u> Statements in Section 4.6 of the Viread SmPC: *Breast-feeding* *Tenofovir has been shown to be excreted in human milk. There is insufficient information on the effects of tenofovir in newborns/infants. Therefore Viread should not be used during breast-feeding.* *As a general rule, it is recommended that HIV and HBV infected women do not breast-feed their infants in order to avoid transmission of HIV and HBV to the infant.* Update of labeling as appropriate.
Safety in black HBV infected patients	Routine pharmacovigilance activities	<u>Routine Risk Minimization Activities</u> Update of labeling as appropriate.

The CHMP, having considered the data submitted, was of the opinion that the below pharmacovigilance activities in addition to the use of routine pharmacovigilance are needed to investigate further some of the safety concerns:

Description	Due date
Conduct a separate post-authorisation safety study with a representative sample of HIV- and HBV infected children to help establish evidence-based strategies for management of TDF-associated renal and bone toxicity.	Submit the protocol synopsis by 31 December 2012. Interim study results: 31 December 2014 Final study results: 31 December 2016
To conduct a Drug Utilisation Study in HIV-1 and HBV-infected paediatric patients to follow-up the effectiveness of the risk minimisation measures.	Submit draft synopsis by 25 October 2012 Feasibility assessment alongside a full draft protocol expected: by 28 February 2013. Interim study results: 31 December 2014 Final study results: 31 December 2017

The CHMP, having considered the data submitted, was of the opinion that the below additional risk minimisation activities are required for the management of the safety profile of the product:

Physician educational pack containing the Summary of Product Characteristics and an appropriate educational brochure, as detailed below:

- HIV renal educational brochure, including the creatinine clearance slide ruler
- HBV renal educational brochure, including the creatinine clearance slide ruler
- HIV paediatric educational brochure
- HBV paediatric educational brochure

1.7. Changes to the Product Information

The PI was updated accordingly and has been consolidated with parallel procedures X/105/G and II/115.

Section 4.1 "Therapeutic indication"

This section was revised and the extension of the therapeutic indication was restricted for the treatment of HIV 1 infected adolescents, with NRTI resistance or toxicities precluding the use of first line agents, aged 12 to < 18 years.

Section 4.2 "Posology and method of administration"

This section was updated to include dose recommendations for use in HIV adolescents.

Section 4.4 "Special warnings and precautions for use"

Warnings on the management of renal and bone effects were revised.

This section was revised to inform on the uncertainties associated with the long term effects of bone and renal toxicity and to mention that the reversibility of renal toxicity cannot be fully ascertained. Therefore warnings were introduced to promote a multidisciplinary management of paediatric patients to adequately weigh the need for treatment, to adequately settle the monitoring and to foresee the need for supplementation.

Furthermore physicians are alerted that significant laboratory abnormality suggestive of renal toxicity

during treatment should trigger specialised consultation.

Section 4.8 "Undesirable effects"

This section was updated to reflect the two studies on paediatric population (children and adolescents).

Section 5.1 "Pharmacological properties"

This section was updated to state that due to limitations of the study GS-US-104-0321, a benefit of tenofovir disoproxil fumarate over placebo was not demonstrated based on plasma HIV-1 RNA levels at week 24. However, a benefit is expected for the adolescent population based on extrapolation of adult data and comparative pharmacokinetic data.

Annex IIB Conditions of the marketing authorisation

Annex II was updated to reflect key messages that should be included HIV and HBV renal educational brochures

2. Overall conclusion and impact on the benefit/risk balance

Study GS-US-104-0321 have been initially submitted by the MAH in 2010 and assessed in the setting of type II variation II/98 to extend the indication of Viread for the treatment of HIV-infected adolescents. This variation was withdrawn by the applicant.

At that time it was observed that this study failed to meet its primary efficacy endpoint. No significant differences were found in virological response between patients treated with TDF or placebo (+OBR). However, when considering that 300mg TDF yielded to similar exposure in adolescents as compared to adult patients, there was no apparent reason to think that Viread would have different viral efficacy in these populations. The poor efficacy reported in the TDF arm was judged as being more likely to reflect pejorative baseline characteristics (in terms of OBR susceptibility and TDF resistance) in adolescents included in the TDF arm. In favour of this hypothesis, it was found that in subgroup analysis for subjects with OBR GSS ≤ 1 (TDF n=18, placebo n=10) TDF exhibited some activity in this highly pretreated patients contrarily to placebo.

As regards the safety, a trend for a lower increase of total BMD in the tenofovir group compared to the placebo group as well as the occurrence of osteopenia after a medium term duration were observed, which were regarded as a source of concern in the targeted population.

Meanwhile, further new data on the paediatric population has been available from both studies in HIV infected children (-0352) and HBV infected adolescents (-0115). The salient aspect of the benefit/risk assessment of these studies was the renal and bone toxicity. On an efficacy point of view, Viread was perceived as a potential useful additional therapeutic option in children. In both indications, it is a widely used backbone regimen in adult patients due to its virological efficacy and high genetic barrier. Moreover, TDF is a once daily regimen, which is of interest especially in children. Therefore, the CHMP requested a SAG meeting to adequately address the bone and renal safety of tenofovir in the paediatric population with medical need. The SAG scope was further enlarged upon CHMP request. The SAG members were invited to give their position on the risk of bone and renal toxicity of Viread in the context of its use in both HIV and HBV infected paediatric and adult patients. PDCO members as experts provided input to the scientific discussion at the SAG.

The SAG meeting was held the 3 May 2012. The discussion focused on the safety burden of tenofovir in the paediatric population and gave important information on the safety monitoring of the use of tenofovir in paediatric patients. Overall, SAG members highlighted the lack of correlation between DXA

measurements and bone events and the difficulties to provide specific recommendation as regards supplementation.

As regards renal toxicity in adolescents, the SAG members did not foresee any specific reason for the renal toxicity in adults being different in children and adolescents. Only the phosphate loss resulting from tubulopathy could be of differential impact given that paediatric patients are in active process of bone modelling. The current recommendation of renal toxicity monitoring in adults are judged conservative enough and could overall be aligned for paediatric patients, especially having in mind that this paediatric population is expected to be closely managed in clinical practice. As regards the need for treatment interruption in paediatric patients, it was considered that instead of stating a specific threshold for withdrawal, as in adults, it would be more appropriate to give a general message that significant laboratory abnormality suggestive of renal toxicity during treatment should trigger specialised consultation.

As regards bone toxicity, the SAG members have considered that it is currently questioned whether the observed toxicity of the drug could be of any long term consequence. Therefore the discussion on the benefit/risk could then amount balancing theoretical risks versus established benefit (virological suppression). When considering the need for specific monitoring, the SAG members refute the value of any BMD monitoring given the lack of established correlation with clinical event. Furthermore, it represents a burden for paediatric patients and raises practical and technical issues. As regards the need for phosphate and Vit D supplementation, the SAG members have considered that there was no apparent reason to deviate from the general attitude which prevails in clinical practice for a population in active modelling process (i.e. supplementation is considered in case of significant depletion).

Overall, it was concluded that although there is a theoretical risk of long term effect of bone and renal toxicity of tenofovir, it cannot be opposed to the established benefit in a population of paediatric patients in need of treatment. However, the fact that there are uncertainties per se mandates special consideration on the use of tenofovir in a population of active modelling process. In HIV-infected children, the CHMP could support the use of tenofovir in the restricted population of patients with NRTI resistance or toxicity problems precluding the use of first line agents.

Thus, further to new data from studies in HIV infected children and HBV infected adolescents and in the light of the outcome of the SAG, the CHMP considers that the Viread indication should be extended to the HIV-infected adolescents patients.

Benefits

Beneficial effects

Given that the current backbone regimens are not only limited but also have limiting factors, tenofovir represents an additional therapeutic option in adolescents. Tenofovir is a widely used backbone regimen in adult patients due to its virological efficacy and high genetic barrier. Moreover, TDF is a once daily regimen, which is of interest especially in paediatrics.

Extrapolation from the adult experience together comparative PK data (TDF 300mg shows similar exposure in adolescents and in adults) support the extension of indication in adolescents.

Risks

Unfavourable effects

The renal and bone toxicity are a source of particular concern for the long-term use of TDF. This is true

both for adults and for paediatric patients especially considering that they are in evolving modelling process.

Uncertainty in the knowledge about the unfavourable effects

The long-term effect of TDF on bone mineral acquisition during childhood and the potential reversibility of bone toxicity cannot be determined from the non clinical and clinical data available. However, it is acknowledged that given the lack of correlation between BMD and clinical events, it remains theoretical risk. Moreover, the reversibility of the renal toxicity cannot be fully ascertained.

Given the uncertainties related to the use of tenofovir in a population of active modelling process, the CHMP supports the use of tenofovir in the restricted population of treatment NRTI resistance or toxicity problems precluding the use of other first line agent's population.

Moreover, warnings were added to the SmPC to alert physicians on the uncertainties on the long term effect of bone and renal toxicity and the fact that reversibility of renal toxicity cannot be fully ascertained. A statement was introduced to promote a multidisciplinary management of paediatric patients to adequately weigh the need for treatment, to adequately settle the monitoring and to foresee the need for supplementation. Promoting multidisciplinary approach appears pragmatic based on the SAG input that management is to be tailored to the child and mostly refer to good clinical practice in paediatric.

Discussion on the benefit-risk assessment

Overall, and further to the SAG input, the CHMP considers that Viread can be approved for the use in adolescents provided the indication is targeted to patients with NRTI resistance or toxicity problems precluding the use of first line agents.

The MAH should further document the reversibility of the renal toxicity. This included a review by the MAH of all protocols of on-going clinical trials to ensure that all cases of tubulopathy are properly followed up to assert reversibility. Furthermore the follow up of adverse reports of tubulopathy is enhanced by a targeted questionnaire for renal tubulopathy. This questionnaire aims to obtain reversibility data from post marketing reports of renal tubulopathy in the paediatric population.

Further to the SAG input, the CHMP could foresee the use of Viread in adolescents with appropriate SmPC restrictions and additional pharmacovigilance activities as described above.

Overall, the CHMP consider that given the lack of correlation between BMD decrease and clinical event, long term effect of bone and renal toxicity remains theoretical whereas there are established benefits in a population of paediatric patients in need of treatment. However, there are uncertainties that per se mandate special consideration on the use of tenofovir in a population of active modelling process. Therefore the CHMP endorses the use of tenofovir in the restricted population of adolescents with NRTI resistance or toxicity problems precluding the use of first line agents.

The SmPC was revised to include warnings to alert physicians on the uncertainties on the long term effect of bone and renal toxicity and the fact that reversibility of renal toxicity cannot be fully ascertained. A statement was introduced to promote a multidisciplinary management of paediatric patients to adequately weigh the need for treatment, to adequately settle the monitoring and to foresee the need for supplementation. Promoting multidisciplinary approach appears pragmatic based on the SAG input that management is to be tailored to the paediatric patient and mostly refer to good clinical practice in paediatric.

Further studies are included in the RMP that will help to better understand the safety in this population.

3. Recommendations

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends the variation to the terms of the Marketing Authorisation, concerning the following change:

Variation accepted		Type
C.I.6.a	Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	II

Update of sections 4.1, 4.2, 4.4, 4.8 and 5.1 of the SmPC in order to extend the therapeutic indication for the treatment of HIV 1 infected adolescents, with NRTI resistance or toxicities precluding the use of first line agents, aged 12 to < 18 years. The annex II, Labelling and Package Leaflet are updated accordingly.

The requested variation proposed amendments to the Update of Summary of Product Characteristics, annex II, labelling and package leaflet.

Conditions and requirements of the marketing authorisation

Risk management system and PSUR cycle

The MAH shall perform the pharmacovigilance activities detailed in the Pharmacovigilance Plan of the Risk Management Plan (RMP) presented in Module 1.8.2 of the marketing authorisation and any subsequent updates of the RMP agreed by the CHMP.

As per the CHMP Guideline on Risk Management Systems for medicinal products for human use, the updated RMP should be submitted at the same time as the next Periodic Safety Update Report (PSUR).

In addition, an updated RMP should be submitted:

- When new information is received that may impact on the current Safety Specification, Pharmacovigilance Plan or risk minimisation activities
- Within 60 days of an important (pharmacovigilance or risk minimisation) milestone being reached
- at the request of the EMA

The PSUR cycle for the product will follow a yearly cycle until otherwise agreed by the CHMP.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

The Marketing Authorisation Holder (MAH) shall ensure that all physicians who are expected to prescribe/use Viread in adults and/or paediatric patients are provided with a physician educational pack containing the Summary of Product Characteristics and an appropriate educational brochure, as detailed below:

- HIV renal educational brochure, including the creatinine clearance slide ruler
- HBV renal educational brochure, including the creatinine clearance slide ruler
- HIV paediatric educational brochure
- HBV paediatric educational brochure

The HIV and HBV renal educational brochures should contain the following key messages:

- That there is an increased risk of renal disease in HIV and HBV infected patients associated with

tenofovir disoproxil fumarate-containing products such as Viread

- That Viread should only be used in patients with impaired renal function if the potential benefits of treatment are considered to outweigh the potential risks
- The importance of dose interval adjustment of Viread in adult patients with creatinine clearance of 30-49 ml/min
- That Viread is not recommended for patients with severe renal impairment (creatinine clearance < 30 ml/min). If no alternative treatment is available, prolonged dose intervals may be used.
- That use of Viread should be avoided with concomitant or recent use of nephrotoxic medicinal products. If Viread is used with nephrotoxic medicinal products, renal function should be closely monitored according to the recommended schedule.
- That patients should have their baseline renal function assessed prior to initiating Viread therapy
- The importance of regular monitoring of renal function during Viread therapy
- Recommended schedule for monitoring renal function considering the presence or absence of additional risk factors for renal impairment
- That if serum phosphate is < 1.5 mg/dl or creatinine clearance decreases during therapy to < 50 ml/min then renal function should be re-evaluated within one week. If creatinine clearance is confirmed as < 50 ml/min or serum phosphate decreases to < 1.0 mg/dl then consideration should be given to interrupting Viread therapy.
- Instructions on the use of the creatinine clearance slide ruler

The HIV and HBV paediatric educational brochure should contain the following key messages:

- That a multidisciplinary approach is recommended for the management of paediatric patients
- That there is an increased risk of renal disease in HIV and HBV infected patients associated with tenofovir disoproxil fumarate-containing products such as Viread
- That Viread is not recommended for use in paediatric patients with renal impairment
- That use of Viread should be avoided with concomitant or recent use of nephrotoxic medicinal products. If Viread is used with nephrotoxic medicinal products, renal function should be closely monitored according to the recommended schedule.
- That patients should have their baseline renal function assessed prior to initiating Viread therapy
- The importance of regular monitoring of renal function during Viread therapy
- Recommended schedule for monitoring renal function considering the presence or absence of additional risk factors for renal impairment
- That if serum phosphate is confirmed to be < 3.0 mg/dl (0.96 mmol/l) in any paediatric patient receiving tenofovir disoproxil fumarate, renal function should be re-evaluated within one week. If renal abnormalities are detected or suspected then consultation with a nephrologist should be obtained to consider interruption of Viread treatment
- That Viread may cause a reduction in BMD and the effects of Viread associated changes in BMD on long term bone health and future fracture risk are currently unknown in paediatric patients
- That if bone abnormalities are detected or suspected then consultation with an endocrinologist and/or nephrologist should be obtained

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States.

Not applicable.

Paediatric Data

Furthermore, the CHMP reviewed the available paediatric data of studies subject to the agreed Paediatric Investigation Plan P/0109/2012 and the results of these studies are reflected in the Summary of Product Characteristics (SmPC) and, as appropriate, the Package Leaflet.