ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Atripla 600 mg/200 mg/245 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 600 mg of efavirenz, 200 mg of emtricitabine and 245 mg of tenofovir disoproxil (as fumarate).

Excipient(s):

Each film-coated tablet contains 1 mmol (23.6 mg) of sodium.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet.

Pink, capsule shaped, film-coated tablet, debossed with “123” on one side, plain on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Atripla is a fixed-dose combination of efavirenz, emtricitabine and tenofovir disoproxil fumarate. It is indicated for the treatment of human immunodeficiency virus-1 (HIV-1) infection in adults with virologic suppression to HIV-1 RNA levels of < 50 copies/ml on their current combination antiretroviral therapy for more than three months. Patients must not have experienced virological failure on any prior antiretroviral therapy and must be known not to have harboured virus strains with mutations conferring significant resistance to any of the three components contained in Atripla prior to initiation of their first antiretroviral treatment regimen (see sections 4.4 and 5.1).

The demonstration of the benefit of Atripla is primarily based on 48-week data from a clinical study in which patients with stable virologic suppression on a combination antiretroviral therapy changed to Atripla (see section 5.1). No data are currently available from clinical studies with Atripla in treatment-naïve or in heavily pretreated patients.

No data are available to support the combination of Atripla and other antiretroviral agents.

4.2 Posology and method of administration

Therapy should be initiated by a physician experienced in the management of human immunodeficiency virus (HIV) infection.

Posology
Adults: the recommended dose of Atripla is one tablet taken orally once daily.

Method of administration
It is recommended that Atripla be swallowed whole with water.

It is recommended that Atripla be taken on an empty stomach since food may increase efavirenz exposure and may lead to an increase in the frequency of adverse reactions (see sections 4.4 and 4.8).

In order to improve the tolerability to efavirenz with respect to undesirable effects on the nervous system, bedtime dosing is recommended (see section 4.8).

It is anticipated that tenofovir exposure will be approximately 35% lower following administration of Atripla on an empty stomach as compared to the individual component tenofovir disoproxil fumarate when taken with food (see section 5.2). In virologically suppressed patients, the clinical relevance of this reduction can be expected to be limited (see section 5.1). Further data on the clinical translation of the decrease in pharmacokinetic exposure is awaited.

Children and adolescents: Atripla is not recommended for use in children below 18 years of age due to lack of data on safety and efficacy.

Elderly: insufficient numbers of elderly patients have been evaluated in clinical studies of the components of Atripla to determine whether they respond differently than younger patients. Caution should be exercised when prescribing Atripla to the elderly, keeping in mind the greater frequency of decreased hepatic or renal function in these patients.

Dose adjustment: if Atripla is co-administered with rifampicin, an additional 200 mg/day (800 mg total) of efavirenz is recommended (see section 4.5).

Renal insufficiency: Atripla is not recommended for patients with moderate or severe renal impairment (creatinine clearance (CrCl) < 50 ml/min). Patients with moderate or severe renal impairment require dose interval adjustment of emtricitabine and tenofovir disoproxil fumarate that cannot be achieved with the combination tablet (see sections 4.4 and 5.2).

Hepatic impairment: the pharmacokinetics of Atripla have not been studied in patients with hepatic impairment. Patients with mild-to-moderate liver disease (Child-Pugh-Turcotte (CPT), Grade A or B) may be treated with the normal recommended dose of Atripla (see sections 4.3, 4.4 and 5.2). Patients should be monitored carefully for adverse reactions, especially nervous system symptoms related to efavirenz (see sections 4.3 and 4.4).

If Atripla 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).

It is important to take Atripla on a regular dosing schedule to avoid missing doses. Patients should be told that if they forget to take Atripla, they should take the missed dose right away, unless it is less than 12 hours until the next day's dose. In this case, patients should be told not to take the missed dose and to take their next dose at the usual time.

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

If therapy with Atripla is discontinued, consideration should be given to the long half-life of efavirenz (see section 5.2) and long intracellular half-lives of tenofovir and emtricitabine. Because of interpatient variability in these parameters and concerns regarding development of resistance, HIV treatment guidelines should be consulted, also taking into consideration the reason for discontinuation.

4.3 Contraindications

Hypersensitivity to the active substances or to any of the excipients.

Atripla must not be used in patients with severe hepatic impairment (CPT Grade C) (see section 5.2).

Atripla must not be administered concurrently with terfenadine, astemizole, cisapride, midazolam, triazolam, pimozide, bepridil, or ergot alkaloids (for example, ergotamine, dihydroergotamine,

ergonovine, and methylergonovine), because competition for cytochrome P450 (CYP) 3A4 by efavirenz could result in inhibition of metabolism and create the potential for serious and/or life-threatening undesirable effects (for example, cardiac arrhythmias, prolonged sedation or respiratory depression) (see section 4.5).

Herbal preparations containing St. John's wort (*Hypericum perforatum*) must not be used while taking Atripla due to the risk of decreased plasma concentrations and reduced clinical effects of efavirenz (see section 4.5).

Efavirenz significantly decreases voriconazole plasma concentrations while voriconazole also significantly increases efavirenz plasma concentrations. Since Atripla is a fixed-dose combination product, the dose of efavirenz cannot be altered; therefore, voriconazole and Atripla must not be co-administered (see section 4.5).

4.4 Special warnings and precautions for use

General: as a fixed combination, Atripla should not be administered concomitantly with other medicinal products containing any of the same active components, efavirenz, emtricitabine or tenofovir disoproxil fumarate. Due to similarities with emtricitabine, Atripla should not be administered concomitantly with other cytidine analogues, such as lamivudine (see section 4.5). Atripla should not be administered concomitantly with adefovir dipivoxil.

Currently available data indicate a trend that in patients on a PI-based antiretroviral regimen the switch to Atripla may lead to a reduction of the response to the therapy (see section 5.1). These patients should be carefully monitored for rises in viral load and, since the safety profile of efavirenz differs from that of protease inhibitors, for adverse reactions.

Lactic acidosis: lactic acidosis, usually associated with hepatic steatosis, has been reported with the use of nucleoside analogues. Early symptoms (symptomatic hyperlactataemia) include benign digestive symptoms (nausea, vomiting and abdominal pain), non-specific malaise, loss of appetite, weight loss, respiratory symptoms (rapid and/or deep breathing) or neurological symptoms (including motor weakness). Lactic acidosis has a high mortality and may be associated with pancreatitis, liver failure or renal failure. Lactic acidosis generally occurred after a few or several months of treatment.

Treatment with nucleoside analogues must be discontinued in the setting of symptomatic hyperlactataemia and metabolic/lactic acidosis, progressive hepatomegaly, or rapidly elevating aminotransferase levels.

Caution should be exercised when administering nucleoside analogues to any patient (particularly obese women) with hepatomegaly, hepatitis or other known risk factors for liver disease and hepatic steatosis (including certain medicinal products and alcohol). Co-infection with hepatitis C and treatment with alpha interferon and ribavirin may constitute a special risk.

Patients at increased risk must be followed closely.

Opportunistic infections: patients receiving Atripla 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: patients must be advised that antiretroviral therapies, including Atripla, have not been proven to prevent the risk of transmission of HIV to others through sexual contact or contamination with blood. Appropriate precautions must continue to be used.

Liver disease: the pharmacokinetics, safety and efficacy of Atripla have not been established in patients with significant underlying liver disorders (see section 5.2). Atripla is contraindicated in patients with severe hepatic impairment (see section 4.3). Since efavirenz is principally metabolised

by the cytochrome P450 (CYP450) system, caution should be exercised in administering Atripla to patients with mild-to-moderate liver disease. These patients should be carefully monitored for efavirenz adverse reactions, especially nervous system symptoms. Laboratory tests should be performed to evaluate their liver disease at periodic intervals (see section 4.2).

Patients with pre-existing liver dysfunction including chronic active hepatitis have an increased frequency of liver function abnormalities during combination antiretroviral therapy and should be monitored according to standard practice. If there is evidence of worsening liver disease or persistent elevations of serum transaminases to greater than 5 times the upper limit of the normal range, the benefit of continued therapy with Atripla needs to be weighed against the potential risks of significant liver toxicity. In such patients, interruption or discontinuation of treatment must be considered (see section 4.8).

In patients treated with other medicinal products associated with liver toxicity, monitoring of liver enzymes is also recommended.

Patients with HIV and hepatitis B (HBV) or C virus (HCV) co-infection: patients with chronic hepatitis B or C and treated with combination 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 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 Atripla have not been studied 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 an anti-HBV activity when used in antiretroviral combination therapy to control HIV infection. Discontinuation of Atripla 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 Atripla must be closely monitored with both clinical and laboratory follow-up for at least four months after stopping treatment with Atripla. If appropriate, resumption of anti-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.

Psychiatric symptoms: psychiatric adverse reactions have been reported in patients treated with efavirenz. Patients with a prior history of psychiatric disorders appear to be at greater risk of these serious psychiatric adverse reactions. In particular, severe depression was more common in those with a history of depression. There have also been post-marketing reports of severe depression, death by suicide, delusions and psychosis-like behaviour. Patients should be advised that if they experience symptoms such as severe depression, psychosis or suicidal ideation, they should contact their doctor immediately to assess the possibility that the symptoms may be related to the use of efavirenz, and if so, to determine whether the risk of continued therapy outweighs the benefits (see section 4.8).

Nervous system symptoms: symptoms including, but not limited to, dizziness, insomnia, somnolence, impaired concentration and abnormal dreaming are frequently reported undesirable effects in patients receiving efavirenz 600 mg daily in clinical studies. Dizziness was also seen in clinical studies with emtricitabine and tenofovir disoproxil fumarate. Headache has been reported in clinical studies with emtricitabine (see section 4.8). Nervous system symptoms associated with efavirenz usually begin during the first one or two days of therapy and generally resolve after the first two to four weeks. Patients should be informed that if they do occur, these common symptoms are likely to improve with continued therapy and are not predictive of subsequent onset of any of the less frequent psychiatric symptoms.

Seizures: convulsions have been observed in patients receiving efavirenz, generally in the presence of a known medical history of seizures. Patients who are receiving concomitant anticonvulsant medicinal products primarily metabolised by the liver, such as phenytoin, carbamazepine and phenobarbital, may require periodic monitoring of plasma levels. In a drug interaction study, carbamazepine plasma concentrations were decreased when carbamazepine was co-administered with efavirenz (see section 4.5). Caution must be taken in any patient with a history of seizures.

Renal impairment: Atripla is not recommended for patients with moderate or severe renal impairment. Patients with moderate or severe renal impairment require a dose adjustment of emtricitabine and tenofovir disoproxil fumarate that cannot be achieved with the combination tablet (see sections 4.2 and 5.2). Use of Atripla should be avoided with concurrent or recent use of a nephrotoxic medicinal product. If concomitant use of Atripla and nephrotoxic agents (e.g. aminoglycosides, amphotericin B, foscarnet, ganciclovir, pentamidine, vancomycin, cidofovir, interleukin-2) is unavoidable, renal function must be monitored weekly (see section 4.5).

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 Atripla and renal function (creatinine clearance and serum phosphate) is also monitored every four weeks during the first year and then every three months. In patients with a history of renal dysfunction or in patients who are at risk for renal dysfunction, consideration must be given to more frequent monitoring of renal function.

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 Atripla, renal function must be re-evaluated within one week, including measurements of blood glucose, blood potassium and urine glucose concentrations (see section 4.8, proximal tubulopathy). Since Atripla is a combination product and the dosing interval of the individual components cannot be altered, treatment with Atripla must be interrupted in patients with confirmed creatinine clearance < 50 ml/min or decreases in serum phosphate to < 1.0 mg/dl (0.32 mmol/l). Where discontinuation of therapy with one of the components of Atripla is indicated or where dose modification is necessary, separate preparations of efavirenz, emtricitabine and tenofovir disoproxil fumarate are available.

Skin reactions: mild-to-moderate rash has been reported with the individual components of Atripla. The rash associated with the efavirenz component usually resolves with continued therapy. Appropriate antihistamines and/or corticosteroids may improve tolerability and hasten the resolution of rash. Severe rash associated with blistering, moist desquamation or ulceration has been reported in less than 1% of patients treated with efavirenz (see section 4.8). The incidence of erythema multiforme or Stevens-Johnson syndrome was approximately 0.1%. Atripla must be discontinued in patients developing severe rash associated with blistering, desquamation, mucosal involvement or fever. Patients who discontinued treatment with other non-nucleoside reverse transcriptase inhibitors due to rash may be at higher risk of developing rash during treatment with Atripla.

Lipodystrophy and metabolic abnormalities: combination antiretroviral therapy has been associated with the redistribution of body fat (lipodystrophy) in HIV patients. The long-term consequences of these events are currently unknown. Knowledge about the mechanism is incomplete. A connection between visceral lipomatosis and protease inhibitors (PI) and lipoatrophy and nucleoside reverse transcriptase inhibitors (NRTIs) has been hypothesised. A higher risk of lipodystrophy has been associated with individual factors such as older age, and with drug-related factors such as longer duration of antiretroviral treatment and associated metabolic disturbances. Clinical examination should include evaluation for physical signs of fat redistribution. Consideration should be given to the measurement of fasting serum lipids and blood glucose. Lipid disorders should be managed as clinically appropriate (see section 4.8).

Effect of food: the administration of Atripla with food may increase efavirenz exposure (see section 5.2) and may lead to an increase in frequency of adverse reactions (see section 4.8). It is recommended that Atripla be taken on an empty stomach, preferably at bedtime.

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 events 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 combination antiretroviral therapy (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 pneumonia caused by *Pneumocystis jiroveci* (formerly known as *Pneumocystis carinii*). Any inflammatory symptoms should be evaluated and treatment instituted when necessary.

Osteonecrosis: although the etiology 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 combination antiretroviral therapy (CART). Patients should be advised to seek medical advice if they experience joint aches and pain, joint stiffness or difficulty in movement.

Bone: 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 the hip were significantly greater in this group until 96 weeks. However, there was no increased risk of fractures or evidence for clinically relevant bone abnormalities over 144 weeks.

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

Other antiretroviral agents: no data are available on the safety and efficacy of Atripla in combination with other antiretroviral agents.

Didanosine: co-administration of Atripla and didanosine is not recommended since exposure to didanosine is significantly increased following co-administration with tenofovir disoproxil fumarate (see section 4.5).

Patients with HIV-1 harbouring mutations: Atripla should be avoided in patients with HIV-1 harbouring the K65R, M184V/I or K103N mutation (see sections 4.1 and 5.1).

Excipients: this medicinal product contains 1 mmol (23.6 mg) of sodium per dose which should be taken into consideration by patients on a controlled sodium diet.

4.5 Interaction with other medicinal products and other forms of interaction

No drug interaction studies have been conducted using Atripla. As Atripla contains efavirenz, emtricitabine and tenofovir disoproxil fumarate, any interactions that have been identified with these agents individually may occur with Atripla. Interaction studies with these agents have only been performed in adults.

As a fixed combination, Atripla should not be administered concomitantly with other medicinal products containing any of the components, efavirenz, emtricitabine or tenofovir disoproxil as fumarate. Due to similarities with emtricitabine, Atripla should not be administered concomitantly with other cytidine analogues, such as lamivudine. Atripla should not be administered concomitantly with adefovir dipivoxil.

Efavirenz is an inducer of CYP3A4 and an inhibitor of some CYP450 isoenzymes including CYP3A4 (see section 5.2). Other compounds that are substrates of CYP3A4 may have decreased plasma concentrations when co-administered with efavirenz. Efavirenz exposure may also be altered when given with medicinal products or food (for example, grapefruit juice) which affect CYP3A4 activity. *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.

Contraindications of concomitant use
Atripla must not be administered concurrently with terfenadine, astemizole, cisapride, midazolam, triazolam, pimozide, bepridil, or ergot alkaloids (for example, ergotamine, dihydroergotamine, ergonovine, and methylergonovine), since inhibition of their metabolism may lead to serious, life-threatening events (see section 4.3).

Voriconazole: co-administration of standard doses of efavirenz and voriconazole is contraindicated. Since Atripla is a fixed-dose combination product, the dose of efavirenz cannot be altered; therefore, voriconazole and Atripla must not be co-administered (see section 4.3 and Table 1).

St. John's wort (Hypericum perforatum): co-administration of Atripla and St. John's wort or herbal preparations containing St. John's wort is contraindicated (see section 4.3).

Concomitant use not recommended
Atazanavir/ritonavir: insufficient data are available to make a dosing recommendation for atazanavir/ritonavir in combination with Atripla. Therefore co-administration of atazanavir/ritonavir and Atripla is not recommended (see Table 1).

Didanosine: co-administration of Atripla 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 Atripla 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 Atripla 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 Atripla and protease inhibitors, antiretroviral agents other than protease inhibitors and other non-antiretroviral medicinal products are listed in Table 1 below (increase is indicated as "↑", decrease as "↓", no change as "↔", twice daily as "b.i.d.", once daily as "q.d." and once every 8 hours as "q8h"). If available, 90% confidence intervals are shown in parentheses.

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

Medicinal product by therapeutic areas (dose in mg)	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 Atripla (efavirenz 600 mg, emtricitabine 200 mg, tenofovir disoproxil fumarate 300 mg)
ANTI-INFECTIVES		
Antiretrovirals		
Protease inhibitors		
Amprenavir/Efavirenz (1,200 b.i.d./600 q.d.)	Amprenavir: AUC: ~↓ 40% C_{max}: ~↓ 40% C_{min}: ~↓ 40% (CYP3A4 induction, the effect of efavirenz is compensated by the pharmacokinetic booster effect of ritonavir) For co-administration of efavirenz with low-dose ritonavir in combination with a protease inhibitor, see section on ritonavir below.	Co-administration of amprenavir/ritonavir and Atripla is not recommended.
Amprenavir/Emtricitabine	Interaction not studied.	
Amprenavir/Tenofovir disoproxil fumarate	Interaction not studied.	
Atazanavir/Ritonavir/Tenofovir disoproxil fumarate (300 q.d./100 q.d./300 q.d.)	Atazanavir: AUC: ↓ 25% (↓ 42 to ↓ 3) C_{max}: ↓ 28% (↓ 50 to ↑ 5) C_{min}: ↓ 26% (↓ 46 to ↑ 10) Co-administration of atazanavir/ritonavir with tenofovir resulted in increased exposure to tenofovir. Higher tenofovir concentrations could potentiate tenofovir-associated adverse events, including renal disorders.	Co-administration of atazanavir/ritonavir and Atripla is not recommended.
Atazanavir/Ritonavir/Efavirenz	Co-administration of efavirenz with atazanavir in combination with low-dose ritonavir resulted in substantial decreases in atazanavir exposure due to CYP3A4 induction, necessitating dosage adjustment of atazanavir (refer to the Summary of Product Characteristics for the medicinal product containing atazanavir). Co-administration of efavirenz and atazanavir in combination with ritonavir may lead to increases in efavirenz exposure which may worsen the tolerability profile of efavirenz.	
Atazanavir/Ritonavir/Emtricitabine	Interaction not studied.	

Indinavir/Efavirenz (800 q8h/200 q.d.) Indinavir/Efavirenz (1,000 q8h/600 q.d.)	Efavirenz: AUC: ↔ C_{max}: ↔ C_{min}: ↔ Indinavir: Morning AUC: ↓ 33%* (↓ 26 to ↓ 39) Afternoon AUC: ↓ 37%* (↓ 26 to ↓ 46) Evening AUC: ↓ 46%* (↓ 37 to ↓ 54) Morning C_{max}: ↔* Afternoon C_{max}: ↔* Evening C_{max}: ↓ 29%* (↓ 11 to ↓ 43) Morning C_{min}: ↓ 39%* (↓ 24 to ↓ 51) Afternoon C_{min}: ↓ 52%* (↓ 47 to ↓ 57) Evening C_{min}: ↓ 57%* (↓ 50 to ↓ 63) * when compared to indinavir 800 q8h alone (CYP3A4 induction) For co-administration of efavirenz with low-dose ritonavir in combination with a protease inhibitor, see section on ritonavir below.	Insufficient data are available to make a dosing recommendation for indinavir when dosed with Atripla. While the clinical significance of decreased indinavir concentrations has not been established, the magnitude of the observed pharmacokinetic interaction should be taken into consideration when choosing a regimen containing both efavirenz, a component of Atripla, and indinavir.
Indinavir/Emtricitabine (800 q8h/200 q.d.)	Indinavir: AUC: ↔ C_{max}: ↔ Emtricitabine: AUC: ↔ C_{max}: ↔	
Indinavir/Tenofovir disoproxil fumarate (800 q8h/300 q.d.)	Indinavir: AUC: ↔ C_{max}: ↔ Tenofovir: AUC: ↔ C_{max}: ↔	
Lopinavir/Ritonavir/Tenofovir disoproxil fumarate (400 b.i.d./100 b.i.d./300 q.d.)	Lopinavir/Ritonavir: AUC: ↔ C_{max}: ↔ C_{min}: ↔ Tenofovir: AUC: ↑ 32% (↑ 25 to ↑ 38) C_{max}: ↔ C_{min}: ↑ 51% (↑ 37 to ↑ 66) Higher tenofovir concentrations could potentiate tenofovir-associated adverse events, including renal disorders.	Insufficient data are available to make a dosing recommendation for lopinavir/ritonavir when dosed with Atripla. Co-administration of lopinavir/ritonavir and Atripla is not recommended.

Lopinavir/Ritonavir/Efavirenz	Co-administration of lopinavir/ritonavir with efavirenz resulted in a substantial decrease in lopinavir exposure, necessitating dosage adjustment of lopinavir/ritonavir. When used in combination with efavirenz and two NRTIs, 533/133 mg lopinavir/ritonavir (soft capsules) twice daily yielded similar lopinavir plasma concentrations as compared to lopinavir/ritonavir (soft capsules) 400/100 mg twice daily without efavirenz (historical data). Refer to the Summary of Product Characteristics for lopinavir/ritonavir tablets for pharmacokinetic data when this formulation was administered with efavirenz. For co-administration of efavirenz with low-dose ritonavir in combination with a protease inhibitor, see section on ritonavir below.	
Lopinavir/Ritonavir/Emtricitabine	Interaction not studied.	
Ritonavir/Efavirenz (500 b.i.d./600 q.d.)	Ritonavir: Morning AUC: ↑ 18% (↑ 6 to ↑ 33) Evening AUC: ↔ Morning C_{max}: ↑ 24% (↑ 12 to ↑ 38) Evening C_{max}: ↔ Morning C_{min}: ↑ 42% (↑ 9 to ↑ 86) Evening C_{min}: ↑ 24% (↑ 3 to ↑ 50) Efavirenz: AUC: ↑ 21% (↑ 10 to ↑ 34) C_{max}: ↑ 14% (↑ 4 to ↑ 26) C_{min}: ↑ 25% (↑ 7 to ↑ 46) (inhibition of CYP-mediated oxidative metabolism) When efavirenz was given with ritonavir 500 mg or 600 mg twice daily, the combination was not well tolerated (for example, dizziness, nausea, paraesthesia and elevated liver enzymes occurred). Sufficient data on the tolerability of efavirenz with low-dose ritonavir (100 mg, once or twice daily) are not available.	Co-administration of ritonavir at doses of 600 mg and Atripla is not recommended. When using Atripla in a regimen including low-dose ritonavir, the possibility of an increase in the incidence of efavirenz-associated adverse events should be considered, due to possible pharmacodynamic interaction.
Ritonavir/Emtricitabine (600 b.i.d./600 q.d.)	Interaction not studied.	
Ritonavir/Tenofovir disoproxil fumarate (600 b.i.d./600 q.d.)	Interaction not studied.	
Saquinavir/Efavirenz (1,200 soft capsule formulation q8h/600 q.d.)	Saquinavir: AUC: ↓ 62% (↓ 45 to ↓ 74) C_{max}: ↓ 50% (↓ 28 to ↓ 66) C_{min}: ↓ 56% (↓ 16 to ↓ 77) (decrease in saquinavir concentrations: CYP3A4 induction) Efavirenz: AUC: ↓ 12% (↓ 4 to ↓ 19) C_{max}: ↓ 13% (↓ 5 to ↓ 20) C_{min}: ↓ 14% (↓ 2 to ↓ 24)	Use of Atripla in combination with saquinavir as the sole protease inhibitor is not recommended.

Saquinavir/Tenofovir disoproxil fumarate (1,000 q.d./300 q.d.)	Saquinavir: AUC: ↔ C_{max}: ↔ Tenofovir: AUC: ↔ C_{max}: ↔ Co-administration of tenofovir disoproxil fumarate with ritonavir boosted saquinavir also resulted in no pharmacokinetic interaction.	
Saquinavir/Emtricitabine	Interaction not studied.	
Saquinavir/Ritonavir/Efavirenz	No data are available on the potential interactions of efavirenz with the combination of saquinavir and ritonavir. For co-administration of efavirenz with low-dose ritonavir in combination with a protease inhibitor, see section on ritonavir above.	Insufficient data are available to make a dosing recommendation for saquinavir/ritonavir when dosed with Atripla. Co-administration of saquinavir/ritonavir and Atripla is not recommended.
NRTIs and NNRTIs		
NRTIs/Efavirenz	Specific interaction studies have not been performed with efavirenz and NRTIs other than lamivudine (see section 4.4), zidovudine and tenofovir disoproxil fumarate. Clinically significant interactions would not be expected since the NRTIs are metabolised via a different route than efavirenz and would be unlikely to compete for the same metabolic enzymes and elimination pathways.	
NNRTIs/Efavirenz	Interaction not studied. The potential for pharmacokinetic or pharmacodynamic interactions is unknown.	Since use of two NNRTIs proved not beneficial in terms of efficacy and safety, co-administration of Atripla and another NNRTI is not recommended.
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 events. Rare cases of 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 virologic failure within several tested combinations.	Co-administration of Atripla and didanosine is not recommended (see section 4.4).
Didanosine/Efavirenz	Interaction not studied.	
Didanosine/Emtricitabine	Interaction not studied.	

Antibiotics		
Clarithromycin/Efavirenz (500 b.i.d./400 q.d.)	Clarithromycin: AUC: ↓ 39% (↓ 30 to ↓ 46) C_{max}: ↓ 26% (↓ 15 to ↓ 35) Clarithromycin 14-hydroxymetabolite: AUC: ↑ 34% (↑ 18 to ↑ 53) C_{max}: ↑ 49% (↑ 32 to ↑ 69) Efavirenz: AUC: ↔ C_{max}: ↑ 11% (↑ 3 to ↑ 19) (CYP3A4 induction) Rash developed in 46% of uninfected volunteers receiving efavirenz and clarithromycin.	The clinical significance of these changes in clarithromycin plasma levels is not known. Alternatives to clarithromycin (e.g. azithromycin) may be considered. Other macrolide antibiotics, such as erythromycin, have not been studied in combination with Atripla.
Clarithromycin/Emtricitabine	Interaction not studied.	
Clarithromycin/Tenofovir disoproxil fumarate	Interaction not studied.	
Antimycobacterials		
Rifabutin/Efavirenz (300 q.d./600 q.d.)	Rifabutin: AUC: ↓ 38% (↓ 28 to ↓ 47) C_{max}: ↓ 32% (↓ 15 to ↓ 46) C_{min}: ↓ 45% (↓ 31 to ↓ 56) Efavirenz: AUC: ↔ C_{max}: ↔ C_{min}: ↓ 12% (↓ 24 to ↑ 1) (CYP3A4 induction)	The daily dose of rifabutin should be increased by 50% when given with Atripla. Consider doubling the rifabutin dose in regimens where rifabutin is given 2 or 3 times a week in combination with Atripla.
Rifabutin/Emtricitabine	Interaction not studied.	
Rifabutin/Tenofovir disoproxil fumarate	Interaction not studied.	
Rifampicin/Efavirenz (600 q.d./600 q.d.)	Efavirenz: AUC: ↓ 26% (↓ 15 to ↓ 36) C_{max}: ↓ 20% (↓ 11 to ↓ 28) C_{min}: ↓ 32% (↓ 15 to ↓ 46) (CYP3A4 and CYP2B6 induction)	An additional 200 mg/day (800 mg total) of efavirenz is recommended when rifampicin is co-administered with Atripla. No dose adjustment of rifampicin is recommended when given with Atripla.
Rifampicin/Tenofovir disoproxil fumarate (600 q.d./300 q.d.)	Rifampicin: AUC: ↔ C_{max}: ↔ Tenofovir: AUC: ↔ C_{max}: ↔	
Rifampicin/Emtricitabine	Interaction not studied.	
Antifungals		
Itraconazole/Efavirenz (200 b.i.d./600 q.d.)	Itraconazole: AUC: ↓ 39% (↓ 21 to ↓ 53) C_{max}: ↓ 37% (↓ 20 to ↓ 51) C_{min}: ↓ 44% (↓ 27 to ↓ 58) (decrease in itraconazole concentrations: CYP3A4 induction) Hydroxyitraconazole: AUC: ↓ 37% (↓ 14 to ↓ 55) C_{max}: ↓ 35% (↓ 12 to ↓ 52) C_{min}: ↓ 43% (↓ 18 to ↓ 60) Efavirenz: AUC: ↔ C_{max}: ↔ C_{min}: ↔	No dose recommendations can be made for the use of Atripla in combination with itraconazole. An alternative antifungal treatment should be considered.
Itraconazole/Emtricitabine	Interaction not studied.	
Itraconazole/Tenofovir disoproxil fumarate	Interaction not studied.	

Voriconazole/Efavirenz (200 b.i.d./400 q.d.)	Voriconazole: AUC: ↓ 77% C_{max}: ↓ 61% Efavirenz: AUC: ↑ 44% C_{max}: ↑ 38% (competitive inhibition of oxidative metabolism) Co-administration of standard doses of efavirenz and voriconazole is contraindicated (see section 4.3).	Since Atripla is a fixed-dose combination product, the dose of efavirenz cannot be altered; therefore, voriconazole and Atripla must not be co-administered.
Voriconazole/Emtricitabine	Interaction not studied.	
Voriconazole/Tenofovir disoproxil fumarate	Interaction not studied.	
ANTICONVULSANTS		
Carbamazepine/Efavirenz (400 q.d./600 q.d.)	Carbamazepine: AUC: ↓ 27% (↓ 20 to ↓ 33) C_{max}: ↓ 20% (↓ 15 to ↓ 24) C_{min}: ↓ 35% (↓ 24 to ↓ 44) Efavirenz: AUC: ↓ 36% (↓ 32 to ↓ 40) C_{max}: ↓ 21% (↓ 15 to ↓ 26) C_{min}: ↓ 47% (↓ 41 to ↓ 53) (decrease in carbamazepine concentrations: CYP3A4 induction; decrease in efavirenz concentrations: CYP3A4 and CYP2B6 induction) Co-administration of higher doses of either efavirenz or carbamazepine has not been studied.	No dose recommendation can be made for the use of Atripla with carbamazepine. An alternative anticonvulsant should be considered. Carbamazepine plasma levels should be monitored periodically.
Carbamazepine/Emtricitabine	Interaction not studied.	
Carbamazepine/Tenofovir disoproxil fumarate	Interaction not studied.	
Phenytoin, Phenobarbital, and other anticonvulsants that are substrates of CYP450 isoenzymes	Interaction not studied with efavirenz, emtricitabine, or tenofovir disoproxil fumarate. There is a potential for reduction or increase in the plasma concentrations of phenytoin, phenobarbital and other anticonvulsants that are substrates of CYP450 isoenzymes with efavirenz.	When Atripla is co-administered with an anticonvulsant that is a substrate of CYP450 isoenzymes, periodic monitoring of anticonvulsant levels should be conducted.
Vigabatrin/Efavirenz Gabapentin/Efavirenz	Interaction not studied. Clinically significant interactions are not expected since vigabatrin and gabapentin are exclusively eliminated unchanged in the urine and are unlikely to compete for the same metabolic enzymes and elimination pathways as efavirenz.	Atripla and vigabatrin or gabapentin can be co-administered without dose adjustment.
Vigabatrin/Emtricitabine Gabapentin/Emtricitabine	Interaction not studied.	
Vigabatrin/Tenofovir disoproxil fumarate Gabapentin/Tenofovir disoproxil fumarate	Interaction not studied.	

ANTIDEPRESSANTS		
Selective Serotonin Reuptake Inhibitors (SSRIs)		
Sertraline/Efavirenz (50 q.d./600 q.d.)	Sertraline: AUC: ↓ 39% (↓ 27 to ↓ 50) C_{max}: ↓ 29% (↓ 15 to ↓ 40) C_{min}: ↓ 46% (↓ 31 to ↓ 58) Efavirenz: AUC: ↔ C_{max}: ↑ 11% (↑ 6 to ↑ 16) C_{min}: ↔ (CYP3A4 induction)	When co-administered with Atripla, sertraline dose increases should be guided by clinical response.
Sertraline/Emtricitabine	Interaction not studied.	
Sertraline/Tenofovir disoproxil fumarate	Interaction not studied.	
Paroxetine/Efavirenz (20 q.d./600 q.d.)	Paroxetine: AUC: ↔ C_{max}: ↔ C_{min}: ↔ Efavirenz: AUC: ↔ C_{max}: ↔ C_{min}: ↔	Atripla and paroxetine can be co-administered without dose adjustment.
Paroxetine/Emtricitabine	Interaction not studied.	
Paroxetine/Tenofovir disoproxil fumarate	Interaction not studied.	
Fluoxetine/Efavirenz	Interaction not studied. Since fluoxetine shares a similar metabolic profile with paroxetine, i.e. a strong CYP2D6 inhibitory effect, a similar lack of interaction would be expected for fluoxetine.	Atripla and fluoxetine can be co-administered without dose adjustment.
Fluoxetine/Emtricitabine	Interaction not studied.	
Fluoxetine/Tenofovir disoproxil fumarate	Interaction not studied.	
CARDIOVASCULAR AGENTS		
Calcium Channel Blockers		
Diltiazem/Efavirenz (240 q.d./600 q.d.)	Diltiazem: AUC: ↓ 69% (↓ 55 to ↓ 79) C_{max}: ↓ 60% (↓ 50 to ↓ 68) C_{min}: ↓ 63% (↓ 44 to ↓ 75) Desacetyl diltiazem: AUC: ↓ 75% (↓ 59 to ↓ 84) C_{max}: ↓ 64% (↓ 57 to ↓ 69) C_{min}: ↓ 62% (↓ 44 to ↓ 75) N-monodesmethyl diltiazem: AUC: ↓ 37% (↓ 17 to ↓ 52) C_{max}: ↓ 28% (↓ 7 to ↓ 44) C_{min}: ↓ 37% (↓ 17 to ↓ 52) Efavirenz: AUC: ↑ 11% (↑ 5 to ↑ 18) C_{max}: ↑ 16% (↑ 6 to ↑ 26) C_{min}: ↑ 13% (↑ 1 to ↑ 26) (CYP3A4 induction) The increase in efavirenz pharmacokinetic parameters is not considered clinically significant.	Dose adjustments of diltiazem when co-administered with Atripla should be guided by clinical response (refer to the Summary of Product Characteristics for diltiazem).
Diltiazem/Emtricitabine	Interaction not studied.	
Diltiazem/Tenofovir disoproxil fumarate	Interaction not studied.	

Verapamil, Felodipine, Nifedipine and Nicardipine	Interaction not studied with efavirenz, emtricitabine, or tenofovir disoproxil fumarate. When efavirenz is co-administered with a calcium channel blocker that is a substrate of the CYP3A4 enzyme, there is a potential for reduction in the plasma concentrations of the calcium channel blocker.	Dose adjustments of calcium channel blockers when co-administered with Atripla should be guided by clinical response (refer to the Summary of Product Characteristics for the calcium channel blocker).
LIPID LOWERING MEDICINAL PRODUCTS		
HMG Co-A Reductase Inhibitors		
Atorvastatin/Efavirenz (10 q.d./600 q.d.)	Atorvastatin: AUC: ↓ 43% (↓ 34 to ↓ 50) C_{max}: ↓ 12% (↓ 1 to ↓ 26) 2-hydroxy atorvastatin: AUC: ↓ 35% (↓ 13 to ↓ 40) C_{max}: ↓ 13% (↓ 0 to ↓ 23) 4-hydroxy atorvastatin: AUC: ↓ 4% (↓ 0 to ↓ 31) C_{max}: ↓ 47% (↓ 9 to ↓ 51) Total active HMG Co-A reductase inhibitors: AUC: ↓ 34% (↓ 21 to ↓ 41) C_{max}: ↓ 20% (↓ 2 to ↓ 26)	Cholesterol levels should be periodically monitored when atorvastatin, pravastatin, or simvastatin is co-administered with Atripla. Dosage adjustments of statins may be required (refer to the Summary of Product Characteristics for the statin).
Atorvastatin/Emtricitabine	Interaction not studied.	
Atorvastatin/Tenofovir disoproxil fumarate	Interaction not studied.	
Pravastatin/Efavirenz (40 q.d./600 q.d.)	Pravastatin: AUC: ↓ 40% (↓ 26 to ↓ 57) C_{max}: ↓ 18% (↓ 59 to ↑ 12)	
Pravastatin/Emtricitabine	Interaction not studied.	
Pravastatin/Tenofovir disoproxil fumarate	Interaction not studied.	
Simvastatin/Efavirenz (40 q.d./600 q.d.)	Simvastatin: AUC: ↓ 69% (↓ 62 to ↓ 73) C_{max}: ↓ 76% (↓ 63 to ↓ 79) Simvastatin acid: AUC: ↓ 58% (↓ 39 to ↓ 68) C_{max}: ↓ 51% (↓ 32 to ↓ 58) Total active HMG Co-A reductase inhibitors: AUC: ↓ 60% (↓ 52 to ↓ 68) C_{max}: ↓ 62% (↓ 55 to ↓ 78) Total HMG Co-A reductase inhibitors: AUC: ↓ 60% (↓ 54 to ↓ 74) C_{max}: ↓ 70% (↓ 58 to ↓ 85) (CYP3A4 induction) Co-administration of efavirenz with atorvastatin, pravastatin, or simvastatin did not affect efavirenz AUC or C_{max} values.	
Simvastatin/Emtricitabine	Interaction not studied.	
Simvastatin/Tenofovir disoproxil fumarate	Interaction not studied.	
HORMONAL CONTRACEPTIVES		
Ethinyloestradiol/Efavirenz (50 µg single dose/400 q.d.)	Ethinyloestradiol: AUC: ↑ 37% (↑ 25 to ↑ 51) C_{max}: ↔ Efavirenz: AUC: ↔ C_{max}: ↔ (mechanism unknown) The clinical significance of the effect on ethinyloestradiol AUC is not known.	Because the potential interaction of efavirenz, a component of Atripla, with oral contraceptives has not been fully characterised, a reliable method of barrier contraception must be used in addition to oral contraceptives

Ethinyloestradiol/Tenofovir disoproxil fumarate (-/300 q.d.)	Ethinyloestradiol: AUC: ↔ C_{max}: ↔ Tenofovir: AUC: ↔ C_{max}: ↔	(see section 4.6).
Norgestimate/Ethinyloestradiol/ Emtricitabine	Interaction not studied.	
IMMUNOSUPPRESSANTS		
Tacrolimus/Efavirenz	Interaction not studied. ↓ exposure of tacrolimus may be expected (CYP3A4 induction). Tacrolimus is not anticipated to impact exposure of efavirenz.	Dose adjustments of tacrolimus may be required. Close monitoring of tacrolimus concentrations for at least two weeks (until stable concentrations are reached) is recommended when starting or stopping treatment with Atripla.
Tacrolimus/Emtricitabine/Tenofovir disoproxil fumarate (0.1 mg/kg q.d./200 mg/300 mg q.d.)	Tacrolimus: AUC: ↔ C_{max}: ↔ C_{24}: ↔ Emtricitabine: AUC: ↔ C_{max}: ↔ C_{24}: ↔ Tenofovir disoproxil fumarate: AUC: ↔ C_{max}: ↔ C_{24}: ↔	
OPIOIDS		
Methadone/Efavirenz (35-100 q.d./600 q.d.)	Methadone: AUC: ↓ 52% (↓ 33 to ↓ 66) C_{max}: ↓ 45% (↓ 25 to ↓ 59) (CYP3A4 induction) In a study of HIV infected intravenous drug users, co-administration of efavirenz with methadone resulted in decreased plasma levels of methadone and signs of opiate withdrawal. The methadone dose was increased by a mean of 22% to alleviate withdrawal symptoms.	Patients receiving methadone and Atripla concomitantly should be monitored for signs of withdrawal and their methadone dose increased as required to alleviate withdrawal symptoms.
Methadone/Tenofovir disoproxil fumarate (40-110 q.d./300 q.d.)	Methadone: AUC: ↔ C_{max}: ↔ C_{min}: ↔ Tenofovir: AUC: ↔ C_{max}: ↔ C_{min}: ↔	
Methadone/Emtricitabine	Interaction not studied.	
HERBAL PRODUCTS		
St. John's wort (*Hypericum perforatum*)/Efavirenz	Plasma levels of efavirenz can be reduced by concomitant use of St. John's wort due to induction of drug metabolising enzymes and/or transport proteins by St. John's wort.	Co-administration of Atripla and St. John's wort is contraindicated. If a patient is already taking St. John's wort, stop St. John's wort, check viral levels and if possible
St. John's wort (*Hypericum perforatum*)/Emtricitabine	Interaction not studied.	

St. John's wort (*Hypericum perforatum*)/Tenofovir disoproxil fumarate	Interaction not studied.	efavirenz levels. Efavirenz levels may increase on stopping St. John's wort. The inducing effect of St. John's wort may persist for at least 2 weeks after cessation of treatment.

Studies conducted with other medicinal products: there were no clinically significant pharmacokinetic interactions when efavirenz was administered with azithromycin, cetirizine, lorazepam, nelfinavir, zidovudine, aluminium/magnesium hydroxide antacids, famotidine or fluconazole. The potential for interactions with efavirenz and other imidazole antifungals, such as ketoconazole, has not been studied.

There were no clinically significant pharmacokinetic interactions when emtricitabine was administered with stavudine, zidovudine or famciclovir. There were no clinically significant pharmacokinetic interactions when tenofovir disoproxil fumarate was co-administered with adefovir dipivoxil, emtricitabine, nelfinavir or ribavirin.

4.6 Pregnancy and lactation

Atripla should not be used during pregnancy unless clearly necessary (there are no other appropriate treatment options).

Women of child bearing potential: pregnancy should be avoided in women receiving Atripla. Barrier contraception should always be used in combination with other methods of contraception (for example, oral or other hormonal contraceptives) while on therapy with Atripla. Because of the long half-life of efavirenz, use of adequate contraceptive measures for 12 weeks after discontinuation of Atripla is recommended. Women of childbearing potential should undergo pregnancy testing before initiation of Atripla.

Pregnancy: there are no adequate or well-controlled studies of Atripla or its components in pregnant women. In post-marketing experience through an antiretroviral pregnancy registry, more than 200 pregnancies with first-trimester exposure to efavirenz as part of a combination antiretroviral regimen have been reported with no specific malformation pattern. Retrospectively in this registry, a small number of cases of neural tube defects, including meningomyelocele, have been reported but causality has not been established. Studies of efavirenz in animals have shown reproductive toxicity including marked teratogenic effects (see section 5.3).

Lactation: studies in rats have demonstrated that efavirenz and tenofovir are excreted in milk; concentrations of efavirenz were much higher than those in maternal plasma. It is not known whether efavirenz, emtricitabine or tenofovir are excreted in human milk. Because of the potential for both HIV transmission and the potential for serious undesirable effects in breast-feeding infants, mothers should be instructed not to breast-feed if they are receiving Atripla.

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, dizziness has been reported during treatment with efavirenz, emtricitabine and tenofovir disoproxil fumarate. Efavirenz may also cause impaired concentration and/or somnolence. Patients should be instructed that if they experience these symptoms they should avoid potentially hazardous tasks such as driving and operating machinery.

4.8 Undesirable effects

Assessment of adverse reactions for the fixed combination Atripla is based on experience from:

- a 48-week clinical study of Atripla (see Table 2)
- a clinical study in which efavirenz, emtricitabine and tenofovir disoproxil fumarate were co-administered (see Table 3)
- clinical study and post-marketing experience with the individual components of Atripla (see Table 4).

In Tables 2, 3 and 4 undesirable effects are presented in order of decreasing seriousness within each frequency grouping. Frequencies are defined as very common (≥ 1/10), common (≥ 1/100, < 1/10) or uncommon (≥ 1/1,000, < 1/100).

Adverse reactions from clinical study experience with Atripla
In a 48-week open-label randomised clinical study in HIV infected patients with successful virological suppression on their current antiretroviral regimen, patients either changed to Atripla (n=203) or continued on their original antiretroviral treatment regimen (n=97). Treatment-emergent adverse reactions considered possibly or probably related to study drugs reported in patients who received Atripla in study AI266073 are listed by body system organ class and frequency in Table 2.

Table 2: All treatment-emergent adverse reactions considered possibly or probably related to Atripla reported in study AI266073 (over 48 weeks)

	Atripla (n=203)
Metabolism and nutrition disorders:	
Common	anorexia
Uncommon	fat redistribution, hypertriglyceridaemia, weight decreased, increased appetite
Psychiatric disorders:	
Common	nightmare, depression, depressed mood, anxiety, insomnia, mood altered, abnormal dreams, sleep disorder
Uncommon	confusional state, disorientation, personality change, mood swings, libido decreased
Nervous system disorders:	
Very common	dizziness
Common	somnolence, headache
Uncommon	incoherent speech
Eye disorders:	
Uncommon	vision blurred, altered visual depth perception
Ear and labyrinth disorders:	
Uncommon	vertigo
Vascular disorders:	
Common	hot flush
Gastrointestinal disorders:	
Common	diarrhoea, nausea
Uncommon	pancreatitis acute, vomiting, paraesthesia oral, hypoaesthesia oral, flatulence, dry mouth
Hepatobiliary disorders:	
Uncommon	hepatitis acute
Skin and subcutaneous tissue disorders:	
Common	rash, night sweats
Uncommon	pruritus
Musculoskeletal and connective tissue disorders:	
Uncommon	myalgia

	Atripla (n=203)
Renal and urinary disorders:	
Common	blood creatinine increased
Reproductive system and breast disorders:	
Uncommon	breast enlargement
General disorders and administration site conditions:	
Common	fatigue, energy increased
Uncommon	feeling abnormal, feeling jittery, chills

Adverse reactions from clinical study experience with efavirenz + emtricitabine + tenofovir disoproxil fumarate
The following data are derived from a clinical study (GS-01-934) in which efavirenz, emtricitabine and tenofovir disoproxil fumarate were co-administered without regard to food as individual formulations or as a dual fixed combination of emtricitabine and tenofovir disoproxil fumarate with efavirenz.

Selected treatment-emergent adverse reactions considered possibly or probably related to study drugs from this study reported in patients after 144 weeks of treatment are listed by body system organ class and frequency in Table 3.

Table 3: Selected treatment-emergent adverse reactions considered possibly or probably related to study drugs (efavirenz, emtricitabine and tenofovir disoproxil fumarate) in clinical study GS-01-934 over 144 weeks

	Efavirenz+emtricitabine+tenofovir disoproxil fumarate (n=257)
Blood and lymphatic system disorders:	
Uncommon	neutropenia
Nervous system disorders:	
Very common	dizziness
Common	somnolence, stupor, lethargy, headache, disturbance of attention
Uncommon	amnesia, ataxia, balance disorder, dysgeusia
Eye disorders:	
Uncommon	vision blurred
Ear and labyrinth disorders:	
Common	vertigo
Respiratory, thoracic and mediastinal disorders:	
Uncommon	dyspnoea
Gastrointestinal disorders:	
Very common	nausea
Common	diarrhoea, vomiting, abdominal pain, flatulence, abdominal distension, dry mouth
Uncommon	dyspepsia
Skin and subcutaneous tissue disorders:	
Very common	rash
Common	pruritus, skin hyperpigmentation, dermatitis
Uncommon	urticaria, dry skin, eczema
Metabolism and nutrition disorders:	
Common	decreased appetite, increased appetite
Uncommon	hypertriglyceridaemia, anorexia
Vascular disorders:	
Common	hot flush

	Efavirenz+emtricitabine+tenofovir disoproxil fumarate (n=257)
General disorders and administration site conditions:	
Common	fatigue, fever
Uncommon	asthenia, feeling drunk
Psychiatric disorders:	
Very common	abnormal dreams
Common	nightmares, depression, insomnia, sleep disorder, euphoric mood
Uncommon	paranoia, psychomotor agitation, delusion, confusional state, anxiety, aggression, nervousness, disorientation

Laboratory test abnormalities: Liver enzymes: in a 144-week clinical study (GS-01-934), elevations of aspartate aminotransferase (AST > 5 times ULN (upper limit of normal)) and of alanine aminotransferase (ALT > 5 times ULN) were reported in 3% and 2% of patients treated with efavirenz, emtricitabine, and tenofovir disoproxil fumarate (n=257) and 3% and 3% of patients treated with efavirenz and fixed-dose zidovudine/lamivudine (n=254), respectively.

Adverse reactions associated with the individual components of Atripla
The adverse reactions from clinical study and post-marketing experience with the individual components of Atripla in antiretroviral combination therapy are listed in Table 4 below by body system organ class and frequency.

The most notable adverse reactions that have been reported in clinical studies with efavirenz are rash and nervous system symptoms. The administration of efavirenz with food may increase efavirenz exposure and may lead to an increase in the frequency of adverse reactions (see section 4.4). There have been post-marketing reports in association with tenofovir disoproxil fumarate of renal and urinary disorders including renal failure, proximal tubulopathy (including Fanconi syndrome), acute tubular necrosis and nephrogenic diabetes insipidus.

Table 4: Adverse reactions associated with the individual components of Atripla based on clinical study and post-marketing safety experience

	Efavirenz	Emtricitabine	Tenofovir disoproxil fumarate
Blood and lymphatic system disorders:			
Common		neutropenia	
Uncommon		anaemia	
Nervous system disorders:			
Very common		headache	dizziness
Common	somnolence, headache, disturbance in attention, dizziness	dizziness	
Uncommon	convulsions, amnesia, thinking abnormal, ataxia, coordination abnormal, agitation		
Not known*	cerebellar coordination and balance disturbances		
Eye disorders:			
Uncommon	vision blurred		
Ear and labyrinth disorders:			
Uncommon	vertigo		

	Efavirenz	Emtricitabine	Tenofovir disoproxil fumarate
Respiratory, thoracic and mediastinal disorders:			
Not known*			dyspnoea
Gastrointestinal disorders:			
Very common		diarrhoea, nausea	diarrhoea, vomiting, nausea
Common	diarrhoea, vomiting, abdominal pain, nausea	elevated amylase including elevated pancreatic amylase, elevated serum lipase, vomiting, abdominal pain, dyspepsia	flatulence
Uncommon	pancreatitis acute		
Not known*			pancreatitis
Renal and urinary disorders:			
Not known*			renal failure (acute and chronic), acute tubular necrosis, proximal renal tubulopathy including Fanconi syndrome, nephritis, acute interstitial nephritis, nephrogenic diabetes insipidus, increased creatinine, proteinuria
Skin and subcutaneous tissue disorders:			
Very common	rash (all grades, 18%)		
Common	pruritus	allergic reaction, vesiculobullous rash, pustular rash, maculopapular rash, rash, pruritus, urticaria, skin discolouration (increased pigmentation)	
Uncommon	Stevens-Johnson syndrome, erythema multiforme, severe rash (< 1%)		
Not known*	photoallergic dermatitis		rash
Musculoskeletal and connective tissue disorders:			
Very common		elevated creatine kinase	
Not known*			rhabdomyolysis, osteomalacia (manifested as bone pain and infrequently contributing to fractures), muscular weakness, myopathy
Metabolism and nutrition disorders:			
Very common			hypophosphataemia
Common		hyperglycaemia, hypertriglyceridaemia	
Not known*			lactic acidosis, hypokalaemia

	Efavirenz	Emtricitabine	Tenofovir disoproxil fumarate
General disorders and administration site conditions:			
Common	fatigue	pain, asthenia	
Not known*			asthenia
Immune system disorders:			
Uncommon	hypersensitivity		
Hepatobiliary disorders:			
Common		elevated serum aspartate aminotransferase (AST) and/or elevated serum alanine aminotransferase (ALT), hyperbilirubinaemia	
Uncommon	hepatitis acute		
Not known*	hepatic failure		hepatitis, increased transaminases, hepatic steatosis
Reproductive system and breast disorders:			
Uncommon	gynaecomastia		
Psychiatric disorders:			
Common	depression (severe in 1.6%), anxiety, abnormal dreams, insomnia	abnormal dreams, insomnia	
Uncommon	suicide attempt, suicide ideation, mania, paranoia, hallucination, euphoric mood, affect lability, confusional state, aggression		
Not known*	completed suicide, psychosis, delusion, neurosis		

* These adverse reactions have been identified through post-marketing safety surveillance and the frequency is not known.

The following adverse reactions, listed under the body system headings above, may occur as a consequence of proximal renal tubulopathy: rhabdomyolysis, osteomalacia (manifested as bone pain and infrequently contributing to fractures), hypokalaemia, muscular weakness, myopathy and hypophosphataemia. These events are not considered to be causally associated with tenofovir disoproxil fumarate therapy in the absence of proximal renal tubulopathy.

Rash with efavirenz: rashes are usually mild-to-moderate maculopapular skin eruptions that occur within the first two weeks of initiating therapy with efavirenz. In most patients rash resolves with continuing therapy with efavirenz within one month. In clinical studies, 1.7% of patients treated with efavirenz discontinued therapy because of rash. Efavirenz can be reinitiated in patients interrupting therapy because of rash. Use of appropriate antihistamines and/or corticosteroids is recommended when efavirenz is restarted.

Experience with efavirenz in patients who discontinued other antiretroviral agents of the non-nucleoside reverse transcriptase inhibitor (NNRTI) class is limited. Nineteen patients who discontinued nevirapine because of rash have been treated with efavirenz. Nine of these patients

developed mild-to-moderate rash while receiving therapy with efavirenz, and two discontinued because of rash.

Psychiatric symptoms with efavirenz: patients with a history of psychiatric disorders appear to be at greater risk of serious psychiatric adverse reactions listed in the efavirenz column of Table 4 with the frequency of events ranging from 0.3% for manic reactions to 2.0% for both severe depression and suicidal ideation.

Nervous system symptoms with efavirenz: in clinical controlled studies, nervous system symptoms of moderate-to-severe intensity were experienced by 19.4% of patients compared to 9.0% of patients receiving control regimens. These symptoms were severe in 2.0% of patients receiving efavirenz 600 mg daily and in 1.3% of patients receiving control regimens. In clinical studies 2.1% of patients treated with 600 mg of efavirenz discontinued therapy because of nervous system symptoms.

Nervous system symptoms usually begin during the first one or two days of therapy and generally resolve after the first two to four weeks. Nervous system symptoms may occur more frequently when efavirenz is taken concomitantly with meals possibly due to increased efavirenz plasma levels (see section 5.2). Dosing at bedtime seems to improve the tolerability of these symptoms (see section 4.2).

Analysis of long-term data from a clinical study (median follow-up 180 weeks, 102 weeks and 76 weeks for patients treated with efavirenz + zidovudine + lamivudine, efavirenz + indinavir, and indinavir + zidovudine + lamivudine, respectively) showed that, beyond 24 weeks of therapy, the incidences of new-onset nervous system symptoms among efavirenz-treated patients were generally similar to those in the control arm.

Lactic acidosis: lactic acidosis, usually associated with hepatic steatosis, has been reported with the use of nucleoside analogues (see section 4.4).

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 efavirenz, 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.

Amylase: in clinical studies, asymptomatic increases in serum amylase levels > 1.5 times the ULN were seen in 10% of patients treated with efavirenz and 6% of patients treated with control regimens. The clinical significance of asymptomatic increases in serum amylase is unknown.

Lipids, lipodystrophy and metabolic abnormalities: combination antiretroviral therapy has been associated with metabolic abnormalities such as hypertriglyceridaemia, hypercholesterolaemia, insulin-resistance, hyperglycaemia and hyperlactataemia (see section 4.4).

Combination antiretroviral therapy has been associated with redistribution of body fat (lipodystrophy) in HIV patients including the loss of peripheral and facial subcutaneous fat, increased intra-abdominal and visceral fat, breast hypertrophy and dorsocervical fat accumulation (buffalo hump) (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 (see section 4.4).

Cannabinoid test interaction: efavirenz does not bind to cannabinoid receptors. False positive urine cannabinoid test results have been reported in uninfected volunteers who received efavirenz. False positive test results have only been observed with the CEDIA DAU Multi-Level THC assay, which is

used for screening, and have not been observed with other cannabinoid assays tested including tests used for confirmation of positive results.

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

4.9 Overdose

Some patients accidentally taking 600 mg efavirenz twice daily have reported increased nervous system symptoms. One patient experienced involuntary muscle contractions.

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

Administration of activated charcoal may be used to aid removal of unabsorbed efavirenz. There is no specific antidote for overdose with efavirenz. Since efavirenz is highly protein bound, dialysis is unlikely to remove significant quantities of it from blood.

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: Antivirals for treatment of HIV infections, combinations,
ATC code: J05AR06

Mechanism of action: efavirenz is an NNRTI of HIV-1. Efavirenz non-competitively inhibits HIV-1 reverse transcriptase (RT) and does not significantly inhibit human immunodeficiency virus-2 (HIV-2) RT or cellular deoxyribonucleic acid (DNA) polymerases (α, β, γ, and δ). Emtricitabine is a nucleoside analogue of cytidine. Tenofovir disoproxil fumarate is converted *in vivo* to tenofovir, a nucleoside monophosphate (nucleotide) analogue of adenosine monophosphate.

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: efavirenz demonstrated antiviral activity against most non-clade B isolates (subtypes A, AE, AG, C, D, F, G, J, and N) but had reduced antiviral activity against group O viruses. Emtricitabine displayed antiviral activity against HIV-1 clades A, B, C, D, E, F, and G. Tenofovir displayed antiviral activity against HIV-1 clades A, B, C, D, E, F, G, and O. Both emtricitabine and tenofovir showed strain specific activity against HIV-2 and antiviral activity against HBV.

In combination studies evaluating the *in vitro* antiviral activity of efavirenz and emtricitabine together, efavirenz and tenofovir together, and emtricitabine and tenofovir together, additive to synergistic antiviral effects were observed.

Resistance: resistance to efavirenz can be selected *in vitro* and resulted in single or multiple amino acid substitutions in HIV-1 RT, including L100I, V108I, V179D, and Y181C. K103N was the most frequently observed RT substitution in viral isolates from patients who experienced rebound in viral load during clinical studies of efavirenz. Substitutions at RT positions 98, 100, 101, 108, 138, 188, 190 or 225 were also observed, but at lower frequencies, and often only in combination with K103N. Cross-resistance profiles for efavirenz, nevirapine and delavirdine *in vitro* demonstrated that the K103N substitution confers loss of susceptibility to all three NNRTIs.

The potential for cross-resistance between efavirenz and NRTIs is low because of the different binding sites on the target and mechanism of action. The potential for cross-resistance between efavirenz and PIs is low because of the different enzyme targets involved.

Resistance to emtricitabine or tenofovir has been seen *in vitro* and in some HIV-1 infected patients due to the development of an M184V or M184I substitution in RT with emtricitabine or a K65R substitution in RT with tenofovir. No other pathways of resistance to emtricitabine or tenofovir have been identified. 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. Both the K65R and M184V/I mutation remain fully susceptible to efavirenz.

Patients with HIV-1 expressing three or more thymidine analogue associated mutations (TAMs) that included either an M41L or an L210W substitution in RT showed reduced susceptibility to tenofovir disoproxil fumarate.

In vivo resistance (antiretroviral-naïve patients): extremely limited resistance data from patients treated with Atripla are currently available. However, in a 144-week open-label randomised clinical study (GS-01-934) in antiretroviral-naïve patients, where efavirenz, emtricitabine and tenofovir disoproxil fumarate were used as individual formulations (or as efavirenz and the fixed combination of emtricitabine and tenofovir disoproxil fumarate (Truvada) from week 96 to 144), genotyping was performed on plasma HIV-1 isolates from all patients with confirmed HIV RNA > 400 copies/ml at week 144 or early study drug discontinuation (see section on *Clinical experience*). As of week 144:

- The M184V/I mutation developed in 2/19 (10.5%) isolates analysed from patients in the efavirenz + emtricitabine + tenofovir disoproxil fumarate group and in 10/29 (34.5%) isolates analysed from the efavirenz + lamivudine/zidovudine 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 mutation.
- Genotypic resistance to efavirenz, predominantly the K103N mutation, developed in virus from 13/19 (68%) patients in the efavirenz + emtricitabine + tenofovir disoproxil fumarate group and in virus from 21/29 (72%) patients in the efavirenz + lamivudine/zidovudine group. A summary of resistance mutation development is shown in Table 5.

Table 5: Development of resistance in study GS-01-934 through week 144

	Efavirenz+ emtricitabine+ tenofovir disoproxil fumarate (N=244)		Efavirenz+lamivudine/ zidovudine (N=243)	
Resistance analysis by week 144	19		31	
On-therapy genotypes	19	(100%)	29	(100%)
Efavirenz resistance[1]	13	(68%)	21	(72%)
K103N	8	(42%)	18*	(62%)
K101E	3	(16%)	3	(10%)
G190A/S	2	(10.5%)	4	(14%)
Y188C/H	1	(5%)	2	(7%)
V108I	1	(5%)	1	(3%)
P225H	0		2	(7%)
M184V/I	2	(10.5%)	10*	(34.5%)
K65R	0		0	
TAMs[2]	0		2	(7%)

* p-value < 0.05, Fisher's Exact test comparing efavirenz + emtricitabine + tenofovir disoproxil fumarate group to efavirenz + lamivudine/zidovudine group among all patients.

[1] Other efavirenz resistance mutations included A98G (n=1), K103E (n=1), V179D (n=1), and M230L (n=1).

[2] Thymidine analogue associated mutations included D67N (n=1) and K70R (n=1).

Please refer to the Summary of Product Characteristics for the individual components for additional information regarding *in vivo* resistance with these medicinal products.

Clinical experience

In a 144-week open-label randomised clinical study (GS-01-934) antiretroviral treatment-naïve HIV-1 infected patients received either a once-daily regimen of efavirenz, emtricitabine and tenofovir disoproxil fumarate or a fixed combination of lamivudine and zidovudine (Combivir) administered twice daily and efavirenz once daily (please refer to the Summary of Product Characteristics for Truvada). Patients who completed 144 weeks of treatment with either treatment arm in study GS-01-934 were given the option to continue in an open-label extended phase of the study with Atripla on an empty stomach. Preliminary 24-week data are available from a total of 286 patients who changed to Atripla: 160 had previously received efavirenz, emtricitabine and tenofovir disoproxil fumarate, and 126 had previously received Combivir and efavirenz. The majority of patients from both initial treatment groups maintained virologic suppression after changing to Atripla. In 91% of the patients the HIV-1 RNA plasma concentrations remained < 50 copies/ml and in 97% < 400 copies/ml, after 24 weeks of Atripla treatment (intention to treat analysis (ITT), missing=failure).

Study AI266073 was a 48-week open-label randomised clinical study in HIV infected patients comparing the efficacy of Atripla to antiretroviral therapy consisting of at least two nucleoside or nucleotide reverse transcriptase inhibitors (NRTIs) with a protease inhibitor or non-nucleoside reverse transcriptase inhibitor; however not a regimen containing all Atripla components (efavirenz, emtricitabine and tenofovir disoproxil fumarate). Atripla was administered on an empty stomach (see section 4.2). Patients had never experienced virological failure on a previous antiretroviral therapy, had no known HIV-1 mutations that confer resistance to any of the three components within Atripla, and had been virologically suppressed for at least three months at baseline. Patients either changed to Atripla (N=203) or continued on their original antiretroviral treatment regimen (N=97). Forty-eight

week data showed that high levels of virologic suppression, comparable to the original treatment regimen, were maintained in patients who were randomised to change to Atripla (see Table 6).

Table 6: 48-week efficacy data from study AI266073 in which Atripla was administered to virologically suppressed patients on combination antiretroviral therapy

Endpoint	Treatment group		
	Atripla (N=203) n/N (%)	**Stayed on original treatment regimen (N=97) n/N (%)**	**Difference between Atripla and original treatment regimen (95%CI)**
	patients with HIV-1 RNA < 50 copies/ml		
PVR (KM)	94.5%	85.5%	8.9% (-7.7% to 25.6%)
M=Excluded	179/181 (98.9%)	85/87 (97.7%)	1.2% (-2.3% to 6.7%)
M=Failure	179/203 (88.2%)	85/97 (87.6%)	0.5% (-7.0% to 9.3%)
Modified LOCF	190/203 (93.6%)	94/97 (96.9%)	-3.3% (-8.3% to 2.7%)
	patients with HIV-1 RNA < 200 copies/ml		
PVR (KM)	98.4%	98.9%	-0.5% (-3.2% to 2.2%)
M=Excluded	181/181 (100%)	87/87 (100%)	0% (-2.4% to 4.2%)
M=Failure	181/203 (89.2%)	87/97 (89.7%)	-0.5% (-7.6% to 7.9%)

PVR (KM): Pure virologic response assessed using the Kaplan Meier (KM) method
M: Missing
Modified LOCF: Post-hoc analysis where patients who failed virologically or discontinued for adverse events were treated as failures; for other drop-outs, the LOCF (last observation carried forward) method was applied

When the two strata were analysed separately, response rates in the stratum with prior PI-treatment were numerically lower for patients switched to Atripla [92.4% versus 94.0% for the PVR (sensitivity analysis) for Atripla and SBR patients respectively; a difference (95%CI) of -1.6% (-10.0%, 6.7%)]. In the prior-NNRTI stratum, response rates were 98.9% vs 97.4% for Atripla and SBR patients respectively; a difference (95%CI) of 1.4% (-4.0%, 6.9%).

No data are currently available from clinical studies with Atripla in treatment-naïve patients or in heavily pretreated patients. There is no clinical experience with Atripla in patients who are experiencing virological failure in a first-line antiretroviral treatment regimen or in combination with other antiretroviral agents.

Patients coinfected with HIV and HBV: 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).

5.2 Pharmacokinetic properties

The separate pharmaceutical forms of efavirenz, emtricitabine and tenofovir disoproxil fumarate were used to determine the pharmacokinetics of efavirenz, emtricitabine and tenofovir disoproxil fumarate, administered separately in HIV infected patients. The bioequivalence of one Atripla film-coated tablet with one efavirenz 600 mg film-coated tablet plus one emtricitabine 200 mg hard capsule plus one tenofovir disoproxil 245 mg film-coated tablet (equivalent to 300 mg tenofovir disoproxil fumarate) administered together, was established following single dose administration to fasting healthy subjects in study GS-US-177-0105 (see Table 7).

Table 7: Summary of pharmacokinetic data from study GS-US-177-0105

Parameters	Efavirenz (n=45)			Emtricitabine (n=45)			Tenofovir disoproxil fumarate (n=45)		
	Test	Reference	GMR (%) (90%CI)	Test	Reference	GMR (%) (90%CI)	Test	Reference	GMR (%) (90%CI)
C_{max} (ng/ml)	2,264.3 (26.8)	2,308.6 (30.3)	98.79 (92.28, 105.76)	2,130.6 (25.3)	2,384.4 (20.4)	88.84 (84.02, 93.94)	325.1 (34.2)	352.9 (29.6)	91.46 (84.64, 98.83)
$AUC_{0\text{-last}}$ (ng·h/ml)	125,623.6 (25.7)	132,795.7 (27.0)	95.84 (90.73, 101.23)	10,682.6 (18.1)	10,874.4 (14.9)	97.98 (94.90, 101.16)	1,948.8 (32.9)	1,969.0 (32.8)	99.29 (91.02, 108.32)
AUC_{inf} (ng·h/ml)	146,074.9 (33.1)	155,518.6 (34.6)	95.87 (89.63, 102.55)	10,854.9 (17.9)	11,054.3 (14.9)	97.96 (94.86, 101.16)	2,314.0 (29.2)	2,319.4 (30.3)	100.45 (93.22, 108.23)
$T_{1/2}$ (h)	180.6 (45.3)	182.5 (38.3)		14.5 (53.8)	14.6 (47.8)		18.9 (20.8)	17.8 (22.6)	

Test: single fixed-dose combination tablet taken under fasted conditions.
Reference: single dose of a 600 mg efavirenz tablet, 200 mg emtricitabine capsule and 300 mg tenofovir disoproxil fumarate tablet taken under fasted conditions.
Values for Test and Reference are mean (% coefficient of variation).
GMR=geometric least-squares mean ratio, CI=confidence interval

Absorption: in HIV infected patients, peak efavirenz plasma concentrations were attained by 5 hours and steady-state concentrations reached in 6 to 7 days. In 35 patients receiving efavirenz 600 mg once daily, steady-state peak concentration (C_{max}) was 12.9 ± 3.7 µM (29%) [mean ± standard deviation (S.D.) (coefficient of variation (%CV))], steady-state C_{min} was 5.6 ± 3.2 µM (57%), and AUC was 184 ± 73 µM•h (40%).

Emtricitabine is rapidly absorbed with peak plasma concentrations occurring at 1 to 2 hours post-dose. Following multiple dose oral administration of emtricitabine to 20 HIV infected patients, steady-state C_{max} was 1.8 ± 0.7 µg/ml (mean ± S.D.) (39%CV), steady-state C_{min} was 0.09 ± 0.07 µg/ml (80%) and the AUC was 10.0 ± 3.1 µg•h/ml (31%) over a 24 hour dosing interval.

Following oral administration of a single 300 mg dose of tenofovir disoproxil fumarate to HIV-1 infected patients in the fasted state, maximum tenofovir concentrations were achieved within one hour and the C_{max} and AUC (mean ± S.D.) (%CV) values were 296 ± 90 ng/ml (30%) and 2,287 ± 685 ng•h/ml (30%), respectively. The oral bioavailability of tenofovir from tenofovir disoproxil fumarate in fasted patients was approximately 25%.

Effect of food: Atripla has not been evaluated in the presence of food.

Administration of efavirenz capsules with a high fat meal increased the mean AUC and C_{max} of efavirenz by 28% and 79%, respectively, compared to administration in a fasted state. Compared to fasted administration, dosing of tenofovir disoproxil fumarate and emtricitabine in combination with either a high fat meal or a light meal increased the mean AUC and C_{max} of tenofovir by 35% and 15%, respectively without affecting emtricitabine exposures.

Atripla is recommended for administration on an empty stomach since food may increase efavirenz exposure and may lead to an increase in the frequency of adverse reactions (see sections 4.4 and 4.8). It is anticipated that tenofovir exposure will be approximately 35% lower following administration of Atripla on an empty stomach as compared to the individual component tenofovir disoproxil fumarate when taken with food. Forty-eight week data from a clinical study (AI266073) showed maintenance of virologic suppression for patients who had stable virologic suppression on combination

antiretroviral therapy and subsequently changed to Atripla with a recommendation for administration of Atripla on an empty stomach.

Distribution: efavirenz is highly bound (> 99%) to human plasma proteins, predominantly albumin.

In vitro binding of emtricitabine to human plasma proteins is < 4% and independent of concentrations over the range of 0.02 to 200 µg/ml. Following intravenous administration the volume of distribution of emtricitabine was approximately 1.4 l/kg. After oral administration, emtricitabine is widely distributed throughout the body. The mean plasma to blood concentration ratio was approximately 1.0 and the mean semen to plasma concentration ratio was approximately 4.0.

In vitro binding of tenofovir to human plasma or serum protein is < 0.7% and 7.2%, respectively over the tenofovir concentration range 0.01 to 25 µg/ml. Following intravenous administration the volume of distribution of tenofovir was approximately 800 ml/kg. After oral administration, tenofovir is widely distributed throughout the body.

Biotransformation: studies in humans and *in vitro* studies using human liver microsomes have demonstrated that efavirenz is principally metabolised by the cytochrome P450 system to hydroxylated metabolites with subsequent glucuronidation of these hydroxylated metabolites. These metabolites are essentially inactive against HIV-1. The *in vitro* studies suggest that CYP3A4 and CYP2B6 are the major isoenzymes responsible for efavirenz metabolism and that it inhibits P450 isoenzymes 2C9, 2C19, and 3A4. In *in vitro* studies efavirenz did not inhibit CYP2E1 and inhibited CYP2D6 and CYP1A2 only at concentrations well above those achieved clinically.

Efavirenz plasma exposure may be increased in patients with homozygous G516T genetic variant of the CYP2B6 isoenzyme. The clinical implications of such an association are unknown; however, the potential for an increased frequency and severity of efavirenz-associated adverse events cannot be excluded.

Efavirenz has been shown to induce P450 enzymes, resulting in the induction of its own metabolism. In uninfected volunteers, multiple doses of 200 to 400 mg per day for 10 days resulted in a lower than predicted extent of accumulation (22 to 42% lower) and a shorter terminal half-life of 40 to 55 hours (single dose half-life 52 to 76 hours).

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: efavirenz has a relatively long terminal half-life of at least 52 hours after single doses (see also data from bioequivalence study described above) and 40 to 55 hours after multiple doses. Approximately 14 to 34% of a radiolabelled dose of efavirenz was recovered in the urine and less than 1% of the dose was excreted in urine as unchanged efavirenz.

Following oral administration, the elimination half-life of emtricitabine is approximately 10 hours. 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 tenofovir is approximately 12 to 18 hours. Tenofovir is primarily excreted by the kidney by both filtration and an active tubular transport system with approximately 70 to 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.

Age, gender and ethnicity: the pharmacokinetics of emtricitabine and tenofovir are similar in male and female patients. Although limited data suggest that females as well as Asian and Pacific Island patients may have higher exposure to efavirenz, they do not appear to be less tolerant of efavirenz.

Pharmacokinetic studies have not been performed with efavirenz, emtricitabine or tenofovir in the elderly (over 65 years).

Pharmacokinetic studies with Atripla have not been performed in infants and children (see section 4.2).

Renal impairment: the pharmacokinetics of efavirenz, emtricitabine and tenofovir disoproxil fumarate after co-administration of the separate pharmaceutical forms or as Atripla have not been studied in HIV infected patients with renal impairment.

Pharmacokinetic parameters were determined following administration of single doses of the individual preparations 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 (normal renal function when creatinine clearance > 80 ml/min; mild impairment with creatinine clearance=50 to 79 ml/min; moderate impairment with creatinine clearance=30 to 49 ml/min and severe impairment with creatinine clearance=10 to 29 ml/min).

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

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

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

The pharmacokinetics of efavirenz have not been studied in patients with renal impairment. However, less than 1% of an efavirenz dose is excreted unchanged in the urine, so the impact of renal impairment on exposure to efavirenz is likely to be minimal.

Atripla is not recommended for patients with moderate or severe renal impairment (creatinine clearance < 50 ml/min). Patients with moderate or severe renal impairment require dose interval adjustment of emtricitabine and tenofovir disoproxil fumarate that cannot be achieved with the combination tablet (see sections 4.2 and 4.4).

Hepatic impairment: the pharmacokinetics of Atripla have not been studied in HIV infected patients with hepatic impairment. Atripla should be administered with caution to patients with mild-to-moderate liver disease (see sections 4.3 and 4.4).

Atripla must not be used in patients with severe hepatic impairment (see section 4.3).

In the single patient studied with severe hepatic impairment (CPT, Grade C), half-life of efavirenz was doubled indicating a potential for a much greater degree of accumulation.

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

A single 300 mg dose of tenofovir disoproxil fumarate was administered to non-HIV infected patients with varying degrees of hepatic impairment defined according to CPT classification. Tenofovir pharmacokinetics were not substantially altered in subjects with hepatic impairment suggesting that no dose adjustment of tenofovir disoproxil fumarate is required in these subjects.

5.3 Preclinical safety data

Malformations were observed in 3 of 20 foetuses/newborns from efavirenz-treated cynomolgus monkeys given doses resulting in plasma efavirenz concentrations similar to those seen in humans. Anencephaly and unilateral anophthalmia with secondary enlargement of the tongue were observed in one foetus, micro-ophthalmia was observed in another foetus, and cleft palate was observed in a third foetus. Efavirenz induced foetal resorptions in rats. No malformations were observed in foetuses from efavirenz-treated rats and rabbits.

Conventional reproductive/developmental toxicity studies with emtricitabine and tenofovir disoproxil fumarate revealed no special hazard for humans.

Carcinogenicity studies using efavirenz showed an increased incidence of hepatic and pulmonary tumours in female mice, but not in male mice. The mechanism of tumour formation and the potential relevance for humans are not known. Carcinogenicity studies using efavirenz in male mice and in male and female rats were negative. While the carcinogenic potential in humans is unknown, these data suggest that the clinical benefit of efavirenz outweighs the potential carcinogenic risk to humans.

Tenofovir disoproxil fumarate did not show any carcinogenic potential in a long-term oral carcinogenicity study in rats. A long-term oral carcinogenicity study in mice showed a low incidence of duodenal tumours, considered likely related to high local concentrations in the gastrointestinal tract at a dose of 600 mg/kg/day. While the mechanism of tumour formation is uncertain, the findings are unlikely to be of relevance to humans.

Emtricitabine did not show any carcinogenic potential in long-term studies in rats and mice.

Efavirenz and emtricitabine were negative in conventional genotoxic assays. Tenofovir disoproxil fumarate was positive in two out of three *in vitro* genotoxicity studies but negative in the *in vivo* micronucleus assay. The combination of emtricitabine and tenofovir disoproxil fumarate was positive in the *in vitro* mouse lymphoma assay, with comparable results to those obtained for tenofovir disoproxil fumarate alone. The combination of emtricitabine and tenofovir disoproxil fumarate was negative in the bacterial reverse mutation assay (Ames assay).

Biliary hyperplasia was observed in cynomolgus monkeys given efavirenz for ≥ 1 year at a dose resulting in mean AUC values approximately 2-fold greater than those in humans given the recommended dose. The biliary hyperplasia regressed upon cessation of dosing. Biliary fibrosis has been observed in rats. Non-sustained convulsions were observed in some monkeys receiving efavirenz for ≥ 1 year, at doses yielding plasma AUC values 4- to 13-fold greater than those in humans given the recommended dose (see sections 4.4 and 4.8).

Preclinical studies of tenofovir disoproxil fumarate conducted in rats, dogs and monkeys revealed effects on bone and a decrease in serum phosphate concentration. Bone toxicity was diagnosed as osteomalacia (monkeys) and reduced bone mineral density (rats and dogs). 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 bone mineral density. The mechanisms of these toxicities are not completely understood.

A one month dog study using the combination of emtricitabine and tenofovir disoproxil fumarate found no exacerbation of toxicological effects compared to the separate components.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:
Croscarmellose sodium
Hydroxypropylcellulose
Magnesium stearate
Microcrystalline cellulose
Sodium laurilsulfate

Film-coating:
Iron oxide black
Iron oxide red
Macrogol 3350
Poly(vinyl alcohol)
Talc
Titanium dioxide

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 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 silica gel desiccant.

The following pack sizes are available: outer cartons containing 1 x 30 film-coated tablet and 3 x 30 film-coated tablet bottles. Not all pack sizes may be marketed.

6.6 Special precautions for disposal

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

7. MARKETING AUTHORISATION HOLDER

Bristol-Myers Squibb and Gilead Sciences Limited
IDA Business & Technology Park
Carrigtohill
Co. Cork
Ireland

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/07/430/001
EU/1/07/430/002

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

13 December 2007

10. DATE OF REVISION OF THE TEXT

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

ANNEX II

A. MANUFACTURING AUTHORISATION HOLDERS RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OF THE MARKETING AUTHORISATION

A. MANUFACTURING AUTHORISATION HOLDERS RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturers responsible for batch release

Gilead Sciences Limited
Unit 13 Stillorgan Industrial Park
Blackrock
Co. Dublin
Ireland

Gilead Sciences Limited
IDA Business & Technology Park
Carrigtohill Co. Cork
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, section 4.2).

- **CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT**

The MAH shall ensure that additional risk minimisation activities to address the renal safety concerns related to tenofovir disoproxil fumarate, one of the active substances contained in Atripla, are being implemented for this fixed combination like for all medicinal products containing tenofovir disoproxil fumarate.

- **OTHER CONDITIONS**

Pharmacovigilance system

The MAH must ensure that the system of pharmacovigilance, as described in version 2.0 (28/02/2008) and included in the Type II variation (EMEA/H/C/000797/II/0003) is in place and functioning before and whilst the product is on the market.

Risk Management Plan

The MAH commits to performing the studies and additional pharmacovigilance activities detailed in the Pharmacovigilance Plan, as agreed in version 3 (February 2008) of the Risk Management Plan (RMP) presented with the first PSUR and any subsequent updates of the RMP agreed by the CHMP.

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

In addition, an updated RMP should be submitted

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

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

Atripla 600 mg/200 mg/245 mg film-coated tablets
efavirenz, emtricitabine and tenofovir disoproxil

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 600 mg of efavirenz, 200 mg of emtricitabine and 245 mg of tenofovir disoproxil (as fumarate).

3. LIST OF EXCIPIENTS

Contains sodium. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

30 film-coated tablets
3 x 30 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.

Oral 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

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

Bristol-Myers Squibb and Gilead Sciences Limited
IDA Business & Technology Park
Carrigtohill
Co. Cork
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/07/430/001 30 film-coated tablets
EU/1/07/430/002 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

Atripla
[outer packaging only]

B. PACKAGE LEAFLET

PACKAGE LEAFLET: INFORMATION FOR THE USER

Atripla 600 mg/200 mg/245 mg film-coated tablets
efavirenz, emtricitabine and tenofovir disoproxil

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 any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects get serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:

1. WHAT ATRIPLA IS AND WHAT IT IS USED FOR

Atripla contains three active substances that are used to treat human immunodeficiency virus (HIV) infection:

- Efavirenz is a non-nucleoside reverse transcriptase inhibitor (NNRTI)
- Emtricitabine is a nucleoside reverse transcriptase inhibitor (NRTI)
- Tenofovir is a nucleotide reverse transcriptase inhibitor (NtRTI)

Each of these active substances, also known as antiretroviral medicines, work by interfering with an enzyme (reverse transcriptase) that is essential for the virus to multiply.

Atripla is a treatment for Human Immunodeficiency Virus (HIV) infection in adults aged 18 and over who have previously been treated with other antiretroviral medicines and have their HIV-1 infection under control for at least three months. Patients must not have experienced failure of a previous HIV therapy.

2. BEFORE YOU TAKE ATRIPLA

Do not take Atripla

- **if you are allergic** (hypersensitive) to efavirenz, emtricitabine, tenofovir, tenofovir disoproxil fumarate, or any of the other ingredients of Atripla listed at the end of this leaflet.

- **if you have severe liver disease.**

- **if you are currently taking** any of the following medicines:
  - **astemizole or terfenadine** (used to treat hay fever or other allergies)
  - **bepridil** (used to treat heart disease)
  - **cisapride** (used to treat heartburn)
  - **ergot alkaloids** (for example, ergotamine, dihydroergotamine, ergonovine, and methylergonovine) (used to treat migraines and cluster headaches)
  - **midazolam or triazolam** (used to help you sleep)
  - **pimozide** (used to treat certain mental conditions)

- **St. John's wort** (*Hypericum perforatum*) (a herbal remedy used for depression and anxiety)
- **voriconazole** (used to treat fungal infections)

If you are taking any of these medicines, tell your doctor immediately. Taking these medicines with Atripla could cause serious or life-threatening side effects or stop these medicines from working properly.

Take special care with Atripla

- **Women should not get pregnant during treatment with Atripla and for 12 weeks thereafter (see *Pregnancy and breast-feeding*).**

- **Do not give Atripla to children** and adolescents under 18 years of age. The use of Atripla in children and adolescents has not yet been studied.

- **You can still pass on HIV** when taking this medicine, so it is important to take precautions to avoid infecting other people through sexual contact or blood transfer. This medicine is not a cure for HIV infection. While taking Atripla you may still develop infections or other illnesses associated with HIV infection.

- You must remain under the care of your doctor while taking Atripla.

- **Tell your doctor:**

  - **if you are taking other medicines** that contain efavirenz, emtricitabine, tenofovir disoproxil, lamivudine or adefovir dipivoxil. Atripla should not be taken with any of these medicines.

  - **if you have or have had kidney disease,** or if tests have shown problems with your kidneys. Atripla is not recommended if you have moderate to severe kidney disease.

    Atripla 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.

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

  - **if you have a history of mental illness,** including depression, or of substance or alcohol abuse. Tell your doctor immediately if you feel depressed, have suicidal thoughts or have strange thoughts (see Section 4, *Possible side effects*).

  - **if you have a history of convulsions (fits or seizures)** or if you are being treated with anticonvulsant therapy such as carbamazepine, phenobarbital and phenytoin. If you are taking any of these medicines, your doctor may need to check the level of anticonvulsant medicine in your blood to ensure that it is not affected while taking Atripla. Your doctor may give you a different anticonvulsant.

  - **if you have a history of liver disease, including chronic active hepatitis.** Patients with liver disease including chronic hepatitis B or C, who are treated with combination antiretrovirals, have a higher risk of severe and potentially life-threatening liver problems. Your doctor may conduct blood tests in order to check how well your liver is working. **If you have severe liver disease, do not take Atripla** (see earlier in Section 2, *Do not take Atripla).*

If you have hepatitis B infection, symptoms may become worse after discontinuation of Atripla. Your doctor may then conduct blood tests at regular intervals in order to check how well your liver is working (see Section 3, *If you stop taking Atripla).*

- **if you are diabetic, overweight or have high cholesterol.** Combination antiretroviral therapies (including Atripla) may raise blood sugar levels, increase blood fats (hyperlipaemia), cause changes to body fat, and resistance to insulin (see Section 4, *Possible side effects*).

- **if you are over 65.** Insufficient numbers of patients over 65 years of age have been studied. If you are over 65 years of age and are prescribed Atripla, your doctor will monitor you carefully.

- **Once you start taking Atripla, look out for:**

  - **possible signs of lactic acidosis.** Some HIV medicines, including Atripla, that contain nucleoside analogues can cause lactic acidosis (excess of lactic acid in your blood), together with an enlarged liver. **Deep, rapid breathing, drowsiness,** and symptoms such as **feeling sick** (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, and people with liver disease. While you are being treated with Atripla, your doctor will monitor you closely for any signs that you may be developing lactic acidosis. If you notice any symptoms of lactic acidosis, please tell your doctor immediately.

  - **signs of dizziness, difficulty sleeping, drowsiness, difficulty concentrating or abnormal dreaming.** These side effects may start in the first 1 or 2 days of treatment and usually go away after the first 2 to 4 weeks.

  - **any signs of skin rash.** Rashes may be caused by Atripla. If you see any signs of a severe rash with blistering or fever, stop taking Atripla and tell your doctor at once. If you had a rash while taking another NNRTI, you may be at higher risk of getting a rash with Atripla.

  - **any signs of inflammation or infection.** In some patients with advanced HIV infection (AIDS) and a history of opportunistic infection, signs and symptoms of inflammation from previous infections may occur soon after anti-HIV treatment is started. It is believed that these symptoms are due to improvement in the body's immune response, enabling the body to fight infections that may have been present with no obvious symptoms. If you notice any symptoms of infection, please tell your doctor at once.

  - **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 please inform your doctor.

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

Taking other medicines

You must not take Atripla with certain medicines. These are listed under *Do not take Atripla,* at the start of Section 2. They include some common medicines and some herbal remedies (including St. John's wort) which can cause serious interactions.

Tell your doctor or pharmacist if you are taking or have recently taken any other medicines. This includes non-prescription medicines and herbal remedies.

Also, Atripla should not be taken with any other medicines that contain efavirenz, emtricitabine, tenofovir disoproxil, lamivudine or adefovir dipivoxil.

Tell your doctor if you are taking other medicines which may damage your kidneys. Some examples include:
- aminoglycosides, vancomycin (medicines for bacterial infections)
- foscarnet, ganciclovir, cidofovir (medicines for viral infections)
- amphotericin B, pentamidine (medicines for fungal infections)
- interleukin-2 (to treat cancer)

Atripla may interact with other medicines. As a result, the amounts of Atripla or other medicines in your blood may be affected. This may stop your medicines from working properly, or may make any side effects worse. In some cases, your doctor may need to adjust your dose or check your blood levels. **It is important to tell your doctor if you are taking any of the following:**

- **Medicines containing didanosine (for HIV infection):** taking Atripla with other antiviral medicines that contain didanosine can raise the levels of didanosine in your blood and may reduce CD4 cell counts. Inflammation of the pancreas and lactic acidosis (excess lactic acid in the blood), which sometimes caused death, have been reported rarely when medicines containing tenofovir disoproxil fumarate and didanosine were taken together. Your doctor will carefully consider whether to treat you with medicines containing tenofovir and didanosine.
- **Other medicines used for HIV infection:** the following protease inhibitors: amprenavir, indinavir, lopinavir/ritonavir, ritonavir, or ritonavir boosted atazanavir or saquinavir. Your doctor may consider giving you an alternative medicine or changing the dose of the protease inhibitors.
- **Medicines used to lower blood fats (also called statins):** atorvastatin, pravastatin, simvastatin. Atripla can reduce the amount of statins in your blood. Your doctor will check your cholesterol levels and will consider changing the dose of your statin, if needed.
- **Medicines used to treat convulsions/seizures (anticonvulsants):** carbamazepine, phenytoin, phenobarbital. Atripla can reduce the amount of the anticonvulsant in your blood. Carbamazepine can reduce the amount of efavirenz, one of the components of Atripla, in your blood. Your doctor may need to consider giving you a different anticonvulsant.
- **Medicines used to treat bacterial infections,** including tuberculosis and AIDS-related mycobacterium avium complex: clarithromycin, rifabutin, rifampicin. Your doctor may need to consider changing your dose or giving you an alternative antibiotic. In addition, your doctor may consider giving you an additional dose of efavirenz to treat your HIV infection.
- **Medicines used to treat fungal infections (antifungals):** itraconazole. Atripla can reduce the amount of itraconazole in your blood. Your doctor may need to consider giving you a different antifungal.
- **Hormonal contraceptives (e.g. the pill or contraceptive implant).** Because the potential for efavirenz, a component of Atripla, to interact with hormonal contraceptives has not been fully studied, a reliable method of barrier contraception (for example, a condom) should always be used in addition to the hormonal contraceptive (see Section *Pregnancy and breast-feeding*).
- **Methadone,** a medicine used to treat opiate addiction, as your doctor may need to change your methadone dose.
- **Sertraline,** a medicine used to treat depression, as your doctor may need to change your dose of sertraline.
- **Diltiazem or similar medicines (called calcium channel blockers):** when you start taking Atripla, your doctor may need to adjust your dose of the calcium channel blocker.
- **Medicines containing tacrolimus** (a medicine used to prevent organ transplant rejection, also called immunosuppressant). When you start or stop taking Atripla your doctor will closely monitor your plasma levels of tacrolimus and may need to adjust its dose.

Pregnancy and breast-feeding

Women should not get pregnant during treatment with Atripla **and for 12 weeks thereafter**. Your doctor may require you to take a pregnancy test to ensure you are not pregnant before starting treatment with Atripla.

If you could get pregnant while receiving Atripla, you need to use a reliable form of barrier contraception (for example, a condom) with other methods of contraception including oral (pill) or other hormonal contraceptives (for example, implants, injection). Efavirenz, one of the active components of Atripla, may remain in your blood for a time after therapy is stopped. Therefore, you should continue to use contraceptive measures, as above, for 12 weeks after you stop taking Atripla.

Tell your doctor immediately if you are pregnant or intend to become pregnant. If you are pregnant, you should take Atripla only if you and your doctor decide it is clearly needed.

Serious birth defects have been seen in unborn animals and in the babies of women treated with efavirenz during pregnancy. If you have taken Atripla during your pregnancy, your doctor may request regular blood tests and other diagnostic tests to monitor the development of your child.

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

Do not breast-feed during treatment with Atripla. Both HIV and the ingredients of Atripla may pass through breast milk and cause serious harm to your baby.

Driving and using machines

No studies on the effects on the ability to drive and use machines have been performed. **Atripla may cause dizziness, impaired concentration and drowsiness.** If you are affected, do not drive and do not use any tools or machines.

Important information about some of the ingredients of Atripla

This medicine contains 1 mmol (23.6 mg) of sodium per tablet which should be taken into consideration if you are on a controlled sodium diet.

3. HOW TO TAKE ATRIPLA

Always take Atripla exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure.

The usual dose for adults is one tablet taken each day by mouth. Atripla should be taken on an empty stomach (commonly defined as 1 hour before or 2 hours after a meal). Swallow Atripla whole with water.

Atripla must be taken every day.

It can help to take Atripla at bedtime. This may make some side effects (for example, dizziness, drowsiness) less troublesome.

If your doctor decides to stop one of the components of Atripla, you may be given efavirenz, emtricitabine and/or tenofovir disoproxil separately or with other medicines for the treatment of your HIV infection.

If you take more Atripla than you should

If you accidentally take too many Atripla tablets, 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 Atripla

It is important not to miss a dose of Atripla.

If you do miss a dose of Atripla, 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, do not take 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 the tablet (just after taking Atripla), you should take another tablet. Do not wait until your next dose is due.

If you stop taking Atripla

Don't stop taking Atripla without talking to your doctor. Stopping Atripla can seriously affect your response to future treatment. If Atripla is stopped, speak to your doctor before you restart taking Atripla tablets. Your doctor may consider giving you the components of Atripla separately if you are having problems or need your dose adjusted.

When your supply of Atripla starts to run low, get more from your doctor or pharmacist. This is very important because the amount of virus may start to increase if the medicine is stopped for even a short time. The virus may then become harder to treat.

If you have both HIV infection and hepatitis B, it is especially important not to stop your Atripla treatment without talking to your doctor first. Some patients have had blood tests or symptoms indicating that their hepatitis has got worse after stopping emtricitabine or tenofovir disoproxil fumarate (two of the three components of Atripla). If Atripla is stopped your doctor may recommend that you resume hepatitis B treatment. You may require blood tests to check how your liver is working for 4 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, which may be life-threatening.

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 product, ask your doctor or pharmacist.

4. POSSIBLE SIDE EFFECTS

Like all medicines, Atripla can cause side effects, although not everybody gets them. When treating HIV infection, it is not always possible to tell whether some of the unwanted effects are caused by Atripla or by other medicines that you are taking at the same time, or by the HIV disease itself. **Tell your doctor if you notice any of the following side effects:**

Very common side effects
(These can affect more than 1 user in 10)

- dizziness, headache, diarrhoea, feeling sick (nausea), vomiting
- rashes (including red spots or blotches sometimes with blistering and swelling of the skin), which may be allergic reactions

Tests may also show:
- decreases in phosphate levels in the blood
- increased levels of creatine kinase in the blood that may result in muscle pain and weakness

Common side effects
(These can affect 1 to 10 users in 100)

- changes in skin colour including darkening of the skin in patches often starting on hands and soles of feet
- pain, stomach pain
- difficulty sleeping, abnormal dreams, nightmares, sweating at night, difficulty concentrating, drowsiness
- feeling worried or depressed, mood being affected
- problems with digestion resulting in discomfort after meals, wind (flatulence)
- loss of appetite
- hot flushes
- feeling weak, tiredness and lack of energy
- increased energy
- itching

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

Uncommon side effects
(These can affect 1 to 10 users in 1,000)

- angry behaviour, suicidal thoughts, strange thoughts, paranoia, unable to think clearly, seeing or hearing things that are not really there (hallucinations), suicide attempts, personality change, feeling abnormal
- forgetfulness, confusion, problems with co-ordination, fitting (seizures), disorientation, incoherent speech, feeling jittery
- blurred vision, visual disturbance
- a feeling of spinning or tilting (vertigo)
- tingling or numbness of the mouth, dry mouth
- allergic reaction (hypersensitivity) that may cause severe skin reactions (Stevens-Johnson syndrome, erythema multiforme, see section 2)
- yellow skin or eyes, itching, or pain in the abdomen (stomach) caused by inflammation of the liver
- pain in the abdomen (stomach), caused by inflammation of the pancreas
- fat redistribution, weight decreased, increased appetite
- breast enlargement in males
- anaemia (low red blood cell count)
- decreased sexual drive
- muscle pain
- chills

Other possible effects (frequency cannot be estimated from the available data)
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
- tiredness
- feeling sick (nausea), vomiting and stomach pain.

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

Unwanted effects to the kidney have been reported. These include changes to your urine, increased level of creatinine in your blood, and back pain caused by kidney problems, including kidney failure and damage to kidney tubule cells. Your doctor may do blood tests to see if your kidneys are working properly. You may also experience inflammation of the kidney, passing a lot of urine and feeling thirsty.

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 may also occur in patients who develop damage to the kidney tubule cells.

Psychiatric side effects in addition to those listed above include delusions (false beliefs), neurosis, psychosis (personality changes). Some patients have committed suicide. These problems tend to occur more often in those who have a history of mental illness. Always notify your doctor immediately if you have these symptoms.

Other unwanted effects include: itchy rash to the skin caused by a reaction to sunlight, shortness of breath, fatty liver, disturbances of coordination and balance.

Combination antiretroviral therapy (such as Atripla) may change your body shape, by changing the way body fat is distributed. You may lose fat from your legs, arms and face; gain fat around the abdomen (tummy) and internal organs; get larger breasts or fatty lumps on the back of the neck ('buffalo hump'). The cause and the long-term effects of these changes are not yet known.

Combination antiretroviral therapy may also cause increased fat levels in the blood (hyperlipaemia) and resistance to insulin. Your doctor will test for these changes.

If any of the side effects get serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

5. HOW TO STORE ATRIPLA

Keep out of the reach and sight of children.

Do not use Atripla after the expiry date which is stated on the bottle label 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.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. FURTHER INFORMATION

What Atripla contains

- The active substances are efavirenz, emtricitabine and tenofovir disoproxil. Each Atripla film-coated tablet contains 600 mg of efavirenz, 200 mg of emtricitabine and 245 mg of tenofovir disoproxil (as fumarate).
- The other ingredients in the tablet are croscarmellose sodium, hydroxypropylcellulose, magnesium stearate, microcrystalline cellulose, sodium laurilsulfate.
- The other ingredients in the tablet film coating are iron oxide black, iron oxide red, macrogol 3350, poly(vinyl alcohol), talc, titanium dioxide.

What Atripla looks like and contents of the pack

Atripla film-coated tablets are pink, capsule shaped tablets, engraved on one side with the number "123" and plain on the other side. Atripla comes in bottles of 30 tablets (with a silica gel sachet that must be kept in the bottle to help protect your tablets). The silica gel desiccant is contained in a separate sachet and should not be swallowed.

The following pack sizes are available: outer cartons containing 1 x 30 film-coated tablet and 3 x 30 film-coated tablet bottles. Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer

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