ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Truvada 200 mg/245 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 200 mg of emtricitabine and 245 mg of tenofovir disoproxil (equivalent to 300 mg of tenofovir disoproxil fumarate or 136 mg of tenofovir).

Excipient with known effect:

Each tablet contains 96 mg lactose monohydrate.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet.

Blue, capsule-shaped, film-coated tablet, of dimensions 19 mm x 8.5 mm, debossed on one side with "GILEAD" and on the other side with "701".

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Truvada is a fixed dose combination of emtricitabine and tenofovir disoproxil fumarate. It is indicated in antiretroviral combination therapy for the treatment of HIV-1 infected adults aged 18 years and over.

The demonstration of the benefit of the combination emtricitabine and tenofovir disoproxil fumarate in antiretroviral therapy is based solely on studies performed in treatment-naïve patients (see section 5.1).

4.2 Posology and method of administration

Therapy should be initiated by a physician experienced in the management of HIV infection.

Posology
Adults: The recommended dose of Truvada is one tablet, taken orally, once daily. In order to optimise the absorption of tenofovir, it is recommended that Truvada should be taken with food. Even a light meal improves absorption of tenofovir from the combination tablet (see section 5.2).

Where discontinuation of therapy with one of the components of Truvada is indicated or where dose modification is necessary, separate preparations of emtricitabine and tenofovir disoproxil fumarate are available. Please refer to the Summary of Product Characteristics for these medicinal products.

If a patient misses a dose of Truvada within 12 hours of the time it is usually taken, the patient should take Truvada with food as soon as possible and resume their normal dosing schedule. If a patient misses a dose of Truvada by more than 12 hours and it is almost time for their next dose, the patient should not take the missed dose and simply resume the usual dosing schedule.

If the patient vomits within 1 hour of taking Truvada, another tablet should be taken. If the patient vomits more than 1 hour after taking Truvada they do not need to take another dose.

Special populations

Older people: No data are available on which to make a dose recommendation for patients over the age of 65 years. However, no adjustment in the recommended daily dose for adults should be required unless there is evidence of renal insufficiency.

Renal impairment: Emtricitabine and tenofovir are eliminated by renal excretion and the exposure to emtricitabine and tenofovir increases in patients with renal dysfunction. There are limited data on the safety and efficacy of Truvada 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 Truvada should only be used if the potential benefits of treatment are considered to outweigh the potential risks. Patients with renal impairment may require close monitoring of renal function (see section 4.4). Dose interval adjustments are recommended for patients with creatinine clearance between 30 and 49 ml/min. These dose adjustments have not been confirmed in clinical studies and the clinical response to treatment should be closely monitored in these patients (see sections 4.4 and 5.2).

Mild renal impairment (creatinine clearance 50-80 ml/min): Limited data from clinical studies support once daily dosing of Truvada in patients with mild renal impairment (see section 4.4).

Moderate renal impairment (creatinine clearance 30-49 ml/min): Administration of Truvada every 48 hours is recommended, based on modelling of single-dose pharmacokinetic data for emtricitabine and tenofovir disoproxil fumarate in non-HIV infected subjects with varying degrees of renal impairment (see section 4.4).

Severe renal impairment (creatinine clearance < 30 ml/min) and haemodialysis patients: Truvada is not recommended for patients with severe renal impairment (creatinine clearance < 30 ml/min) and in patients who require haemodialysis because appropriate dose reductions cannot be achieved with the combination tablet.

Hepatic impairment: The pharmacokinetics of Truvada and emtricitabine have not been studied in patients with hepatic impairment. The pharmacokinetics of tenofovir have been studied in patients with hepatic impairment and no dose adjustment is required for tenofovir disoproxil fumarate in these patients. Based on minimal hepatic metabolism and the renal route of elimination for emtricitabine, it is unlikely that a dose adjustment would be required for Truvada in patients with hepatic impairment (see sections 4.4 and 5.2).

If Truvada is discontinued in patients co-infected with HIV and HBV, these patients should be closely monitored for evidence of exacerbation of hepatitis (see section 4.4).

Paediatric population: The safety and efficacy of Truvada in children under the age of 18 years have not been established (see section 5.2).

Method of administration

Truvada tablets should be taken once daily, orally with food.

If patients have difficulty in swallowing, Truvada can be disintegrated in approximately 100 ml of water, orange juice or grape juice and taken immediately.

4.3 Contraindications

Hypersensitivity to the active substances or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Co-administration of other medicinal products
Truvada should not be administered concomitantly with other medicinal products containing emtricitabine, tenofovir disoproxil (as fumarate) or other cytidine analogues, such as lamivudine (see section 4.5). Truvada should not be administered concomitantly with adefovir dipivoxil.

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 (see section 4.5). 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.

Triple nucleoside therapy
There have been reports of a high rate of virological failure and of emergence of resistance at an early stage when tenofovir disoproxil fumarate was combined with lamivudine and abacavir as well as with lamivudine and didanosine as a once daily regimen. There is close structural similarity between lamivudine and emtricitabine and similarities in the pharmacokinetics and pharmacodynamics of these two agents. Therefore, the same problems may be seen if Truvada is administered with a third nucleoside analogue.

Opportunistic infections
Patients receiving Truvada or any other antiretroviral therapy may continue to develop opportunistic infections and other complications of HIV infection, and therefore should remain under close clinical observation by physicians experienced in the treatment of patients with HIV associated diseases.

Transmission of HIV
While effective viral suppression with antiretroviral therapy has been proven to substantially reduce the risk of sexual transmission, a residual risk cannot be excluded. Precautions to prevent transmission should be taken in accordance with national guidelines.

Renal impairment
Emtricitabine and tenofovir are primarily excreted by the kidneys by a combination of glomerular filtration and active tubular secretion. Renal failure, renal impairment, elevated creatinine, hypophosphataemia and proximal tubulopathy (including Fanconi syndrome) have been reported with the use of tenofovir disoproxil fumarate in clinical practice (see section 4.8).

It is recommended that creatinine clearance is calculated in all patients prior to initiating therapy with Truvada and renal function (creatinine clearance and serum phosphate) is also monitored after two to four weeks of treatment, after three months of treatment and every three to six months thereafter in patients without renal risk factors. In patients at risk for renal impairment, a more frequent monitoring of renal function is required.

Patients with renal impairment (creatinine clearance < 80 ml/min), including haemodialysis patients:
Renal safety with Truvada has only been studied to a very limited degree in patients with impaired renal function (creatinine clearance < 80 ml/min). Dose interval adjustments are recommended for patients with creatinine clearance 30-49 ml/min (see section 4.2). Limited clinical study data suggest that the prolonged dose interval is not optimal and could result in increased toxicity and possibly inadequate response. Furthermore, in a small clinical study, a subgroup of patients with creatinine clearance between 50 and 60 ml/min who received tenofovir disoproxil fumarate in combination with emtricitabine every 24 hours had a 2-4-fold higher exposure to tenofovir and worsening of renal function (see section 5.2). Therefore, a careful benefit-risk assessment is needed when Truvada is used in patients with creatinine clearance < 60 ml/min, and renal function should be closely

monitored. In addition, the clinical response to treatment should be closely monitored in patients receiving Truvada at a prolonged dosing interval. The use of Truvada is not recommended in patients with severe renal impairment (creatinine clearance < 30 ml/min) and in patients who require haemodialysis since appropriate dose reductions cannot be achieved with the combination tablet (see sections 4.2 and 5.2).

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 Truvada, 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). Consideration should also be given to interrupting treatment with Truvada in patients with creatinine clearance decreased to < 50 ml/min or decreases in serum phosphate to < 1.0 mg/dl (0.32 mmol/l). Interrupting treatment with Truvada should also be considered in case of progressive decline of renal function when no other cause has been identified.

Use of Truvada should be avoided with concurrent or recent use of a nephrotoxic medicinal product (see section 4.5). If concomitant use of Truvada and nephrotoxic agents is unavoidable, renal function should be monitored weekly.

Cases of acute renal failure after initiation of high dose or multiple non-steroidal anti-inflammatory drugs (NSAIDs) have been reported in patients treated with tenofovir disoproxil fumarate and with risk factors for renal dysfunction. If Truvada is co-administered with an NSAID, renal function should be monitored adequately.

A higher risk of renal impairment has been reported in patients receiving tenofovir disoproxil fumarate in combination with a ritonavir or cobicistat boosted protease inhibitor. A close monitoring of renal function is required in these patients (see section 4.5). In patients with renal risk factors, the co-administration of tenofovir disoproxil fumarate with a boosted protease inhibitor should be carefully evaluated.

Patients with HIV-1 harbouring mutations
Truvada should be avoided in antiretroviral-experienced patients with HIV-1 harbouring the K65R mutation (see section 5.1).

Bone effects
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.

In other studies (prospective and cross-sectional), the most pronounced decreases in BMD were seen in patients treated with tenofovir disoproxil fumarate as part of a regimen containing a boosted protease inhibitor. Alternative treatment regimens should be considered for patients with osteoporosis that are at a high risk for fractures.

Bone abnormalities (infrequently contributing to fractures) may be associated with proximal renal tubulopathy (see section 4.8). If bone abnormalities are suspected then appropriate consultation should be obtained.

Patients with HIV and hepatitis B or C virus co-infection
Patients with chronic hepatitis B or C treated with antiretroviral therapy are at an increased risk for severe and potentially fatal hepatic adverse reactions.

Physicians should refer to current HIV treatment guidelines for the optimal management of HIV infection in patients co-infected with hepatitis B virus (HBV).

In case of concomitant antiviral therapy for hepatitis B or C, please refer also to the relevant Summary of Product Characteristics for these medicinal products.

The safety and efficacy of Truvada have not been established for the treatment of chronic HBV infection. Emtricitabine and tenofovir individually and in combination have shown activity against HBV in pharmacodynamic studies (see section 5.1). Limited clinical experience suggests that emtricitabine and tenofovir disoproxil fumarate have anti-HBV activity when used in antiretroviral combination therapy to control HIV infection.

Discontinuation of Truvada therapy in patients co-infected with HIV and HBV may be associated with severe acute exacerbations of hepatitis. Patients co-infected with HIV and HBV who discontinue Truvada should be closely monitored with both clinical and laboratory follow-up for at least several months after stopping treatment. 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 disease

The safety and efficacy of Truvada have not been established in patients with significant underlying liver disorders. The pharmacokinetics of Truvada and emtricitabine have not been studied in patients with hepatic impairment. The pharmacokinetics of tenofovir have been studied in patients with hepatic impairment and no dose adjustment is required in these patients. Based on minimal hepatic metabolism and the renal route of elimination for emtricitabine, it is unlikely that a dose adjustment would be required for Truvada in patients with hepatic impairment (see section 5.2).

Patients with pre-existing liver dysfunction, including chronic active hepatitis, have an increased frequency of liver function abnormalities during combination antiretroviral therapy (CART) and should be monitored according to standard practice. If there is evidence of worsening liver disease in such patients, interruption or discontinuation of treatment must be considered.

Weight and metabolic parameters

An increase in weight and in levels of blood lipids and glucose may occur during antiretroviral therapy. Such changes may in part be linked to disease control and life style. For lipids, there is in some cases evidence for a treatment effect, while for weight gain there is no strong evidence relating this to any particular treatment. For monitoring of blood lipids and glucose reference is made to established HIV treatment guidelines. Lipid disorders should be managed as clinically appropriate.

Mitochondrial dysfunction

Nucleoside and nucleotide analogues have been demonstrated *in vitro* and *in vivo* to cause a variable degree of mitochondrial damage. There have been reports of mitochondrial dysfunction in HIV negative infants exposed *in utero* and/or postnatally to nucleoside analogues. The main adverse reactions reported are haematological disorders (anaemia, neutropenia), metabolic disorders (hyperlactataemia, hyperlipasaemia). These events are often transitory. Some late-onset neurological disorders have been reported (hypertonia, convulsion, abnormal behaviour). Whether the neurological disorders are transient or permanent is currently unknown. Any child exposed *in utero* to nucleoside and nucleotide analogues, even HIV negative children, should have clinical and laboratory follow-up and should be fully investigated for possible mitochondrial dysfunction in case of relevant signs or symptoms. These findings do not affect current national recommendations to use antiretroviral therapy in pregnant women to prevent vertical transmission of HIV.

Immune Reactivation Syndrome

In HIV infected patients with severe immune deficiency at the time of institution of CART, an inflammatory reaction to asymptomatic or residual opportunistic pathogens may arise and cause serious clinical conditions, or aggravation of symptoms. Typically, such reactions have been observed within the first few weeks or months of initiation of CART. Relevant examples are cytomegalovirus retinitis, generalised and/or focal mycobacterial infections, and *Pneumocystis jirovecii* pneumonia. Any inflammatory symptoms should be evaluated and treatment instituted when necessary.

Autoimmune disorders (such as Graves' disease) have also been reported to occur in the setting of immune reactivation; however, the reported time to onset is more variable and these events can occur many months after initiation of treatment.

HIV infected patients co-infected with hepatitis B virus may experience acute exacerbations of hepatitis associated with immune reactivation syndrome following the initiation of antiretroviral therapy.

Osteonecrosis
Although the aetiology is considered to be multifactorial (including corticosteroid use, alcohol consumption, severe immunosuppression, higher body mass index), cases of osteonecrosis have been reported particularly in patients with advanced HIV-disease and/or long-term exposure to CART. Patients should be advised to seek medical advice if they experience joint aches and pain, joint stiffness or difficulty in movement.

Older people
Truvada 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 Truvada.

Truvada contains lactose monohydrate. Consequently, patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency, or glucose-galactose malabsorption should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

As Truvada contains emtricitabine and tenofovir disoproxil fumarate, any interactions that have been identified with these agents individually may occur with Truvada. Interaction studies have only been performed in adults.

The steady-state pharmacokinetics of emtricitabine and tenofovir were unaffected when emtricitabine and tenofovir disoproxil fumarate were administered together *versus* each medicinal product dosed alone.

In vitro and clinical pharmacokinetic interaction studies have shown the potential for CYP450 mediated interactions involving emtricitabine and tenofovir disoproxil fumarate with other medicinal products is low.

Concomitant use not recommended
Due to similarities with emtricitabine, Truvada should not be administered concomitantly with other cytidine analogues, such as lamivudine (see section 4.4).

As a fixed combination, Truvada should not be administered concomitantly with other medicinal products containing any of the components, emtricitabine or tenofovir disoproxil fumarate.

Truvada should not be administered concomitantly with adefovir dipivoxil.

Didanosine: The co-administration of Truvada and didanosine is not recommended (see section 4.4 and Table 1).

Renally eliminated medicinal products: Since emtricitabine and tenofovir are primarily eliminated by the kidneys, co-administration of Truvada with medicinal products that reduce renal function or compete for active tubular secretion (e.g. cidofovir) may increase serum concentrations of emtricitabine, tenofovir and/or the co-administered medicinal products.

Use of Truvada should be avoided with concurrent or recent use of a nephrotoxic medicinal product. Some examples include, but are not limited to, aminoglycosides, amphotericin B, foscarnet, ganciclovir, pentamidine, vancomycin, cidofovir or interleukin-2 (see section 4.4).

Other interactions

Interactions between the components of Truvada and protease inhibitors and nucleoside reverse transcriptase inhibitors, are listed in Table 1 below (increase is indicated as "↑", decrease as "↓", no change as "↔", twice daily as "b.i.d." and once daily as "q.d."). If available, 90% confidence intervals are shown in parentheses.

Table 1: Interactions between the individual components of Truvada and other medicinal products

Medicinal product by therapeutic areas	**Effects on drug levels Mean percent change in AUC, C_{max}, C_{min} with 90% confidence intervals if available (mechanism)**	**Recommendation concerning co-administration with Truvada (emtricitabine 200 mg, tenofovir disoproxil fumarate 300 mg)**
ANTI-INFECTIVES		
Antiretrovirals		
Protease inhibitors		
Atazanavir/Ritonavir/Tenofovir disoproxil fumarate (300 mg q.d./100 mg q.d./300 mg q.d.)	Atazanavir: AUC: ↓ 25% (↓ 42 to ↓ 3) C_{max}: ↓ 28% (↓ 50 to ↑ 5) C_{min}: ↓ 26% (↓ 46 to ↑ 10) Tenofovir: AUC: ↑ 37% C_{max}: ↑ 34% C_{min}: ↑ 29%	No dose adjustment is recommended. The increased exposure of tenofovir could potentiate tenofovir associated adverse events, including renal disorders. Renal function should be closely monitored (see section 4.4).
Atazanavir/Ritonavir/Emtricitabine	Interaction not studied.	
Darunavir/Ritonavir/Tenofovir disoproxil fumarate (300 mg q.d./100 mg q.d./300 mg q.d.)	Darunavir: AUC: ↔ C_{min}: ↔ Tenofovir: AUC: ↑ 22% C_{min}: ↑ 37%	No dose adjustment is recommended. The increased exposure of tenofovir could potentiate tenofovir associated adverse events, including renal disorders. Renal function should be closely monitored (see section 4.4).
Darunavir/Ritonavir/Emtricitabine	Interaction not studied.	
Lopinavir/Ritonavir/Tenofovir disoproxil fumarate (400 mg b.i.d./100 mg b.i.d/300 mg q.d.)	Lopinavir/Ritonavir: AUC: ↔ C_{max}: ↔ C_{min}: ↔ Tenofovir: AUC: ↑ 32% (↑ 25 to ↑ 38) C_{max}: ↔ C_{min}: ↑ 51% (↑ 37 to ↑ 66)	No dose adjustment is recommended. The increased exposure of tenofovir could potentiate tenofovir associated adverse events, including renal disorders. Renal function should be closely monitored (see section 4.4).
Lopinavir/Ritonavir/Emtricitabine	Interaction not studied.	

Medicinal product by therapeutic areas	Effects on drug levels Mean percent change in AUC, C_{max}, C_{min} with 90% confidence intervals if available (mechanism)	Recommendation concerning co-administration with Truvada (emtricitabine 200 mg, tenofovir disoproxil fumarate 300 mg)
NRTIs		
Didanosine/Tenofovir disoproxil fumarate	Co-administration of tenofovir disoproxil fumarate and didanosine results in a 40-60% increase in systemic exposure to didanosine that may increase the risk for 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.	Co-administration of Truvada and didanosine is not recommended (see section 4.4).
Didanosine/Emtricitabine	Interaction not studied.	

Studies conducted with other medicinal products

Emtricitabine: In vitro, emtricitabine did not inhibit metabolism mediated by any of the following human CYP450 isoforms: 1A2, 2A6, 2B6, 2C9, 2C19, 2D6 and 3A4. Emtricitabine did not inhibit the enzyme responsible for glucuronidation.

There are no clinically significant pharmacokinetic interactions when emtricitabine is co-administered with indinavir, zidovudine, stavudine or famciclovir.

Tenofovir disoproxil fumarate: Co-administration of lamivudine, indinavir, efavirenz, nelfinavir or saquinavir (ritonavir boosted), methadone, ribavirin, rifampicin, adefovir dipivoxil or the hormonal contraceptive norgestimate/ethinyl oestradiol with tenofovir disoproxil fumarate did not result in any clinically significant pharmacokinetic interaction.

Truvada: Co-administration of tacrolimus with Truvada did not result in any clinically significant pharmacokinetic interaction.

4.6 Fertility, pregnancy and lactation

Pregnancy

A moderate amount of data on pregnant women (between 300-1,000 pregnancy outcomes) indicate no malformations or foetal/neonatal toxicity associated with emtricitabine and tenofovir disoproxil fumarate. Animal studies on emtricitabine and tenofovir disoproxil fumarate do not indicate reproductive toxicity (see section 5.3). Therefore the use of Truvada may be considered during pregnancy, if necessary.

Breast-feeding
Emtricitabine and tenofovir have been shown to be excreted in human milk. There is insufficient information on the effects of emtricitabine and tenofovir in newborns/infants. Therefore Truvada should not be used during breast-feeding.

As a general rule, it is recommended that HIV infected women do not breast-feed their infants under any circumstances in order to avoid transmission of HIV to the infant.

Fertility
No human data on the effect of Truvada are available. Animal studies do not indicate harmful effects of emtricitabine or tenofovir disoproxil fumarate on fertility.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. However, patients should be informed that dizziness has been reported during treatment with both emtricitabine and tenofovir disoproxil fumarate.

4.8 Undesirable effects

Summary of the safety profile
The most frequently reported adverse reactions considered possibly or probably related to emtricitabine and/or tenofovir disoproxil fumarate were nausea (12%) and diarrhoea (7%) in an open-label randomised clinical trial (GS-01-934, see section 5.1). The safety profile of emtricitabine and tenofovir disoproxil fumarate in this study was consistent with the previous experience with these agents when each was administered with other antiretroviral agents.

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 Truvada (see section 4.4).

Co-administration of tenofovir disoproxil fumarate 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).

Discontinuation of Truvada therapy in patients co-infected with HIV and HBV may be associated with severe acute exacerbations of hepatitis (see section 4.4).

Tabulated summary of adverse reactions
The adverse reactions considered at least possibly related to treatment with the components of Truvada from clinical trial and post-marketing experience are listed in Table 2, below, by body system organ class and frequency. Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness. Frequencies are defined as very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100) or rare (≥ 1/10,000 to < 1/1,000).

Table 2: Tabulated summary of adverse reactions associated with the individual components of Truvada based on clinical study and post-marketing experience

Frequency	Emtricitabine	Tenofovir disoproxil fumarate
Blood and lymphatic system disorders:		
Common:	neutropenia	
Uncommon:	anaemia[2]	
Immune system disorders:		
Common:	allergic reaction	

Metabolism and nutrition disorders:		
Very common:		hypophosphataemia[1]
Common:	hyperglycaemia, hypertriglyceridaemia	
Uncommon:		hypokalaemia[1]
Rare:		lactic acidosis
Psychiatric disorders:		
Common:	insomnia, abnormal dreams	
Nervous system disorders:		
Very common:	headache	dizziness
Common:	dizziness	headache
Gastrointestinal disorders:		
Very common:	diarrhoea, nausea	diarrhoea, vomiting, nausea
Common:	elevated amylase including elevated pancreatic amylase, elevated serum lipase, vomiting, abdominal pain, dyspepsia	abdominal pain, abdominal distension, flatulence
Uncommon:		pancreatitis
Hepatobiliary disorders:		
Common:	elevated serum aspartate aminotransferase (AST) and/or elevated serum alanine aminotransferase (ALT), hyperbilirubinaemia	increased transaminases
Rare:		hepatic steatosis, hepatitis
Skin and subcutaneous tissue disorders:		
Very common:		rash
Common:	vesiculobullous rash, pustular rash, maculopapular rash, rash, pruritus, urticaria, skin discolouration (increased pigmentation)[2]	
Uncommon:	angioedema[3]	
Rare:		angioedema
Musculoskeletal and connective tissue disorders:		
Very common:	elevated creatine kinase	
Uncommon:		rhabdomyolysis[1], muscular weakness[1]
Rare:		osteomalacia (manifested as bone pain and infrequently contributing to fractures)[1,3], myopathy[1]
Renal and urinary disorders:		
Uncommon:		increased creatinine, proteinuria
Rare:		renal failure (acute and chronic), acute tubular necrosis, proximal renal tubulopathy including Fanconi syndrome, nephritis (including acute interstitial nephritis)[3], nephrogenic diabetes insipidus
General disorders and administration site conditions:		
Very common:		asthenia
Common:	pain, asthenia	

[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] Anaemia was common and skin discolouration (increased pigmentation) was very common when emtricitabine was administered to paediatric patients.

[3] This adverse reaction was identified through post-marketing surveillance but not observed in randomised controlled clinical trials in adults or paediatric HIV clinical trials for emtricitabine or in randomised controlled clinical trials or the tenofovir disoproxil fumarate expanded access program for tenofovir disoproxil fumarate. The frequency category was estimated from a statistical calculation based on the total number of patients exposed to emtricitabine in randomised controlled clinical trials (n = 1,563) or tenofovir disoproxil fumarate in randomised controlled clinical trials and the expanded access program (n = 7,319).

Description of selected adverse reactions

Renal impairment: As Truvada may cause renal damage monitoring of renal function is recommended (see sections 4.4 and 4.8). Proximal renal tubulopathy generally resolved or improved after tenofovir disoproxil fumarate discontinuation. However, in some patients, declines in creatinine clearance did not completely resolve despite tenofovir disoproxil fumarate discontinuation. Patients at risk of renal impairment (such as patients with baseline renal risk factors, advanced HIV disease, or patients receiving concomitant nephrotoxic medications) are at increased risk of experiencing incomplete recovery of renal function despite tenofovir disoproxil fumarate discontinuation (see section 4.4).

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.

Metabolic parameters: Weight and levels of blood lipids and glucose may increase during antiretroviral therapy (see section 4.4).

Immune Reactivation Syndrome: In HIV infected patients with severe immune deficiency at the time of initiation of CART, an inflammatory reaction to asymptomatic or residual opportunistic infections may arise. Autoimmune disorders (such as Graves' disease) have also been reported; however, the reported time to onset is more variable and these events can occur many months after initiation of treatment (see section 4.4).

Osteonecrosis: Cases of osteonecrosis have been reported, particularly in patients with generally acknowledged risk factors, advanced HIV disease or long-term exposure to CART. The frequency of this is unknown (see section 4.4).

Paediatric population

Insufficient safety data are available for children below 18 years of age. Truvada is not recommended in this population (see section 4.2).

Other special population(s)

Older people: Truvada 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 Truvada (see section 4.4).

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 Truvada (see sections 4.2, 4.4 and 5.2).

HIV/HBV or HCV co-infected patients: Only a limited number of patients were co-infected with HBV (n=13) or HCV (n=26) in study GS-01-934. The adverse reaction profile of emtricitabine and tenofovir disoproxil fumarate in patients co-infected with HIV/HBV or HIV/HCV was similar to that observed in patients infected with HIV without co-infection. However, as would be expected in this patient population, elevations in AST and ALT occurred more frequently than in the general HIV infected population.

Exacerbations of hepatitis after discontinuation of treatment: In HIV infected patients co-infected with HBV, clinical and laboratory evidence of hepatitis have occurred after discontinuation of treatment (see section 4.4).

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

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

Up to 30% of the emtricitabine dose and approximately 10% of the tenofovir dose can be removed by haemodialysis. It is not known whether emtricitabine or tenofovir can be removed by peritoneal dialysis.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antiviral for systemic use; antivirals for treatment of HIV infections, combinations. ATC code: J05AR03

Mechanism of action and pharmacodynamic effects
Emtricitabine is a nucleoside analogue of cytidine. Tenofovir disoproxil fumarate is converted *in vivo* to tenofovir, a nucleoside monophosphate (nucleotide) analogue of adenosine monophosphate. Both emtricitabine and tenofovir have activity that is specific to human immunodeficiency virus (HIV-1 and HIV-2) and hepatitis B virus.

Emtricitabine and tenofovir are phosphorylated by cellular enzymes to form emtricitabine triphosphate and tenofovir diphosphate, respectively. *In vitro* studies have shown that both emtricitabine and tenofovir can be fully phosphorylated when combined together in cells. Emtricitabine triphosphate and tenofovir diphosphate competitively inhibit HIV-1 reverse transcriptase, resulting in DNA chain termination.

Both emtricitabine triphosphate and tenofovir diphosphate are weak inhibitors of mammalian DNA polymerases and there was no evidence of toxicity to mitochondria *in vitro* and *in vivo*.

Antiviral activity in vitro: Synergistic antiviral activity was observed with the combination of emtricitabine and tenofovir *in vitro*. Additive to synergistic effects were observed in combination studies with protease inhibitors, and with nucleoside and non-nucleoside analogue inhibitors of HIV reverse transcriptase.

Resistance: Resistance has been seen *in vitro* and in some HIV-1 infected patients due to the development of the M184V/I mutation with emtricitabine or the K65R mutation with tenofovir. Emtricitabine-resistant viruses with the M184V/I mutation were cross-resistant to lamivudine, but retained sensitivity to didanosine, stavudine, tenofovir and zidovudine. The K65R mutation can also be selected by abacavir or didanosine and results in reduced susceptibility to these agents plus lamivudine, emtricitabine and tenofovir. Tenofovir disoproxil fumarate should be avoided in patients with HIV-1 harbouring the K65R mutation. In addition, a K70E substitution in HIV-1 reverse transcriptase has been selected by tenofovir and results in low-level reduced susceptibility to abacavir, emtricitabine, lamivudine and tenofovir.

Patients with HIV-1 expressing three or more thymidine analogue associated mutations (TAMs) that included either the M41L or L210W reverse transcriptase mutation showed reduced susceptibility to tenofovir disoproxil fumarate.

In vivo resistance (antiretroviral-naïve patients): In an open-label randomised clinical study (GS-01-934) in antiretroviral-naïve patients, genotyping was performed on plasma HIV-1 isolates from all patients with confirmed HIV RNA > 400 copies/ml at weeks 48, 96 or 144 or at the time of early study drug discontinuation. As of week 144:

- The M184V/I mutation developed in 2/19 (10.5%) isolates analysed from patients in the emtricitabine/tenofovir disoproxil fumarate/efavirenz group and in 10/29 (34.5%) isolates analysed from the lamivudine/zidovudine/efavirenz group (p-value < 0.05, Fisher's Exact test comparing the emtricitabine+tenofovir disoproxil fumarate group to the lamivudine/zidovudine group among all subjects).
- No virus analysed contained the K65R or K70E mutation.
- Genotypic resistance to efavirenz, predominantly the K103N mutation, developed in virus from 13/19 (68%) patients in the emtricitabine/tenofovir disoproxil fumarate/efavirenz group and in virus from 21/29 (72%) patients in the comparative group.

Clinical efficacy and safety

In an open-label randomised clinical study (GS-01-934), antiretroviral-naïve HIV-1 infected patients received either a once daily regimen of emtricitabine, tenofovir disoproxil fumarate and efavirenz (n=255) or a fixed combination of lamivudine and zidovudine (Combivir) administered twice daily and efavirenz once daily (n=254). Patients in the emtricitabine and tenofovir disoproxil fumarate group were given Truvada and efavirenz from week 96 to week 144. At baseline the randomised groups had similar median plasma HIV-1 RNA (5.02 and 5.00 $\log_{10}$ copies/ml) and CD4 counts (233 and 241 cells/mm^3). The primary efficacy endpoint for this study was the achievement and maintenance of confirmed HIV-1 RNA concentrations < 400 copies/ml over 48 weeks. Secondary efficacy analyses over 144 weeks included the proportion of patients with HIV-1 RNA concentrations < 400 or < 50 copies/ml, and change from baseline in CD4 cell count.

The 48-week primary endpoint data showed that the combination of emtricitabine, tenofovir disoproxil fumarate and efavirenz provided superior antiviral efficacy as compared with the fixed combination of lamivudine and zidovudine (Combivir) with efavirenz as shown in Table 3. The 144 week secondary endpoint data are also presented in Table 3.

Table 3: 48- and 144-week efficacy data from study GS-01-934 in which emtricitabine, tenofovir disoproxil fumarate and efavirenz were administered to antiretroviral-naïve patients with HIV-1 infection

	GS-01-934 Treatment for 48 weeks		GS-01-934 Treatment for 144 weeks	
	Emtricitabine+ tenofovir disoproxil fumarate+efavirenz	Lamivudine+ zidovudine+efavirenz	Emtricitabine+ tenofovir disoproxil fumarate+efavirenz*	Lamivudine+ zidovudine+efavirenz
HIV-1 RNA < 400 copies/ml (TLOVR)	84% (206/244)	73% (177/243)	71% (161/227)	58% (133/229)
p-value	0.002**		0.004**	
% difference (95%CI)	11% (4% to 19%)		13% (4% to 22%)	
HIV-1 RNA < 50 copies/ml (TLOVR)	80% (194/244)	70% (171/243)	64% (146/227)	56% (130/231)
p-value	0.021**		0.082**	
% difference (95%CI)	9% (2% to 17%)		8% (-1% to 17%)	
Mean change from baseline in CD4 cell count (cells/mm^3)	+190	+158	+312	+271
p-value	0.002[a]		0.089[a]	
Difference (95%CI)	32 (9 to 55)		41 (4 to 79)	

* Patients receiving emtricitabine, tenofovir disoproxil fumarate and efavirenz were given Truvada plus efavirenz from week 96 to 144.

** The p-value based on the Cochran-Mantel-Haenszel Test stratified for baseline CD4 cell count

TLOVR=Time to Loss of Virologic Response

a: Van Elteren Test

In a separate randomised clinical study (M02-418), one hundred and ninety antiretroviral-naïve adults were also treated once daily with emtricitabine and tenofovir disoproxil fumarate in combination with lopinavir/ritonavir given once or twice daily. At 48 weeks, 70% and 64% of patients demonstrated HIV-1 RNA < 50 copies/ml with the once and twice daily regimens of lopinavir/ritonavir, respectively. The mean changes in CD4 cell count from baseline were +185 cells/mm^3 and +196 cells/mm^3 with the once and twice daily regimens of lopinavir/ritonavir, respectively.

Limited clinical experience in patients co-infected with HIV and HBV suggests that treatment with emtricitabine or tenofovir disoproxil fumarate in antiretroviral combination therapy to control HIV infection also results in a reduction in HBV DNA (3 log_{10} reduction or 4 to 5 log_{10} reduction, respectively) (see section 4.4).

Paediatric population

The safety and efficacy of Truvada in children under the age of 18 years have not been established.

5.2 Pharmacokinetic properties

Absorption

The bioequivalence of one Truvada film-coated tablet with one emtricitabine 200 mg hard capsule and one tenofovir disoproxil fumarate 245 mg film-coated tablet was established following single dose administration to fasting healthy subjects. Following oral administration of Truvada to healthy subjects, emtricitabine and tenofovir disoproxil fumarate are rapidly absorbed and tenofovir disoproxil fumarate is converted to tenofovir. Maximum emtricitabine and tenofovir concentrations are observed in serum within 0.5 to 3.0 h of dosing in the fasted state. Administration of Truvada with food resulted in a delay of approximately three quarters of an hour in reaching maximum tenofovir concentrations and increases in tenofovir AUC and C_{max} of approximately 35% and 15%, respectively, when administered with a high fat or light meal, compared to administration in the fasted state. In

order to optimise the absorption of tenofovir, it is recommended that Truvada should be taken with food.

Distribution
Following intravenous administration the volume of distribution of emtricitabine and tenofovir was approximately 1.4 l/kg and 800 ml/kg, respectively. After oral administration of emtricitabine or tenofovir disoproxil fumarate, emtricitabine and tenofovir are widely distributed throughout the body. *In vitro* binding of emtricitabine to human plasma proteins was < 4% and independent of concentration over the range of 0.02 to 200 µg/ml. *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
There is limited metabolism of emtricitabine. The biotransformation of emtricitabine includes oxidation of the thiol moiety to form the 3'-sulphoxide diastereomers (approximately 9% of dose) and conjugation with glucuronic acid to form 2'-O-glucuronide (approximately 4% of dose). *In vitro* studies have determined that neither tenofovir disoproxil fumarate nor tenofovir are substrates for the CYP450 enzymes. Neither emtricitabine nor tenofovir inhibited *in vitro* drug metabolism mediated by any of the major human CYP450 isoforms involved in drug biotransformation. Also, emtricitabine did not inhibit uridine-5'-diphosphoglucuronyl transferase, the enzyme responsible for glucuronidation.

Elimination
Emtricitabine is primarily excreted by the kidneys with complete recovery of the dose achieved in urine (approximately 86%) and faeces (approximately 14%). Thirteen percent of the emtricitabine dose was recovered in urine as three metabolites. The systemic clearance of emtricitabine averaged 307 ml/min. Following oral administration, the elimination half-life of emtricitabine is approximately 10 hours.

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. The apparent clearance of tenofovir averaged approximately 307 ml/min. Renal clearance has been estimated to be 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 elimination half-life of tenofovir is approximately 12 to 18 hours.

Older people
Pharmacokinetic studies have not been performed with emtricitabine or tenofovir in the elderly (over 65 years of age).

Gender
Emtricitabine and tenofovir pharmacokinetics are similar in male and female patients.

Ethnicity
No clinically important pharmacokinetic difference due to ethnicity has been identified for emtricitabine. The pharmacokinetics of tenofovir have not been specifically studied in different ethnic groups.

Paediatric population
In general, the pharmacokinetics of emtricitabine in infants, children and adolescents (aged 4 months up to 18 years) are similar to those seen in adults. Pharmacokinetic studies have not been performed with tenofovir in children and adolescents (under 18 years of age).

Renal impairment
Limited pharmacokinetic data are available for emtricitabine and tenofovir after co-administration of separate preparations or as Truvada in patients with renal impairment. Pharmacokinetic parameters were mainly determined following administration of single doses of emtricitabine 200 mg or tenofovir

disoproxil 245 mg to non-HIV infected patients with varying degrees of renal impairment. The degree of renal impairment was defined according to baseline creatinine clearance (CrCl) (normal renal function when CrCl > 80 ml/min; mild impairment with CrCl = 50-79 ml/min; moderate impairment with CrCl = 30-49 ml/min and severe impairment with CrCl = 10-29 ml/min).

The mean (%CV) emtricitabine drug exposure increased from 12 (25%) µg•h/ml in subjects with normal renal function, to 20 (6%) µg•h/ml, 25 (23%) µg•h/ml and 34 (6%) µg•h/ml, in patients with mild, moderate and severe renal impairment, respectively.

The mean (%CV) tenofovir drug exposure increased from 2,185 (12%) ng•h/ml in patients with normal renal function, to 3,064 (30%) ng•h/ml, 6,009 (42%) ng•h/ml and 15,985 (45%) ng•h/ml, in patients with mild, moderate and severe renal impairment, respectively.

The increased dose interval for Truvada in patients with moderate renal impairment is expected to result in higher peak plasma concentrations and lower C_{min} levels as compared to patients with normal renal function. The clinical implications of this are unknown.

In patients with end-stage renal disease (ESRD) requiring haemodialysis, between dialysis drug exposures substantially increased over 72 hours to 53 (19%) µg•h/ml of emtricitabine, and over 48 hours to 42,857 (29%) ng•h/ml of tenofovir.

It is recommended that the dosing interval for Truvada is modified in patients with creatinine clearance between 30 and 49 ml/min. Truvada is not suitable for patients with CrCl < 30 ml/min or for those on haemodialysis (see section 4.2).

A small clinical study was conducted to evaluate the safety, antiviral activity and pharmacokinetics of tenofovir disoproxil fumarate in combination with emtricitabine in HIV infected patients with renal impairment. A subgroup of patients with baseline creatinine clearance between 50 and 60 ml/min, receiving once daily dosing, had a 2-4-fold increase in tenofovir exposure and worsening renal function.

Hepatic impairment
The pharmacokinetics of Truvada have not been studied in patients with hepatic impairment. However, it is unlikely that a dose adjustment would be required for Truvada in patients with hepatic impairment.

The pharmacokinetics of emtricitabine have not been studied in non-HBV infected subjects with varying degrees of hepatic insufficiency. In general, emtricitabine pharmacokinetics in HBV infected subjects were similar to those in healthy subjects and in HIV infected subjects.

A single 245 mg dose of tenofovir disoproxil was administered to non-HIV infected patients with varying degrees of hepatic impairment defined according to Child-Pugh-Turcotte (CPT) classification. Tenofovir pharmacokinetics were not substantially altered in subjects with hepatic impairment suggesting that no dose adjustment is required in these subjects. The mean (%CV) tenofovir C_{max} and $AUC_{0-\infty}$ values were 223 (34.8%) ng/ml and 2,050 (50.8%) ng•h/ml, respectively, in normal subjects compared with 289 (46.0%) ng/ml and 2,310 (43.5%) ng•h/ml in subjects with moderate hepatic impairment, and 305 (24.8%) ng/ml and 2,740 (44.0%) ng•h/ml in subjects with severe hepatic impairment.

5.3 Preclinical safety data

Emtricitabine: Non-clinical data on emtricitabine reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential and toxicity to reproduction and development.

Tenofovir disoproxil fumarate: Non-clinical safety pharmacology studies on tenofovir disoproxil fumarate reveal no special hazard for humans. Repeated dose toxicity studies in rats, dogs and

monkeys at exposure levels greater than or equal to clinical exposure levels and with possible relevance to clinical use include renal and bone toxicity and a decrease in serum phosphate concentration. Bone toxicity was diagnosed as osteomalacia (monkeys) and reduced bone mineral density (BMD) (rats and dogs). The bone toxicity in young adult rats and dogs occurred at exposures ≥ 5-fold the exposure in paediatric or adult patients; bone toxicity occurred in juvenile infected monkeys at very high exposures following subcutaneous dosing (≥ 40-fold the exposure in patients). Findings in the rat and monkey studies indicated that there was a substance-related decrease in intestinal absorption of phosphate with potential secondary reduction in BMD.

Genotoxicity studies revealed positive results in the *in vitro* mouse lymphoma assay, equivocal results in one of the strains used in the Ames test, and weakly positive results in an UDS test in primary rat hepatocytes. However, it was negative in an *in vivo* mouse bone marrow micronucleus assay.

Oral carcinogenicity studies in rats and mice only revealed a low incidence of duodenal tumours at an extremely high dose in mice. These tumours are unlikely to be of relevance to humans.

Reproductive toxicity studies in rats and rabbits showed no effects on mating, fertility, pregnancy or foetal parameters. However, tenofovir disoproxil fumarate reduced the viability index and weight of pups in peri-postnatal toxicity studies at maternally toxic doses.

Combination of emtricitabine and tenofovir disoproxil fumarate: Genotoxicity and repeated dose toxicity studies of one month or less with the combination of these two components found no exacerbation of toxicological effects compared to studies with the separate components.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:
Croscarmellose sodium
Lactose monohydrate
Magnesium stearate (E572)
Microcrystalline cellulose (E460)
Pregelatinised starch (gluten free)

Film-coating:
Glycerol triacetate (E1518)
Hypromellose (E464)
Indigo carmine aluminium lake (E132)
Lactose monohydrate
Titanium dioxide (E171)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

4 years.

6.4 Special precautions for storage

Store in the original package in order to protect from moisture. Keep the bottle tightly closed.

6.5 Nature and contents of container

High density polyethylene (HDPE) bottle with a polypropylene child-resistant closure containing 30 film-coated tablets and a silica gel desiccant.

The following pack sizes are available: outer cartons containing 1 bottle of 30 film-coated tablets and outer cartons containing 90 (3 bottles of 30) film-coated tablets. Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Gilead Sciences International Limited
Cambridge
CB21 6GT
United Kingdom

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/04/305/001
EU/1/04/305/002

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 21 February 2005
Date of latest renewal: 20 January 2010

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

ANNEX II

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer(s) responsible for batch release

Gilead Sciences Ireland UC
IDA Business & Technology Park
Carrigtohill
County Cork
Ireland

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

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

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

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

· **Periodic Safety Update Reports**

The marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

· **Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING AND THE IMMEDIATE PACKAGING

BOTTLE AND CARTON LABELLING

1. NAME OF THE MEDICINAL PRODUCT

Truvada 200 mg/245 mg film-coated tablets
Emtricitabine/tenofovir disoproxil

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 200 mg of emtricitabine and 245 mg of tenofovir disoproxil (equivalent to 300 mg of tenofovir disoproxil fumarate or 136 mg of tenofovir).

3. LIST OF EXCIPIENTS

Contains lactose monohydrate, see leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

30 film-coated tablets.
90 (3 bottles of 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 SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in the original package in order to protect from moisture. Keep the bottle tightly closed.

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
CB21 6GT
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/04/305/001 30 film-coated tablets
EU/1/04/305/002 90 (3 x 30) film-coated tablets

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Truvada [outer packaging only]

B. PACKAGE LEAFLET

Package leaflet: Information for the user

Truvada 200 mg/245 mg film-coated tablets
Emtricitabine/tenofovir disoproxil

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Truvada is and what it is used for

Truvada is a treatment for Human Immunodeficiency Virus (HIV) infection in adults aged 18 years and over.

Truvada contains two active substances, *emtricitabine* and *tenofovir disoproxil*. Both of these active substances are *antiretroviral* medicines which are used to treat HIV infection. Emtricitabine is a *nucleoside reverse transcriptase inhibitor* and tenofovir is a *nucleotide reverse transcriptase inhibitor.* However, both are generally known as NRTIs and they work by interfering with the normal working of an enzyme (reverse transcriptase) that is essential for the virus to reproduce itself. Truvada should always be used combined with other medicines to treat HIV infection. Truvada can be administered in place of emtricitabine and tenofovir disoproxil used separately at the same doses.

This medicine is not a cure for HIV infection. While taking Truvada you may still develop infections or other illnesses associated with HIV infection. You can still pass on HIV when taking this medicine, although the risk is lowered by effective antiretroviral therapy. Discuss with your doctor the precautions needed to avoid infecting other people.

2. What you need to know before you take Truvada

Do not take Truvada

· **If you are allergic** to emtricitabine, tenofovir, tenofovir disoproxil fumarate, or any of the other ingredients of this medicine (listed in section 6).

If this applies to you, tell your doctor immediately.

Warnings and precautions

· **Tell your doctor if you have had kidney disease, or if tests have shown problems with your kidneys.** Truvada may affect your kidneys. Before starting treatment, your doctor may order blood tests to assess kidney function. Your doctor may also order blood tests during treatment

to monitor your kidneys and may advise you to take the tablets less often. Truvada is not recommended if you have severe kidney disease or are receiving haemodialysis.

Truvada is not usually taken with other medicines that can damage your kidneys (see *Other medicines and Truvada*). If this is unavoidable, your doctor will monitor your kidney function once a week.

- **Talk to your doctor if you are over 65.** Truvada has not been studied in patients over 65 years of age. If you are older than this and are prescribed Truvada, your doctor will monitor you carefully.

- **Talk to your doctor if you have a history of liver disease, including hepatitis.** Patients with liver disease including chronic hepatitis B or C, who are treated with antiretrovirals, have a higher risk of severe and potentially fatal liver complications. If you have hepatitis B infection, your doctor will carefully consider the best treatment regimen for you. Both active substances in Truvada show some activity against hepatitis B virus although emtricitabine is not approved for the treatment of hepatitis B infection. If you have a history of liver disease or chronic hepatitis B infection your doctor may conduct blood tests in order to carefully monitor liver function.

Other precautions

Look out for infections. If you have advanced HIV infection (AIDS) and have an infection, you may develop symptoms of infection and inflammation or worsening of the symptoms of an existing infection once treatment with Truvada is started. These symptoms may indicate that your body's improved immune system is fighting infection. Look out for signs of inflammation or infection soon after you start taking Truvada. If you notice signs of inflammation or infection, **tell your doctor at once.**

In addition to the opportunistic infections, autoimmune disorders (a condition that occurs when the immune system attacks healthy body tissue) may also occur after you start taking medicines for the treatment of your HIV infection. Autoimmune disorders may occur many months after the start of treatment. If you notice any symptoms of infection or other symptoms such as muscle weakness, weakness beginning in the hands and feet and moving up towards the trunk of the body, palpitations, tremor or hyperactivity, please inform your doctor immediately to seek necessary treatment.

Bone problems. Some patients taking combination antiretroviral therapy may develop a bone disease called osteonecrosis (death of bone tissue caused by loss of blood supply to the bone). The length of combination antiretroviral therapy, corticosteroid use, alcohol consumption, severe immunosuppression, higher body mass index, among others, may be some of the many risk factors for developing this disease. Signs of osteonecrosis are joint stiffness, aches and pains (especially of the hip, knee and shoulder) and difficulty in movement. If you notice any of these symptoms inform your doctor.

Bone problems (sometimes resulting in fractures) may also occur due to damage to kidney tubule cells (see section 4, *Possible side effects*).

Children and adolescents

Truvada is not for use in children and adolescents under 18 years of age.

Other medicines and Truvada

You should not take Truvada if you are already taking other medicines that contain the components of Truvada, emtricitabine and tenofovir disoproxil fumarate, or any other antiviral medicines that contain lamivudine or adefovir dipivoxil.

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines.

- **It is especially important to tell your doctor if you are taking other medicines which may damage your kidneys.**
  These include:

  - aminoglycosides (for bacterial infection)
  - amphotericin B (for fungal infection)
  - foscarnet (for viral infection)
  - ganciclovir (for viral infection)
  - pentamidine (for infections)
  - vancomycin (for bacterial infection)
  - interleukin-2 (to treat cancer)
  - cidofovir (for viral infection)
  - non-steroidal anti-inflammatory drugs (NSAIDs, to relieve bone or muscle pains)

- **Other medicines containing didanosine (for HIV infection):** Taking Truvada with other antiviral medicines that contain didanosine can raise the levels of didanosine in your blood and may reduce CD4 cell counts. Rarely, inflammation of the pancreas and lactic acidosis (excess lactic acid in the blood), which sometimes causes death, have been reported when medicines containing tenofovir disoproxil fumarate and didanosine were taken together. Your doctor will carefully consider whether to treat you with combinations of tenofovir and didanosine.

Do not stop your treatment without contacting your doctor.

Truvada with food and drink

- **Truvada should be taken with food.**

Pregnancy and breast-feeding

If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.

- **You must not take Truvada during pregnancy** unless specifically discussed with your doctor. Although there are limited clinical data on the use of Truvada in pregnant women, it is not usually used unless absolutely necessary.

- If you are a woman who could get pregnant during treatment with Truvada, you must use an effective method of contraception to avoid becoming pregnant.

- If you become pregnant, or plan to become pregnant, ask your doctor about the potential benefits and risks of therapy with Truvada to you and your child.

If you have taken Truvada during your pregnancy, your doctor may request regular blood tests and other diagnostic tests to monitor the development of your child. In children whose mothers took NRTIs during pregnancy, the benefit from the protection against HIV outweighed the risk of side effects.

- **Do not breast-feed during treatment with Truvada.** This is because the active substances in this medicine pass into human breast milk.

- If you are a woman with HIV it is recommended that you do not breast-feed, to avoid passing the virus to the baby in breast milk.

Driving and using machines

Truvada can cause dizziness. If you feel dizzy while taking Truvada, **do not drive** and do not use any tools or machines.

Truvada contains lactose

Tell your doctor if you are lactose-intolerant or intolerant to other sugars. Truvada contains lactose monohydrate. If you know you are lactose-intolerant, or if you have been told that you have an intolerance to any other sugars, talk to your doctor before taking this medicine.

3. How to take Truvada

- **Always take this medicine exactly as your doctor has told you.** Check with your doctor or pharmacist if you are not sure.

The recommended dose is:

- **Adults: one tablet each day with food.**

If you have difficulty swallowing, you can use the tip of a spoon to crush the tablet. Then mix the powder with about 100 ml (half a glass) of water, orange juice or grape juice, and drink immediately.

- **Always take the dose recommended by your doctor.** This is to make sure that your medicine is fully effective, and to reduce the risk of developing resistance to the treatment. Do not change the dose unless your doctor tells you to.

- **If you have problems with your kidneys,** your doctor may advise you to take Truvada less frequently.

- **If your doctor decides to stop** one of the components of Truvada or change the dose of Truvada, you may be given emtricitabine and/or tenofovir separately instead of the combined medicine or other medicines for the treatment of HIV infection.

- **Your doctor will prescribe Truvada with other antiretroviral medicines.** Please refer to the patient information leaflets of the other antiretrovirals for guidance on how to take those medicines.

If you take more Truvada than you should

If you accidentally take more than the recommended dose of Truvada, contact your doctor or nearest emergency department for advice. Keep the tablet bottle with you so that you can easily describe what you have taken.

If you forget to take Truvada

It is important not to miss a dose of Truvada.

If you do miss a dose of Truvada within 12 hours of when it is usually taken, take it as soon as you can, and then take your next dose at its regular time.

If it is almost time (less than 12 hours) for your next dose anyway, forget about the missed dose. Wait and take the next dose at the regular time. Do not take a double dose to make up for a forgotten tablet.

If you throw up less than 1 hour after taking Truvada, take another tablet. You do not need to take another tablet if you were sick more than 1 hour after taking Truvada.

If you stop taking Truvada

- **Stopping treatment** with Truvada may reduce the effectiveness of the anti-HIV therapy recommended by your doctor. Speak with your doctor before you stop taking Truvada for any reason, particularly if you are experiencing any side effects or you have another illness. Contact your doctor before you restart taking Truvada tablets.

- **If you have HIV infection and hepatitis B,** it is especially important not to stop your Truvada treatment without talking to your doctor first. Some patients have had blood tests or symptoms indicating that their hepatitis has got worse after stopping Truvada. You may require blood tests for several months after stopping treatment. In some patients with advanced liver disease or cirrhosis, stopping treatment is not recommended as this may lead to worsening of your hepatitis.

  Tell your doctor immediately about new or unusual symptoms after you stop treatment, particularly symptoms you associate with hepatitis B infection.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

During HIV therapy there may be an increase in weight and in levels of blood lipids and glucose. This is partly linked to restored health and life style, and in the case of blood lipids sometimes to the HIV medicines themselves. Your doctor will test for these changes.

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Tell your doctor about any of the following side effects:

Possible serious side effects: tell a doctor immediately

The following side effect is **rare** (this can affect up to 1 in every 1,000 patients):

- **Lactic acidosis (excess lactic acid in the blood)** is a serious side effect that can be life-threatening. The following side effects may be signs of lactic acidosis:
  - deep rapid breathing
  - drowsiness
  - feeling sick (nausea), being sick (vomiting) and stomach pain

If you think you may have lactic acidosis, contact your doctor immediately.

Other possible serious side effects

The following side effects are **uncommon** (these can affect up to 1 in every 100 patients):

- pain in the abdomen (tummy) caused by inflammation of the pancreas
- swelling of the face, lips, tongue or throat

The following side effects are **rare** (these can affect up to 1 in every 1,000 patients):

- fatty liver
- yellow skin or eyes, itching, or pain in the abdomen (tummy) caused by inflammation of the liver
- inflammation of the kidney, passing a lot of urine and feeling thirsty, kidney failure, damage to kidney tubule cells. Your doctor may do blood tests to see if your kidneys are working

properly.
- softening of the bones (with bone pain and sometimes resulting in fractures)

Damage to kidney tubule cells may be associated with breakdown of muscle, softening of the bones (with bone pain and sometimes resulting in fractures), muscle pain, muscle weakness and decreases in potassium or phosphate in the blood.

If you think that you may have any of these serious side effects, talk to your doctor.

Most frequent side effects

The following side effects are **very common** (these can affect at least 10 in every 100 patients):
- diarrhoea, being sick (vomiting), feeling sick (nausea), dizziness, headache, rash
- feeling weak

Tests may also show:
- decreases in phosphate in the blood
- increased creatine kinase

Other possible side effects

The following side effects are **common** (these can affect up to 10 in every 100 patients):
- pain, stomach pain
- difficulty sleeping, abnormal dreams
- problems with digestion resulting in discomfort after meals, feeling bloated, flatulence
- rashes (including red spots or blotches sometimes with blistering and swelling of the skin), which may be allergic reactions, itching, changes in skin colour including darkening of the skin in patches
- other allergic reactions, such as wheezing, swelling or feeling light-headed

Tests may also show:
- low white blood cell count (a reduced white blood cell count can make you more prone to infection)
- increased triglycerides (fatty acids), bile or sugar in the blood
- liver and pancreas problems

The following side effects are **uncommon** (these can affect up to 1 in every 100 patients):
- anaemia (low red blood cell count)
- breakdown of muscle, muscle pain or weakness which may occur due to damage to the kidney tubule cells

Tests may also show:
- decreases in potassium in the blood
- increased creatinine in your blood
- changes to your urine

The following side effects are **rare** (these can affect up to 1 in every 1,000 patients):
- back pain caused by kidney problems

Other possible effects

Children who were administered emtricitabine, one of the components of Truvada, also experienced anaemia (low red blood cell count), commonly and changes in skin colour including darkening of the skin in patches, very commonly. If the production of red blood cells is reduced, a child may have symptoms of tiredness or breathlessness.

Reporting of side effects
If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Truvada

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the bottle and carton after {EXP}. The expiry date refers to the last day of that month.

Store in the original package in order to protect from moisture. Keep the bottle tightly closed.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Truvada contains

- **The active substances are** *emtricitabine* and *tenofovir disoproxil*. Each Truvada film-coated tablet contains 200 mg of emtricitabine and 245 mg of tenofovir disoproxil (equivalent to 300 mg of tenofovir disoproxil fumarate or 136 mg of tenofovir).

- **The other ingredients are** croscarmellose sodium, glycerol triacetate (E1518), hypromellose (E464), indigo carmine aluminium lake (E132), lactose monohydrate, magnesium stearate (E572), microcrystalline cellulose (E460), pregelatinised starch (gluten free) and titanium dioxide (E171).

What Truvada looks like and contents of the pack

Truvada film-coated tablets are blue, capsule-shaped tablets, engraved on one side with the word "GILEAD" and on the other side with the number "701". Truvada comes in bottles of 30 tablets. Each bottle contains a silica gel desiccant that must be kept in the bottle to help protect your tablets. The silica gel desiccant is contained in a separate sachet or canister and should not be swallowed.

The following pack sizes are available: outer cartons containing 1 bottle of 30 film-coated tablets and 90 (3 bottles of 30) film-coated tablets. Not all pack sizes may be marketed.

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Cambridge
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United Kingdom

Manufacturer:
Gilead Sciences Ireland UC
IDA Business & Technology Park
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For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

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Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu.