ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS
1. NAME OF THE MEDICINAL PRODUCT
Viread 245 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
Each film-coated tablet contains 245 mg of tenofovir disoproxil (as fumarate), equivalent to 300 mg of tenofovir disoproxil fumarate, or 136 mg of tenofovir.
For excipients, see 6.1.

3. PHARMACEUTICAL FORM
Film-coated tablet.
Light blue, almond-shaped, film-coated tablets, debossed on one side with the markings “GILEAD” and “4331” and on the other side with the marking “300”.

4. CLINICAL PARTICULARS
4.1 Therapeutic indications
Viread is indicated in combination with other antiretroviral agents in HIV infected patients over 18 years of age experiencing virological failure.

The demonstration of benefit of Viread is based on intensification studies, where tenofovir disoproxil fumarate was added to background therapy, consisting in the majority of cases of a tritherapy regimen in antiretroviral pre-treated patients experiencing an early virological failure (< 10,000 copies/ml, with the majority of patients having < 5,000 copies/ml). Currently, the benefit of Viread in patients with > 10,000 copies/ml is unknown.
In deciding on a new regimen for patients who have failed an antiretroviral regimen, careful consideration should be given to the patterns of mutations associated with different medicinal products and the treatment history of the individual patient. Where available, resistance testing may be appropriate.
Refer to Section 5.1, “Pharmacodynamic properties”.

4.2 Posology and method of administration
Therapy should be initiated by a physician experienced in the management of HIV infection.

Adults: The recommended dose is 245 mg (one tablet) once daily taken orally with food.

Children and adolescents: The safety and efficacy of Viread in patients under the age of 18 years have not been established (see 4.4). Viread must not be administered to children or adolescents until further data become available describing the safety and efficacy of tenofovir disoproxil fumarate in patients under the age of 18 years.

Elderly: No data are available on which to make a dose recommendation for patients over the age of 65 years (see 4.4).

Renal insufficiency: No data are available on which to make a dose recommendation for patients with renal insufficiency (see 4.4).
4.3 Contraindications

- Known hypersensitivity to tenofovir, tenofovir disoproxil fumarate, or to any of the excipients.
- Severe renal impairment.

4.4 Special warnings and special precautions for use

Tenofovir disoproxil fumarate has not been studied in patients under the age of 18.

Tenofovir is principally eliminated via the kidney. In preclinical studies at exposures similar to, or higher than those achieved in clinical trials, nephrotoxicity was observed. Although no significant nephrotoxicity has been observed in clinical trials following treatment with tenofovir disoproxil 245 mg (as fumarate) per day for a mean period of 58 weeks (for approximately 700 patients), monitoring of renal function is recommended since nephrotoxicity of tenofovir can not be strictly excluded.

The monitoring of renal function (serum creatinine and serum phosphate) is recommended at baseline before taking tenofovir disoproxil fumarate and at routine intervals during therapy every four weeks.

If serum phosphate is < 1.5 mg/dl (0.48 mmol/l) or serum creatinine is > 1.7 mg/dl (150 µmol/l), renal function should be re-evaluated within one week. Consideration should be given to interrupting treatment with tenofovir disoproxil fumarate in patients with increases in serum creatinine to > 2.0 mg/dl (177 µmol/l) or decreases in serum phosphate to < 1.0 mg/dl (0.32 mmol/l).

Tenofovir disoproxil fumarate has not been evaluated in patients with a pre-treatment serum creatinine ≥ 1.5 mg/dl (133 µmol/l), a serum phosphate < 2.0 mg/dl (0.65 mmol/l) or in those with a history of clinically important renal disease. Caution should be exercised when administering tenofovir disoproxil fumarate to patients with mild to moderate renal insufficiency.

Hypophosphataemia was observed in clinical trials (see 4.8). Reduced intestinal phosphorus absorption may be the cause of this hypophosphataemia, since significant signs of renal proximal tubulopathy were not frequent. However, the mechanism of hypophosphataemia has not been elucidated. Prolonged hypophosphataemia may induce osteomalacia.

Tenofovir disoproxil fumarate has not been evaluated in patients receiving nephrotoxic medicinal products (e.g. aminoglycosides, amphotericin B, foscarnet, ganciclovir, pentamidine or vancomycin). If concomitant use of tenofovir disoproxil fumarate and nephrotoxic agents is unavoidable, renal function should be monitored weekly.

Tenofovir disoproxil fumarate has not been evaluated in patients receiving medicinal products which are secreted by the same renal transporter, human organic anion transporter 1 (hOAT1) (e.g. cidofovir, a known nephrotoxic medicinal product). This renal transporter (hOAT1) may be responsible for tubular secretion and in part, renal elimination of tenofovir and cidofovir. Consequently, the pharmacokinetics of these medicinal products might be modified if they are co-administered. Unless clearly necessary, concomitant use of these medicinal products is not recommended, but if such use is unavoidable, renal function should be monitored weekly (see 4.5).

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.

Tenofovir disoproxil fumarate has not been evaluated in patients with hepatic impairment. Tenofovir and tenofovir disoproxil fumarate are not metabolised by liver enzymes, so the impact of liver impairment should be limited.
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, caution should be exercised when administering regimens containing nucleoside analogues and tenofovir disoproxil fumarate. These patients should be followed closely.

Co-administration of tenofovir disoproxil fumarate and the buffered tablet formulation of didanosine resulted in increased systemic exposure to didanosine. As a result of this increased exposure, patients receiving tenofovir disoproxil fumarate and didanosine concomitantly should be carefully monitored for didanosine-related adverse events e.g. pancreatitis (see 4.5).

Patients must be advised that antiretroviral therapies, including tenofovir disoproxil fumarate, have not been proven to prevent the risk of transmission of HIV to others through sexual contact or blood contamination. Appropriate precautions must continue to be used.

4.5 Interaction with other medicinal products and other forms of interaction

Based on the results of in vitro experiments and the known elimination pathway of tenofovir, the potential for CYP450 mediated interactions involving tenofovir with other medicinal products is low.

Tenofovir is excreted renally, both by filtration and active secretion via the anionic transporter (hOAT1). Co-administration of tenofovir disoproxil fumarate with other medicinal products that are also actively secreted via the anionic transporter (e.g. cidofovir) may result in increased concentrations of tenofovir or of the co-administered medicinal product (see 4.4).

Tenofovir disoproxil fumarate has been evaluated in combination with didanosine buffered tablet, lamivudine, indinavir, efavirenz, and lopinavir/ritonavir. No interaction was detected with lamivudine, indinavir or efavirenz. When tenofovir disoproxil fumarate was administered with lopinavir/ritonavir, a decrease in \( C_{\text{max}} \) and AUC of about 15% was observed for lopinavir, whereas the same parameters increased by 30% for tenofovir. When didanosine buffered tablet and tenofovir disoproxil fumarate were administered together, the pharmacokinetic parameters for tenofovir were unchanged, however the AUC for didanosine was increased by 44% (see 4.4). An interaction study with enteric coated didanosine capsules has not yet been conducted.

No interaction studies have been performed with hormonal contraceptives.

Tenofovir disoproxil fumarate must be taken with food, as food enhances the bioavailability of tenofovir (see 5.2).

4.6 Pregnancy and lactation

Pregnancy

No clinical data on exposed pregnancies are available for tenofovir disoproxil fumarate.

Animal studies do not indicate direct or indirect harmful effects of tenofovir disoproxil fumarate with respect to pregnancy, foetal development, parturition or postnatal development (see 5.3).

Tenofovir disoproxil fumarate should be used during pregnancy only if the potential benefit justifies the potential risk to the foetus.

However, given that the potential risks to developing human foetuses are unknown, the use of tenofovir disoproxil fumarate in women of childbearing potential must be accompanied by the use of effective contraception.

Lactation

In animal studies it has been shown that tenofovir is excreted into milk. It is not known whether tenofovir is excreted in human milk. Therefore, it is recommended that mothers being treated with tenofovir disoproxil fumarate do not breast-feed their infants.
As a general rule, it is recommended that HIV infected women do not breast-feed their infants in order to avoid transmission of HIV to the infant.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive or use machines have been performed.

4.8 Undesirable effects

Assessment of adverse reactions is based on two studies (see 5.1) in which 653 treatment-experienced patients received treatment with tenofovir disoproxil fumarate (n = 443) or placebo (n = 210) in combination with other antiretroviral medicinal products for 24 weeks.

Approximately one third of patients can be expected to experience adverse reactions following treatment with tenofovir disoproxil fumarate in combination with other antiretroviral agents. This incidence is similar to that reported in patients receiving placebo in combination with other antiretroviral agents. These reactions are usually mild to moderate gastrointestinal events.

The adverse reactions with suspected (at least possible) relationship to treatment are listed below by body system organ class and absolute frequency. Frequencies are defined as very common (> 1/10) or common (> 1/100, < 1/10).

Gastrointestinal system
Very common: diarrhoea, nausea, vomiting
Common: flatulence

Metabolism and nutritional system
Very common: hypophosphataemia

Approximately 1% of tenofovir disoproxil fumarate treated patients discontinued treatment due to the gastrointestinal events.

Mild to moderate (grade 1 and 2) decreases in serum phosphate (to 1.5 mg/dl (0.48 mmol/l) - 2.2 mg/dl (0.70 mmol/l)) were observed in 12% of tenofovir disoproxil fumarate treated patients versus 7% of placebo-treated patients for a mean of 24 weeks (controlled studies) and in 15% of patients treated with tenofovir disoproxil fumarate during a mean of 58 weeks (long term safety data). Most of these decreases resolved without interruption of treatment, but some patients received phosphate supplementation.

There were no significant changes in the types of reactions observed following long-term open-label treatment with tenofovir disoproxil fumarate in combination with other antiretroviral agents for up to 116 weeks.

4.9 Overdose

If overdose occurs the patient must be monitored for evidence of toxicity (see 4.8 and 5.3), and standard supportive treatment applied as necessary.

It is not known whether peritoneal dialysis or haemodialysis increases the rate of elimination of tenofovir.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antiviral for systemic use, ATC code: J05A
**Mechanism of action:** Tenofovir disoproxil fumarate is the fumarate salt of the prodrug tenofovir disoproxil. Tenofovir disoproxil is absorbed and converted to the active substance tenofovir, which is a nucleoside monophosphate (nucleotide) analogue. Tenofovir is then converted to the active metabolite, tenofovir diphosphate, by constitutively expressed cellular enzymes through two phosphorylation reactions in both resting and activated T cells. Tenofovir diphosphate has an intracellular half-life of 10 hours in activated and 50 hours in resting peripheral blood mononuclear cells (PBMCs). Tenofovir diphosphate inhibits viral polymerases by direct binding competition with the natural deoxyribonucleotide substrate and, after incorporation into DNA, by DNA chain termination. Tenofovir diphosphate is a weak inhibitor of cellular polymerases α, β, and γ, with kinetic inhibition constants (K_i) that are >200-fold higher against human DNA polymerase α (5.2 µmol) and >3,000-fold higher against human DNA polymerase β and γ (81.7 and 59.5 µmol, respectively) than its K_i against HIV-1 reverse transcriptase (0.02 µmol). At concentrations of up to 300 µmol, tenofovir has also shown no effect on the synthesis of mitochondrial DNA or the production of lactic acid in *in vitro* assays.

**Pharmacodynamic effects:** Tenofovir has *in vitro* antiviral activity against retroviruses and hepadnaviruses.

The concentration of tenofovir required for 50% inhibition (IC_{50}) of the wild-type laboratory strain HIV-1_{IIIB} is 1-6 µmol in lymphoid cell lines and 1.1 µmol against primary HIV-1 subtype B isolates in PBMCs. Tenofovir is also active against HIV-1 subtypes A, C, D, E, F, G, and O and against HIV_{Bal} in primary monocyte/macrophage cells. Tenofovir shows activity *in vitro* against HIV-2, with an IC_{50} of 4.9 µmol in MT-4 cells and against hepatitis B virus, with an IC_{50} of 1.1 µmol in HepG2 2.2.15 cells.

The activity of tenofovir remains within twofold of wild-type IC_{50} against recombinant HIV-1 expressing didanosine resistance (L74V), zalcitabine resistance (T69D), and multinucleoside drug resistance (Q151M complex) mutations. The activity of tenofovir against HIV-1 strains with zidovudine-associated mutations appears to depend on the type and number of these resistance mutations. In the presence of mutation T215Y, a twofold increase of the IC_{50} was observed. In 10 samples which had multiple zidovudine-associated mutations (mean 3.4), a mean 3.7-fold increase of the IC_{50} was observed (range 0.8 to 8.4).

Multinucleoside resistant HIV-1 with T69S double insertions have reduced susceptibility to tenofovir (IC_{50} > 10-fold). Tenofovir shows full activity against non-nucleoside reverse transcriptase inhibitor resistant HIV-1 with K103N or Y181C mutations. Cross-resistance to protease inhibitor resistance mutations is not expected due to the different viral enzymes targeted.

Strains of HIV-1 with 3- to 4-fold reduced susceptibility to tenofovir and a K65R mutation in reverse transcriptase have been selected *in vitro*. The K65R mutation in reverse transcriptase can also be selected by zalcitabine, didanosine, and abacavir, and causes reduced susceptibility to zalcitabine, didanosine, abacavir, and lamivudine (14-, 4-, 3-, and 25-fold, respectively). The clinical significance of these mutations for patients treated with tenofovir disoproxil fumarate or other antiretroviral medicinal products is unknown.

The clinical activity of tenofovir disoproxil fumarate has not been determined against hepatitis B virus (HBV) in humans. It is unknown whether treatment of patients co-infected with HIV-1 and HBV will result in the development of HBV resistance to tenofovir disoproxil fumarate or other medicinal products.

**Clinical efficacy:** The effects of tenofovir disoproxil fumarate in combination with a stable background regimen of antiretroviral agents has been demonstrated in two randomised placebo-controlled trials of 24-48 weeks duration in treatment-experienced HIV-1 infected adults.

In study GS-98-902, 186 treatment-experienced patients were treated with placebo or three doses of tenofovir disoproxil fumarate (75 mg, 150 mg and 300 mg) in combination with other antiretroviral
agents for 24-48 weeks. Modifications of background antiretroviral therapy were permitted from week 4. The mean baseline CD4 count was 374 cells/mm³, the mean baseline plasma HIV-1 RNA was 3.7 log₁₀ copies/ml and the mean duration of prior HIV treatment was 4.6 years. Baseline genotypic analysis of HIV isolates from 184 patients revealed that 94% of patients had HIV-1 resistance mutations associated with nucleoside reverse transcriptase inhibitors, 57% had mutations associated with protease inhibitors and 32% had mutations associated with non-nucleoside reverse transcriptase inhibitors.

At week 24 the time-weighted average changes from baseline in log₁₀ plasma HIV-1 RNA levels (DAVG₃₄) were 0.02 and -0.58 log₁₀ copies/ml for the placebo recipients and tenofovir disoproxil 245 mg (as fumarate) group, respectively (p < 0.001). The antiviral response to tenofovir disoproxil fumarate was durable through 48 weeks (DAVG₄₈ was -0.62 log₁₀ copies/ml). Changes in CD4 counts did not differ significantly between the tenofovir disoproxil 245 mg (as fumarate) group and the placebo group.

In study GS-99-907, 550 treatment-experienced patients were treated with placebo or tenofovir disoproxil 245 mg (as fumarate) for 24 weeks. The mean baseline CD4 cell count was 427 cells/mm³, the mean baseline plasma HIV-1 RNA was 3.4 log₁₀ copies/ml (78% of patients had a viral load of < 5,000 copies/ml) and the mean duration of prior HIV treatment was 5.4 years. Baseline genotypic analysis of HIV isolates from 253 patients revealed that 94% of patients had HIV-1 resistance mutations associated with nucleoside reverse transcriptase inhibitors, 58% had mutations associated with protease inhibitors and 48% had mutations associated with non-nucleoside reverse transcriptase inhibitors.

At week 24 the time-weighted average change from baseline in log₁₀ plasma HIV-1 RNA levels (DAVG₂₄) was -0.03 log₁₀ copies/ml and -0.61 log₁₀ copies/ml for the placebo and tenofovir disoproxil 245 mg (as fumarate) recipients (p < 0.0001). The virological response was substantially decreased in patients with viral strains of > 10-fold zidovudine phenotypic resistance. Five tenofovir disoproxil 245 mg (as fumarate) treated patients developed the K65R mutation within the first 24 weeks. The clinical significance of the development of this mutation is unknown. A statistically significant difference in favour of tenofovir disoproxil 245 mg (as fumarate) was seen in the time-weighted average change from baseline at week 24 (DAVG₂₄) for CD4 count (+13 cells/mm³ for tenofovir disoproxil 245 mg (as fumarate) versus -11 cells/mm³ for placebo, p-value = 0.0008). At week 24, 45% of tenofovir disoproxil fumarate treated patients had an undetectable viral load (< 400 log₁₀ copies/ml) versus 13% in the placebo-treated patients (p-value < 0.0001). Since entry criteria for this study required a screening viral load of ≤ 10,000 copies/ml, the benefit of tenofovir disoproxil fumarate in patients with > 10,000 copies/ml is currently unknown.

### 5.2 Pharmacokinetic properties

Tenofovir disoproxil fumarate is a water soluble ester prodrug which is rapidly converted in vivo to tenofovir and formaldehyde.

Tenofovir is converted intracellularly to tenofovir monophosphate and to the active component, tenofovir diphosphate.

**Absorption**

Following oral administration of tenofovir disoproxil fumarate to HIV infected patients, tenofovir disoproxil fumarate is rapidly absorbed and converted to tenofovir. Maximum tenofovir concentrations are observed in serum within one hour of dosing in the fasted state and within two hours when taken with food. The oral bioavailability of tenofovir from tenofovir disoproxil fumarate in fasted patients was approximately 25%. Administration of tenofovir disoproxil fumarate with food enhanced the oral bioavailability, with an increase in tenofovir AUC by approximately 40% and Cₘₐₓ by approximately 14%. Following the first dose of tenofovir disoproxil fumarate in fed patients, the median Cₘₐₓ in serum ranged from 213 to 375 ng/ml.

**Distribution**
Following intravenous administration the steady-state volume of distribution of tenofovir was estimated to be approximately 800 ml/kg. After oral administration of tenofovir disoproxil fumarate, tenofovir is distributed to most tissues with the highest concentrations occurring in the kidney, liver and the intestinal contents (preclinical studies). In vitro protein binding of tenofovir to plasma or serum protein was less than 0.7 and 7.2%, respectively, over the tenofovir concentration range 0.01 to 25 µg/ml.

**Biotransformation**

In vitro studies have determined that neither tenofovir disoproxil fumarate nor tenofovir are substrates for the CYP450 enzymes. Moreover, at concentrations substantially higher (approximately 300-fold) than those observed in vivo, tenofovir did not inhibit in vitro drug metabolism mediated by any of the major human CYP450 isoforms involved in drug biotransformation (CYP3A4, CYP2D6, CYP2C9, CYP2E1, or CYP1A1/2). Tenofovir disoproxil fumarate at a concentration of 100 µmol had no effect on any of the CYP450 isoforms, except CYP1A1/2, where a small (6%) but statistically significant reduction in metabolism of CYP1A1/2 substrate was observed. Based on these data, it is unlikely that clinically significant interactions involving tenofovir disoproxil fumarate and medicinal products metabolised by CYP450 would occur.

**Elimination**

Tenofovir is primarily excreted by the kidney by both filtration and an active tubular transport system with approximately 70-80% of the dose excreted unchanged in urine following intravenous administration. Total clearance has been estimated to be approximately 230 ml/h/kg (approximately 300 ml/min). Renal clearance has been estimated to be approximately 160 ml/h/kg (approximately 210 ml/min), which is in excess of the glomerular filtration rate. This indicates that active tubular secretion is an important part of the elimination of tenofovir. Following oral administration the terminal half-life of tenofovir is approximately 12 to 18 hours.

**Linearity/non-linearity**

The pharmacokinetics of tenofovir were independent of tenofovir disoproxil fumarate dose over the dose range 75 to 600 mg and were not affected by repeated dosing at any dose level.

**Age and gender**

Limited data on the pharmacokinetics of tenofovir in women indicate no major gender effect.

Pharmacokinetic studies have not been performed in children and adolescents (under 18) or in the elderly (over 65).

Pharmacokinetics have not been specifically studied in different ethnic groups.

**Intracellular pharmacokinetics**

In non-proliferating human peripheral blood mononuclear cells (PBMCs) the half-life of tenofovir diphosphate was found to be approximately 50 hours, whereas the half-life in phytohaemagglutinin-stimulated PBMCs was found to be approximately 10 hours.

### 5.3 Preclinical safety data

Preclinical studies conducted in rats, dogs and monkeys revealed target organ effects in gastrointestinal tract, kidney, bone and serum phosphate concentration. Different animal species had differing levels of sensitivity to each type of effect. The gastrointestinal tract and kidney changes were associated directly with exposure to drug. Findings in rat and monkey studies indicated that there was a drug-related decrease in intestinal absorption of phosphate with potential secondary reduction in bone mineral density.

Reproductive studies were conducted in rats and rabbits. There were no effects on mating or fertility parameters or on any pregnancy or foetal parameter. There were no gross foetal alterations of soft or skeletal tissues. Tenofovir reduced the viability index and weight of pups in peri-post natal toxicity studies.
Genotoxicity studies have shown that tenofovir disoproxil fumarate was negative in the \textit{in vivo} mouse bone marrow micronucleus assay but was positive for inducing forward mutations in the \textit{in vitro} L5178Y mouse lymphoma cell assay in the presence or absence of S9 metabolic activation. Tenofovir disoproxil fumarate was positive in the Ames test (strain TA 1535) in two out of three studies, once in the presence of S9 mix (6.2 to 6.8 fold-increase) and once without S9 mix.

As long term carcinogenicity studies are ongoing, the potential of tenofovir disoproxil fumarate to cause carcinogenicity can not be excluded.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

\textit{Core:}

- Microcrystalline cellulose
- Pregelatinised starch (gluten free)
- Croscarmellose sodium
- Lactose monohydrate
- Magnesium stearate

\textit{Coating:}

- Lactose monohydrate
- Hypermellose
- Titanium dioxide (E171)
- Glycerol triacetate
- Indigo carmine aluminium lake (E132)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years

6.4 Special precautions for storage

No special precautions for storage.

6.5 Nature and contents of container

Viread is supplied in high density polyethylene (HDPE) bottles with a child-resistant closure containing 30 film-coated tablets with a silica gel desiccant.
6.6  Instructions for use and handling

No special requirements.

7.  MARKETING AUTHORISATION HOLDER

Gilead Sciences International Limited
Cambridge
CB1 6GT
United Kingdom

8.  MARKETING AUTHORIZATION NUMBER(S)

9.  DATE OF FIRST AUTHORIZATION/RENEWAL OF THE AUTHORISATION

10. DATE OF REVISION OF THE TEXT
ANNEX II

A. MANUFACTURING AUTHORISATION HOLDERS RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OF THE MARKETING AUTHORISATION

C. SPECIFIC OBLIGATIONS TO BE FULFILLED BY THE MARKETING AUTHORISATION HOLDER
A. MANUFACTURING AUTHORISATION HOLDERS RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturers responsible for batch release

- Oranienburger Pharmawerk GmbH, Lehmitzstrasse 70-98, 16515 Oranienburg, Germany
  Manufacturing authorisation issued on 14 August 2000 by Landesamt für Soziales und Versorgung, Land Brandenburg, Abt. Landesgesundheitsamt, Dezernat Apotheken, Arzneimittel, Medizinprodukte, Wünsdorfer Platz 3, D-15838 Wünsdorf, Germany

- Gilead Sciences Limited, Unit 13, Stillorgan Industrial Park, Blackrock, Co. Dublin, Ireland
  Manufacturing authorisation issued 30 August 2000, by Irish Medicines Board, The Earlsfort Centre, Earlsfort Terrace, Dublin 2, Ireland

The printed package leaflet of the medicinal product must state the name and address of the manufacturer responsible for the release of the concerned batch.

B. CONDITIONS OF THE MARKETING AUTHORISATION

- CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE IMPOSED ON THE MARKETING AUTHORISATION HOLDER

Medicinal product subject to restricted medical prescription (See Annex I: Summary of Product Characteristics, 4.2)

- OTHER CONDITIONS

The holder of this marketing authorisation must inform the European Commission about the marketing plans for the medicinal product authorised by this decision.

C. SPECIFIC OBLIGATIONS TO BE FULFILLED BY THE MARKETING AUTHORISATION HOLDER

The Marketing Authorisation Holder shall complete the following programme of studies within the specified time frame, the results of which shall form the basis of the annual reassessment of the benefit/risk profile.

TOXICOLOGY

1. In rats, as test article-related renal karyomegaly was observed at all dose levels (0, 30, 100, 300 or 1,000 mg/kg/day) evaluated in this study, the chronic NOEL was reported to be less than 30 mg/kg/day. Although the Expert opinion is that the NOAEL is 30 mg/kg/day, the NOAEL could not be known. The applicant should clarify this issue and the risk of such finding to appear in humans.


2. In dogs, in view of the renal karyomegaly evident in all dose groups (0, 3, 10 or 30 mg/kg/day), the NOEL for TDF administered daily by oral gavage for 42 weeks was reported as less than 3 mg/kg/day. Although the Expert opinion is that based on the findings, the NOAEL in this study is 3 mg/kg/day, a NOAEL could not be established. The applicant should further address this issue and the risk of such finding to appear in humans.

3. Renal effects were observed in rats with high doses indicating the kidney as target organ for toxicity of TDF. According to data contained in the tabular format provided by the applicant (Vol. 1, Part I, page 85) in relation to pharmacological assessment on the renal system, in the high dose group, the volume of urine excreted was significantly reduced and also, the quantities of excreted calcium, sodium, potassium, chloride and bicarbonate were decreased. However, in the Expert Report it is stated that there was increased urinary electrolyte excretion and urine volume in rats dosed at 500 mg/kg but not at 50 mg/kg. The applicant is requested to clarify these results.

Response to request for clarification of results to be submitted 16 November 2001.

4. In contrast to the mechanism of decreased intestinal phosphate absorption, which is proposed by the applicant, based upon short-term (3 days) mechanistic studies, no hypophosphatemia can be observed in the 13- and 42-week rat and dog studies. The applicant is requested to clarify this discrepancy taking into account the decreased bone density and mineral content.

Response to request for clarification of results to be submitted 16 November 2001.

5. A 56-day toxicological study is currently ongoing to evaluate the effects of TDF (0, 30, 250 or 600 mg/kg/day) on phosphate homeostasis in rhesus macaques. The final report for this study should be provided when available.

Final report to be submitted 31 December 2001.

6. The company should provide the final results of the underway biochemical and morphologic evaluations in rats, monkeys and woodchucks in order to identify the potential in vivo effects of TDF on mitochondrial function and mitochondrial DNA incorporation.

Results to be submitted 31 December 2001.

7. The mutagenic potential of TDF has been evaluated using a conventional battery of tests: TDF was positive in the Ames test (strain TA 1535) in two studies out of three (one in the presence of S9 mix and one without S9 mix) and was also clearly positive in the in mouse lymphoma L5178Y TK +/- assay in one study with or without S9 mix and equivocal in a second study with S9 mix. These findings should be clarified by additional in vitro and in vivo UDS test on rats hepatic and intestinal cells, in order to complete the information related to the genetic toxicity of this drug, tenofovir belongs to a new class of molecules requiring a full assessment of the mutagenic potential of the drug.

The report of the in vitro and in vivo UDS study in rat primary hepatocytes will be submitted 28 February 2002. A written proposal for in vitro and in vivo UDS studies in rat intestinal tissue will be submitted 16 November 2001.

8. Moreover, gastrointestinal hyperplasia have been observed in animals which appear to be a rodent specific effect (occurring only at highest dose). However no mechanism has been proposed to explain this species-specific mechanism. The applicant should further investigate this issue in relation with this claimed species-specific effect.


9. Carcinogenicity studies are ongoing in mice and rats. The final reports of these studies, including interim reports, should be provided within a short timeframe. The applicant should integrate the finding for cidofovir in the discussion on carcinogenic potential of tenofovir.

Preliminary data from the rat carcinogenicity study will be submitted as soon as possible. The final report of the rat carcinogenicity study will be submitted by 31 December 2002. Report of the mouse carcinogenicity study will be submitted by 31 August 2003.
The findings on cidofovir will be integrated into the discussion of the results of the tenofovir carcinogenicity studies in the expert report which will be submitted with the accompanying Type II variation to amend the SmPC to reflect the results of the carcinogenicity data.

**CLINICAL DATA:**

1. Overall, the population enrolled in the clinical studies submitted consisted of mainly patients with limited viral load at baseline (in the pivotal study 907, patients were mainly asymptomatic with a baseline viral load <3 log copies/ml, including 78 % of patients in both groups with a viral load < 5000 copies/ml).

    The applicant is requested to undertake a clinical study in experienced patients with a high viral load at baseline.

    The protocol should be presented to the CPMP before starting.

**Protocol for study in patients with high viral load to be submitted 1 February 2002.**

**Results from study in patients with high viral load to be submitted 30 June 2004.**

2. The applicant should provide results of ongoing studies in order to complete the assessment of the efficacy (durability, impact in terms of CD4) and safety profiles of the drug (in particular results of study 903 in antiretroviral naive patients).

    The following data from ongoing studies will be submitted to complete the assessment of the efficacy and safety of Viread:

    - Final report for extended safety data from study 902 31 January 2002
    - 48 week data from pivotal study 907 31 March 2002
    - Long term safety data from study 910 (includes patients rolled over from 902 and 907 until time of approval) 31 August 2003
    - 48 week data from study 903 31 August 2002

**Study 902**

3. It is stated that patients were encouraged to continue their baseline antiretroviral therapies, in addition to the assigned study drug, for at least 4 weeks post-randomisation. Thereafter, changes in background antiretroviral therapy were permitted in consideration of changing at least 2 drugs in the background.

    The company should explain the way chosen to “encourage” patients.

**Response to be submitted 16 November 2001.**

4. Several interim analyses have been planned to monitor safety and efficacy but no data were given regarding number of analyses completed, the changes and the following decisions. The company should provide these data.

**Response to be submitted 16 November 2001.**
Study 907
5. In study 907, 31 patients in the TDF group were found to have less than 400 copies/ml at baseline. It would be of particular interest to know if patients with undetectable viral load at baseline in the TDF group have a sustained virological suppression over the study period. The company should present these specific data in the final study report.


6. Patients in study 907 were to be included on a stable antiretroviral therapy, consisting of no more than four active agents, for at least 8 weeks prior to the time of randomisation. In this context other reasons of early therapeutic failure such as poor adherence, low bioavailability, drug interactions and/or transient “blips” of viral replication cannot be ruled out. The applicant should discuss this issue.


7. Baseline value of viral load and CD4 cell count were scheduled thrice in study 907: screening, pre-baseline, and baseline. The applicant should present the proportion of patients with one, two, and three measurements in each treatment group as well as the intervals between the measurements. Single measurements might lead to a bias, since they fail to detect transient increases in viral load/decreases in CD4+ cells, which may occur during or after (even minor) infections as well as after diagnostic or therapeutic interventions).


Studies 902 – 907
8. Toxicity criteria for studies 902 and 907 were modified by Gilead through amendment (bone densitometry toxicity management, toxicity management guidelines, grade 1 serum creatinine elevation). The applicant should display and justify these modifications.


SAFETY
9. In the 17 patients who received a phosphate supplementation, the phosphatemia was corrected. This is a major element in favour of an intestinal absorption disorder. Indeed, in patients with proximal tubulopathy, the phosphate supplement usually does not correct the hypophosphatemia. Although this analysis is sufficient to say that there is no tubulopathy, the MAH is requested to realise a follow-up measure in a large study of phosphate supplements in order to propose clear recommendations in the SmPC, if appropriate (which dose, which frequency, when to stop phosphate?).

Gilead Sciences agree to evaluate the role of phosphate supplementation in patients who develop confirmed serum phosphate < 2.0 mg/dl in the paediatric study GS-01-928. A copy of this protocol will be submitted by the 31st March 2002.

10. The analysis of the rough data concerning a possible bone toxicity remains reassuring. However, the rates of vitamin D and those of the hydroxyprolinuria should be provided, since they could argue in a direction or the other concerning a possible induced osteomalacia, in one hand, and on the potential interest of a possible systematic oral Ca and vitamin D supplements, in the other hand (ES, FR).

Forty-eight week data from study 903 will include the following bone biomarkers: serum PTH, 1,25 (OH) Vitamin D, osteocalcin, bone specific alkaline phosphatase, C-telopeptide and urinary N-telopeptide at weeks 4, 12, 24, 26 and 48.
These data will be submitted 31 August 2002.
Ninety-six week data from study 903 will be submitted 31 August 2003.

No hydroxyproline levels were measured in the clinical program with tenofovir DF. C-telopeptide and urinary N-telopeptide were measured rather than hydroxyproline as these are accepted and validated markers of bone resorption.

11. Osteodensitometric data are reassuring but are only partial. A more accurate evaluation of bone toxicity, whether it is secondary to hypophosphatemia or not, should be conducted during ongoing or planned studies by means of bone densitometric measurements and follow-up of bone turnover biomarkers (resorption and formation) and should be provided as soon as available.

Forty-eight week data from study 903, including bone mineral density scans at weeks 24 and 48 and the following bone biomarkers: serum PTH, 1,25 (OH) Vitamin D, osteocalcin, bone specific alkaline phosphatase, C-telopeptide and urinary N-telopeptide at weeks 4, 12, 24, 26 and 48, will be submitted 31 August 2002.

Ninety-six week data from study 903 will be submitted 31 August 2003.

12. Laboratories toxicity through 24 weeks:
- despite the antiviral activity of TDF against HBV, patients with hepatitis have a 2.7-fold higher risk of experiencing ALT elevations > grade 2.
- grade 3 to 4 lipase elevations occur almost double as often in the tenofovir group compared with control (26 % vs. 16 %) in studies 902 and 907. The applicant should comment on these issues.


Post marketing surveillance:
TDF has been shown to exhibit in vitro an activity against HBV. Moreover, in clinical studies co-infection HIV/HBV or HCV was not considered as exclusion criteria. In this field, it would be important to address whether the introduction of tenofovir in co-infected patients has any influence in the evolution of HBV/HCV infections. In particular, the applicant should provide outcome of co-infected patients included in the 902 and 907 clinical studies. Furthermore, the applicant should further address this issue in the next PSURs.

Gilead Sciences agree to address this issue in future PSURs.

13. Safety profile at week 24 vs. week 48 should be specifically discussed for the available patients with regard the intended dose of 300 mg once daily. Grade 1 and 2 drug-related AEs should also be tabulated and discussed. In the same way, discontinuations due to AEs should be tabulated by type of responsible AE.


Post marketing surveillance:
Both the number of patients and the length of exposure provided in the dossier are limited to draw definitive conclusions on safety. The applicant should update this information. In particular, the applicant should perform a post marketing surveillance targeting bone, renal and mitochondrial toxicities taking into account the patients’ background therapy. Furthermore, a specific analysis on these events should be presented separately in the next PSURs.

Gilead Sciences agree to update the safety information as data from ongoing and new studies becomes available.
Furthermore Gilead Sciences agreed to address the issues identified above in future PSURs.
ANNEX III

LABELLING AND PACKAGE LEAFLET
A. LABELLING
**PARTICULARS TO APPEAR ON THE OUTER PACKAGING OR, WHERE THERE IS NO OUTER PACKAGING, ON THE IMMEDIATE PACKAGING**

**CARTON AND BOTTLE LABEL TEXT**

1. **NAME OF THE MEDICINAL PRODUCT**
   
   Viread 245 mg film-coated tablets
   Tenofovir disoproxil

2. **STATEMENT OF ACTIVE SUBSTANCE(S)**
   
   Each film-coated tablet contains 245 mg tenofovir disoproxil equivalent to 300 mg tenofovir disoproxil fumarate.

3. **LIST OF EXCIPIENTS**

4. **PHARMACEUTICAL FORM AND CONTENTS**
   
   30 film-coated tablets.

5. **METHOD AND ROUTE(S) OF ADMINISTRATION**
   
   Oral use.
   Read the package leaflet before use.

6. **SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN**
   
   Keep out of the reach and sight of children.

7. **OTHER SPECIAL WARNING(S), IF NECESSARY**

8. **EXPIRY DATE**
   
   EXP {MM/YYYY}

9. **SPECIAL STORAGE CONDITIONS**

10. **SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE**
### 11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Gilead Sciences Intl Ltd  
Cambridge  
CB1 6GT  
United Kingdom

### 12. MARKETING AUTHORISATION NUMBER(S)

EU/0/00/000/000

### 13. MANUFACTURER’S BATCH NUMBER

Lot {number}

### 14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

### 15. INSTRUCTIONS ON USE
B. PACKAGE LEAFLET
PACKAGE LEAFLET

Read all of this leaflet carefully before you start taking this medicine.
- Keep this leaflet. You may need to read it again.
- If you have further questions, please ask your doctor or your pharmacist.
- This medicine has been prescribed for you personally and you should not pass it on to others. It may harm them, even if their symptoms are the same as yours.

In this leaflet:
1. What Viread is and what it is used for
2. Before you take Viread
3. How to take Viread
4. Possible side effects
5. Storing Viread

Viread 245 mg film-coated tablets
Tenofovir disoproxil

- The active substance is tenofovir. Each Viread tablet contains 245 mg of tenofovir disoproxil (in the form of 300 mg tenofovir disoproxil fumarate), equivalent to 136 mg of tenofovir.

- The other ingredients are:
  Tablet core:
  Microcrystalline cellulose
  Pregelatinised starch (gluten free)
  Croscarmellose sodium
  Lactose monohydrate
  Magnesium stearate

  Tablet coating:
  Lactose monohydrate
  Hypromellose
  Titanium dioxide (E171)
  Glycerol triacetate
  Indigo carmine aluminium lake (E132)

Manufacturer: Gilead Sciences Limited or Oranienburger Pharmawerk GmbH
Unit 13, Stillorgan Industrial Park Lehnitzstrasse 70-98
Blackrock D-16515 Oranienburg
County Dublin Germany
Ireland CBI 6GT

Marketing Authorisation Holder: Gilead Sciences International Limited

1. WHAT VIREAD IS AND WHAT IT IS USED FOR

- Viread 245 mg film-coated tablets are almond-shaped and light blue in colour. The tablets are debossed on one side with “GILEAD” and “4331” and on the other side with “300”. Viread 245 mg film-coated tablets are supplied in bottles containing 30 tablets.

- Viread belongs to a group of antiviral medicines, called nucleotide reverse transcriptase inhibitors.
• Viread is used to treat Human Immunodeficiency Virus (HIV) infection in adults if the anti-HIV medicines you are currently receiving do not adequately control the amount of HIV in your blood. This medicine must be taken in combination with other anti-HIV medicines.

• This medicine is not a cure for HIV infection. While taking Viread you may still develop infections or other illnesses associated with HIV infection.

2. BEFORE YOU TAKE VIREAD

Do not take Viread:

• If you are hypersensitive (allergic) to tenofovir, tenofovir disoproxil fumarate or any of the other ingredients of Viread tablets.

• If you have severe problems with your kidneys.

Take special care with Viread:

Viread does not reduce the risk of passing HIV to others through sexual contact or blood contamination. Therefore, it is important to continue to take appropriate precautions to prevent passing HIV to others.

Inform your doctor if you have previously had liver or kidney disease or your blood or urine tests have shown problems with your liver or kidneys.

Viread may have an effect on your kidneys or decrease the amount of phosphate in your blood. Low amounts of phosphate in your blood for long periods may cause bone abnormalities, including bone pain.

Your doctor will order some blood tests to assess the proper function of your kidneys. Depending on the results of these tests, your doctor may advise you to interrupt treatment with Viread.

Viread is closely related to a class of medicines which can cause lactic acidosis (excess of lactic acid in your blood), together with an enlarged liver. The data in animals and humans suggest that the risk of occurrence of lactic acidosis following treatment with Viread is low. Non specific symptoms such as nausea, vomiting and stomach pain, might indicate the development of lactic acidosis. This rare but serious side effect has occasionally been fatal. Lactic acidosis occurs more often in women, particularly if they are very overweight. Your doctor will monitor you regularly while you are receiving Viread.

Pregnancy:
Ask your doctor or pharmacist for advice before taking any medicine.

The safe use of Viread in human pregnancy has not been demonstrated. For this reason, it is important that women of child-bearing age receiving treatment with Viread use an effective method of contraception to avoid becoming pregnant.

Breast-feeding:
It is not known whether the active substance in this medicine is excreted in human breast milk. Consequently, nursing mothers should stop breast-feeding during treatment with Viread.

In general, women infected with HIV should not breast-feed their infants in order to avoid transmission of HIV to their newborn infant through the milk.

Driving and using machines:
The effect of Viread on the ability to drive or use machines has not been assessed.
Taking other medicines:
Please inform your doctor or pharmacist if you are taking or have recently taken any other medicines, even those not prescribed. You should tell your doctor if you are receiving other medicines which may damage your kidneys, such as aminoglycosides, amphotericin B, foscarnet, ganciclovir, pentamidine, vancomycin or cidofovir. A small interaction was seen with didanosine buffered tablets. If your antiretroviral regimen includes both Viread and didanosine, your doctor will carefully monitor for didanosine-related effects. In addition, a small interaction between Viread and lopinavir/ritonavir was seen, however this was not considered clinically important.

3. HOW TO TAKE VIREAD

Take one Viread 245 mg tablet once daily with a meal. Your doctor will prescribe Viread in combination with other antiretroviral medicines. Please refer to the patient information leaflets of the other antiretroviral medicines for guidance on how these medicines should be taken.

Always take the dose recommended by your doctor to ensure that your medicine is fully effective and to reduce the development of resistance to the treatment.

Do not change the amount of Viread you take unless told to do so by your doctor.

Viread is absorbed rapidly. Do not take another Viread 245 mg tablet if vomiting has occurred unless it occurs within 1 hour of taking Viread.

If you take more Viread than you should:
There is no specific antidote for overdose with Viread.

If you accidentally take too many Viread 245 mg tablets consult your doctor.

If you forget to take Viread:
It is important that you do not miss any doses. If you miss a dose of Viread, take it as soon as possible, and then take your next scheduled dose at its regular time. If it is almost time for your next dose, do not take the missed dose. Wait and take the next dose at the regular time. Do not double the next dose.

Effects when treatment with Viread is stopped:
Stopping treatment with Viread may result in a reduction in the effectiveness of the anti-HIV regimen recommended by your doctor.

4. POSSIBLE SIDE EFFECTS

Like all medicines, Viread can have side effects. Patients treated with Viread in combination with other anti-HIV medicines have very commonly experienced diarrhoea, vomiting, nausea and decreases in phosphate in the blood and have commonly experienced flatulence.

If you notice any side effects not mentioned in this leaflet please inform your doctor or pharmacist.

5. STORING VIREAD

Keep out of the reach and sight of children.

There are no special storage instructions.

Do not use after the expiry date stated on the bottle and carton.
This leaflet was last approved on