Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Efavirenz Rowex 600mg Film-coated Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 600 mg of efavirenz.

Excipient with known effect
Each film-coated tablet contains 95.29 mg of lactose (as monohydrate).

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet

Yellow film-coated tablet of capsule shape (9.6 x 19.2 mm) with a break line on both sides.

The tablet can be divided into equal doses.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Efavirenz Rowex is indicated in antiviral combination treatment of human immunodeficiency virus-1 (HIV-1) infected adults, adolescents and children weighing ≥ 40 kg.

Efavirenz Rowex has not been adequately studied in patients with advanced HIV disease, namely in patients with CD4 counts < 50 cells/mm3, or after failure of protease inhibitor (PI) containing regimens. Although cross-resistance of efavirenz with PIs has not been documented, there are at present insufficient data on the efficacy of subsequent use of PI based combination therapy after failure of regimens containing Efavirenz Rowex.

For a summary of clinical and pharmacodynamic information, see section 5.1.

4.2 Posology and method of administration

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

Posology
Efavirenz Rowex must be given in combination with other antiretroviral medicines (see section 4.5).

In order to improve the tolerability of nervous system adverse reactions, bedtime dosing is recommended (see section 4.8).

Adults and adolescents over 40 kg: the recommended dose of Efavirenz Rowex in combination with nucleoside analogue reverse transcriptase inhibitors (NRTIs) with or without a PI (see section 4.5) is 600 mg orally, once daily.

Efavirenz film-coated tablets are not suitable for children weighing less than 40 kg. Other efavirenz formulations are available for these patients. Please refer to the accompanying summary of product characteristics of suitable formulations for the paediatric posology.

Dose adjustment:

If efavirenz is co-administered with voriconazole, the voriconazole maintenance dose must be increased to 400 mg every 12 hours and the efavirenz dose must be reduced by 50%, i.e., to 300 mg once daily. When treatment with voriconazole is stopped, the initial dose of efavirenz should be restored (see section 4.5).

If efavirenz is co-administered with rifampicin to patients weighing 50 kg or more, an increase in the dose of efavirenz to 800 mg/day may be considered (see section 4.5).

Special populations

Renal impairment:

The pharmacokinetics of efavirenz have not been studied in patients with renal insufficiency; however, less than 1% of an efavirenz dose is excreted unchanged in the urine, so the impact of renal impairment on efavirenz elimination should be minimal (see section 4.4).

Hepatic impairment:

Patients with mild liver disease may be treated with their normally recommended dose of efavirenz. Patients should be monitored carefully for dose-related adverse reactions, especially nervous system symptoms (see sections 4.3 and 4.4).

Paediatric population:

The safety and efficacy of efavirenz in children below the age of 3 years or weighing less than 13 kg have not yet been established. Currently available data are described in sections 4.8, 5.1 and 5.2, but no recommendation on a posology can be made.

Method of administration

It is recommended that efavirenz be taken on an empty stomach. The increased efavirenz concentrations observed following administration of efavirenz with food may lead to an increase in frequency of adverse reactions (see sections 4.4. and 5.2).

4.3 Contraindications

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

Patients with severe hepatic impairment (Child Pugh Class C) (see section 5.2).

Co-administration with terfenadine, astemizole, cisapride, midazolam, triazolam, pimozide, bepridil, or ergot alkaloids (for example, ergotamine, dihydroergotamine, ergonovine, and methylergonovine) because competition for CYP3A4 by efavirenz could result in inhibition of metabolism and create the potential for serious and/or life-threatening adverse reactions (for example, cardiac arrhythmias, prolonged sedation or respiratory depression) (see section 4.5).

Herbal preparations containing St. John's wort (*Hypericum perforatum*)due to the risk of decreased plasma concentrations and reduced clinical effects of efavirenz (see section 4.5).

Patients with:
- a family history of sudden death or of congenital prolongation of the QTc interval on electrocardiograms, or with any other clinical condition known to prolong the QTc interval.
- a history of symptomatic cardiac arrhythmias or with clinically relevant bradycardia or with congestive cardiac failure accompanied by reduced left ventricle ejection fraction.
- severe disturbances of electrolyte balance e.g. hypokalaemia or hypomagnesemia.

Patients taking medicinal products that are known to prolong the QTc interval (proarrhythmic).

These medicinal products include:
- antiarrhythmics of classes IA and III,
- neuroleptics, antidepressive agents,
- certain antibiotics including some agents of the following classes: macrolides, fluoroquinolones, imidazole and triazole antifungal agents,
- certain non-sedating antihistamines (terfenadine, astemizole),
- cisapride,

- flecainide,
- certain antimalarials,
- methadone.

Co-administration with elbasvir/grazoprevir due to the expected significant decreases in elbasvir and grazoprevir plasma concentrations (see section 4.5). This effect is due to an induction of CYP3A4 or P-gp by efavirenz and is expected to result in the loss of virologic response of elbasvir/grazoprevir.

4.4 Special warnings and precautions for use

Efavirenz must not be used as a single agent to treat HIV or added on as a sole agent to a failing regimen. Resistant virus emerges rapidly when efavirenz is administered as monotherapy. The choice of new antiretroviral agent(s) to be used in combination with efavirenz should take into consideration the potential for viral cross-resistance (see section 5.1).

Co-administration of efavirenz with the fixed combination tablet containing efavirenz, emtricitabine, and tenofovir disoproxil fumarate is not recommended unless needed for dose adjustment (for example, with rifampicin).

Co-administration of sofosbuvir/velpatasvir with efavirenz is not recommended (see section 4.5).
Concomitant administration of velpatasvir/sofosbuvir/ voxilaprevir with efavirenz is not recommended (see section 4.5).

Co-administration of glecaprevir/pibrentasvir with efavirenz may significantly decrease plasma concentrations of glecaprevir and pibrentasvir, leading to reduced therapeutic effect.
Co-administration of glecaprevir/pibrentasvir with efavirenz is not recommended (see section 4.5).

Concomitant use of *Ginkgo biloba* extracts is not recommended (see section 4.5).

When prescribing medicinal products concomitantly with efavirenz, physicians should refer to the corresponding Summary of Product Characteristics.

If any antiretroviral medicinal product in a combination regimen is interrupted because of suspected intolerance, serious consideration should be given to simultaneous discontinuation of all antiretroviral medicinal products. The antiretroviral medicinal products should be restarted at the same time upon resolution of the intolerance symptoms. Intermittent monotherapy and sequential reintroduction of antiretroviral agents is not advisable because of the increased potential for selection of resistant virus.

Rash
Mild to moderate rash has been reported in clinical studies with efavirenz and usually resolves with continued therapy. Appropriate antihistamines and/or corticosteroids may improve the 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. The incidence of erythema multiforme or Stevens-Johnson syndrome was approximately 0.1%. Efavirenz must be discontinued in patients developing severe rash associated with blistering, desquamation, mucosal involvement or fever. If therapy with efavirenz is discontinued, consideration should also be given to interrupting therapy with other antiretroviral agents to avoid development of resistant virus (see section 4.8).

Experience with efavirenz in patients who discontinued other antiretroviral agents of the NNRTI class is limited (see section 4.8). Efavirenz is not recommended for patients who have had a life-threatening cutaneous reaction (e.g., Stevens-Johnson syndrome) while taking another NNRTI.

Psychiatric symptoms:
*P*sychiatric 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, psychosis-like behaviour and catatonia. 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 risks of continued therapy outweigh 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 adverse reactions in patients receiving efavirenz 600 mg daily in clinical studies (see section 4.8). Nervous system symptoms usually begin during the first one or two days of therapy and generally resolve after the first 2–4 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.

Late-onset neurotoxicity, including ataxia and encephalopathy (impaired consciousness, confusion, psychomotor slowing, psychosis, delirium), may occur months to years after beginning efavirenz therapy. Some events of late-onset neurotoxicity have occurred in patients with CYP2B6 genetic polymorphisms, which are associated with increased efavirenz levels despite standard dosing of Efavirenz. Patients presenting with signs and symptoms of serious neurologic adverse experiences should be evaluated promptly to assess the possibility that these events may be related to efavirenz use, and whether discontinuation of Efavirenz is warranted.

Seizures:
Convulsions have been observed in patients receiving efavirenz, generally in the presence of 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.

Hepatic events:
A few of the post marketing reports of hepatic failure occurred in patients with no preexisting hepatic disease or other identifiable risk factors (see section 4.8). Liver enzyme monitoring should be considered for patients without pre-existing hepatic dysfunction or other risk factors.

QTc prolongation
QTc prolongation has been observed with the use of efavirenz (see sections 4.5 and 5.1).

Consider alternatives to efavirenz for co-administration with a medicinal product with a known risk of Torsade de Pointes or when to be administered to patients at higher risk of Torsade de Pointes.

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

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

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

Osteonecrosis:
Although the aetiology is considered to be multifactorial (including corticosteroid use, alcohol consumption, severe immunosuppression, higher body mass index), cases of osteonecrosis have been reported particularly in patients with advanced HIV-disease and/or long-term exposure to 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.

Special populations:

Liver disease
Efavirenz is contraindicated in patients with severe hepatic impairment (see sections 4.3 and 5.2) and not recommended in patients with moderate hepatic impairment because of insufficient data to determine whether dose adjustment is necessary. Because of the extensive cytochrome P450-mediated metabolism of efavirenz and limited clinical experience in patients with chronic liver disease, caution must be exercised in administering efavirenz to patients with mild hepatic impairment. Patients should be monitored carefully for dose-related adverse reactions, especially nervous system symptoms. Laboratory tests should be performed to evaluate their liver disease at periodic intervals (see section 4.2).

The safety and efficacy of efavirenz has not been established in patients with significant underlying liver disorders. Patients with chronic hepatitis B or C and treated with combination antiretroviral therapy are at increased risk for severe and potentially fatal hepatic adverse reactions. 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 efavirenz 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. In case of concomitant antiviral therapy for hepatitis B or C, please refer also to the relevant product information for these medicinal products.

Renal insufficiency:
The pharmacokinetics of efavirenz have not been studied in patients with renal insufficiency; however, less than 1% of an efavirenz dose is excreted unchanged in the urine, so the impact of renal impairment on efavirenz elimination should be minimal (see section 4.2). There is no experience in patients with severe renal failure and close safety monitoring is recommended in this population.

Elderly patients:
Insufficient numbers of elderly patients have been evaluated in clinical studies to determine whether they respond differently than younger patients.

Paediatric population:

Efavirenz film-coated tablets are not suitable for children weighing less than 40 kg.

Rash was reported in 26 of 57 children (46%) treated with efavirenz during a 48 week period and was severe in three patients. Prophylaxis with appropriate antihistamines prior to initiating therapy with efavirenz in children may be considered.

Efavirenz Rowex contains sodium and lactose
This medicinal product contains less than 1 mmol sodium (23 mg) per film-coated tablet, that is to say essentially 'sodium-free'.

Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicinal product. Individuals with these conditions may take efavirenz oral solution, which is free from lactose.

4.5 Interaction with other medicinal products and other forms of interaction

Efavirenz is an *in vivo* inducer of CYP3A4, CYP2B6 and UGT1A1. Compounds that are substrates of these enzymes may have decreased plasma concentrations when co-administered with efavirenz.
In vitro efavirenz is also an inhibitor of CYP3A4. Theoretically, efavirenz may therefore initially increase the exposure to CYP3A4 substrates and caution is warranted for CYP3A4 substrates with narrow therapeutic index (see section 4.3). Efavirenz may be an inducer of CYP2C19 and CYP2C9; however, inhibition has also been observed *in vitro* and the net effect of co-administration with substrates of these enzymes is not clear (see section 5.2).

Efavirenz exposure may be increased when given with medicinal products (for example, ritonavir) or food (for example, grapefruit juice) which inhibit CYP3A4 or CYP2B6 activity. Compounds or herbal preparations (for example Ginkgo biloba extracts and St. John's wort) which induce these enzymes may give rise to decreased plasma concentrations of efavirenz.
Concomitant use of St. John's wort is contraindicated (see section 4.3).
Concomitant use of Ginkgo biloba extracts is not recommended (see section 4.4).

Concomitant use of efavirenz with praziquantel is not recommended due to significant decrease in plasma concentrations of praziquantel, with risk of treatment failure due to increased hepatic metabolism by efavirenz. In case the combination is needed, an increased dose of praziquantel could be considered.

QT prolonging medicinal products
Efavirenz is contraindicated with concomitant use of medicinal products (they may cause prolonged QTc interval and Torsade de Pointes) such as: antiarrhythmics of classes IA and III, neuroleptics and antidepressant agents, certain antibiotics including some agents of the following classes: macrolides, fluoroquinolones, imidazole, and triazole antifungal agents, certain non-sedating antihistaminics (terfenadine, astemizole), cisapride, flecainide, certain antimalarials and methadone (see section 4.3).

Paediatric population
Interaction studies have only been performed in adults.

Contraindications of concomitant use
Efavirenz 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).

Efavirenz must not be administered with elbasvir/grazoprevir due to the expected significant decreases in elbasvir and grazoprevir plasma concentrations caused by induction of drug metabolising enzymes and/or transport proteins and which are expected to result in the loss of virologic response of elbasvir/grazoprevir (see section 4.5).

St. John's wort (Hypericum perforatum)
Co-administration of efavirenz and St. John's wort or herbal preparations containing St. John's wort is contraindicated. 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. If a patient is already taking St. John's wort, stop St. John's wort, check viral levels and if possible efavirenz levels. Efavirenz levels may increase on stopping St. John's wort and the dose of efavirenz may need adjusting. The inducing effect of St. John's wort may persist for at least 2 weeks after cessation of treatment (see section 4.3).

Co-administration of efavirenz with metamizole, which is an inducer of metabolising enzymes including CYP2B6 and CYP3A4 may cause a reduction in plasma concentrations of efavirenz with potential decrease in clinical efficacy. Therefore, caution is advised when metamizole and efavirenz are administered concurrently; clinical response and/or drug levels should be monitored as appropriate.

Other interactions
Interactions between efavirenz 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 "↔", and once every 8 or 12 hours as "q8h" or "q12h"). If available, 90% or 95% confidence intervals are shown in parentheses. Studies were conducted in healthy subjects unless otherwise noted.

Table 1 Interactions between efavirenz and other medicinal products in adults

Medicinal product by therapeutic areas (dose)	Effects on drug levels Mean percent change in AUC, Cmax, Cmin with confidence intervals if availablea (mechanism)	Recommendation concerning co-administration with efavirenz
ANTI-INFECTIVES		
Protease inhibitors (PI)		
Atazanavir/ ritonavir/Efavirenz (400 mg once daily/100 mg once	Atazanavir (pm): AUC: ↔* (↓9 to ↑10)	Co-administration of efavirenz with atazanavir/ritonavir is not recommended. If the co-administration of atazanavir with an

daily/600 mg once daily, all administered with food)	Cmax: ↑17%* (↑8 to ↑27) Cmin: ↓42%* (↓31 to ↓51)	NNRTI is required, an increase in the dose of both atazanavir and ritonavir to 400 mg and 200 mg, respectively, in combination with efavirenz could be considered with close clinical monitoring.
Atazanavir/ritonavir/Efavirenz (400 mg once daily/200 mg once daily/600 mg once daily, all administered with food)	Atazanavir (pm): AUC: ↔*/** (↓10 to ↑26) Cmax: ↔*/** (↓5 to ↑26) Cmin: ↑ 12%*/** (↓16 to ↑49) (CYP3A4 induction). * When compared to atazanavir 300 mg/ritonavir 100 mg once daily in the evening without efavirenz. This decrease in atazanavir Cmin might negatively impact the efficacy of atazanavir. ** based on historical comparison	
Darunavir/ritonavir/Efavirenz (300 mg twice daily*/100 mg twice daily/600 mg once daily) *lower than recommended doses; similar findings are expected with recommended doses	Darunavir: AUC: ↓13% Cmin: ↓31% Cmax: ↓15% (CYP3A4 induction) Efavirenz: AUC: ↑ 21% Cmin: ↑ 17% Cmax: ↑15% (CYP3A4 inhibition)	Efavirenz in combination with darunavir/ritonavir 800/100 mg once daily may result in suboptimal darunavir Cmin. If efavirenz is to be used in combination with darunavir/ritonavir, the darunavir/ritonavir 600/100 mg twice daily regimen should be used. This combination should be used with caution. See also ritonavir row below.
Fosamprenavir/ritonavir/Efavirenz (700 mg twice daily/100 mg twice daily/600 mg once daily)	No clinically significant pharmacokinetic interaction	No dose adjustment is necessary for any of these medicinal products. See also ritonavir row below.
Fosamprenavir/Nelfinavir/Efavirenz	Interaction not studied.	No dose adjustment is necessary for any of these medicinal products.
Fosamprenavir/Saquinavir/ Efavirenz	Interaction not studied.	Not recommended as the exposure to both PIs is expected to be significantly decreased.
Indinavir/Efavirenz (800 mg q8h/200 mg once daily)	Indinavir: AUC : ↓ 31% (↓ 8 to ↓ 47) Cmin : ↓ 40% A similar reduction in indinavir exposures was observed when indinavir 1000 mg q8h was given with efavirenz 600 mg daily. (CYP3A4 induction) Efavirenz: No clinically significant pharmacokinetic interaction	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 and indinavir. No dose adjustment is necessary for efavirenz when given with indinavir or indinavir/ritonavir. See also ritonavir row below.
Indinavir/ritonavir/Efavirenz (800 mg twice daily/100 mg twice daily/600 mg once daily)	Indinavir: AUC: ↓ 25% (↓ 16 to ↓ 32) b	

	Cmax: ↓ 17% (↓ 6 to ↓ 26)b Cmin: ↓ 50% (↓ 40 to ↓ 59)b Efavirenz: No clinically significant pharmacokinetic interaction The geometric mean Cmin for indinavir (0.33 mg/l) when given with ritonavir and efavirenz was higher than the mean historical Cmin (0.15 mg/l) when indinavir was given alone at 800 mg q8h. In HIV-1 infected patients (n = 6), the pharmacokinetics of indinavir and efavirenz were generally comparable to these uninfected volunteer data.	
Lopinavir/ritonavir soft capsules or oral solution/Efavirenz Lopinavir/ritonavir tablets/ Efavirenz (400/100 mg twice daily/ 600 mg once daily) (500/125 mg twice daily/ 600 mg once daily)	Substantial decrease in lopinavir exposure. Lopinavir concentrations: ↓ 30-40% Lopinavir concentrations: similar to lopinavir/ritonavir 400/100 mg twice daily without efavirenz	With efavirenz, an increase of the lopinavir/ritonavir soft capsule ororal solution doses by 33% should be considered (4 capsules/~6.5 mL twice daily instead of 3 capsules/5 mL twice daily). Caution is warranted since this dose adjustment might be insufficient in some patients. The dose oflopinavir/ritonavir tablets should be increased to 500/125 mg twice daily when co-administered with efavirenz 600 mg once daily. See also ritonavir row below.
Nelfinavir/Efavirenz (750 mg q8h/600 mg once daily)	Nelfinavir: AUC: ↑ 20% (↑ 8 to ↑ 34) Cmax: ↑ 21% (↑ 10 to ↑ 33) The combination was generally well tolerated.	No dose adjustment is necessary for either medicinal product.
Ritonavir/Efavirenz (500 mg twice daily/600 mg once daily)	Ritonavir: Morning AUC: ↑ 18% (↑ 6 to ↑ 33) Evening AUC: ↔ Morning Cmax: ↑ 24% (↑ 12 to ↑ 38) Evening Cmax: ↔ Morning Cmin: ↑ 42% (↑ 9 to ↑ 86) b Evening Cmin: ↑ 24% (↑ 3 to ↑ 50) b Efavirenz: AUC: ↑ 21% (↑ 10 to ↑ 34) Cmax: ↑ 14% (↑ 4 to ↑ 26) Cmin: ↑ 25% (↑ 7 to ↑ 46) b	When using efavirenz with low-dose ritonavir, the possibility of an increase in the incidence of efavirenz-associated adverse events should be considered, due to possible pharmacodynamic interaction.

	(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.	
Saquinavir/ritonavir/Efavirenz	Interaction not studied.	No data are available to make a dose recommendation. See also ritonavir row above. Use of efavirenz in combination with saquinavir as the sole protease inhibitor is not recommended.
CCR5 antagonist		
Maraviroc/Efavirenz (100 mg twice daily/600 mg once daily)	Maraviroc: AUC12: ↓ 45% (↓ 38 to ↓ 51) Cmax: ↓ 51% (↓ 37 to ↓ 62) Efavirenz concentrations not measured, no effect is expected.	Refer to the Summary of Product Characteristics for the medicinal product containing maraviroc.
Integrase strand transfer inhibitor		
Raltegravir/Efavirenz (400 mg single dose/ -)	Raltegravir: AUC: ↓ 36% C12: ↓ 21% Cmax: ↓ 36% (UGT1A1 induction)	No dose adjustment is necessary for raltegravir.
NRTIs and NNRTIs		
NRTIs/Efavirenz	Specific interaction studies have not been performed with efavirenz and NRTIs other than lamivudine, zidovudine, and tenofovir disoproxil fumarate. Clinically significant interactions are not 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.	No dose adjustment is necessary for either medicinal product.
NNRTIs/Efavirenz	Interaction not studied.	Since use of two NNRTIs proved not beneficial in terms of efficacy and safety, co-administration of efavirenz and another NNRTI is not recommended.
Hepatitis C antivirals		

Boceprevir/Efavirenz (800 mg 3 times daily/600 mg once daily)	Boceprevir: AUC: ↔ 19%* Cmax: ↔ 8% Cmin: ↓ 44% Efavirenz: AUC: ↔ 20% Cmax: ↔ 11% (CYP3A induction - effect on boceprevir) *0-8 hours No effect (↔) equals a decrease in mean ratio estimate of ≤20% or increase in mean ratio estimate of ≤25%	Plasma trough concentrations of boceprevir were decreased when administered with efavirenz. The clinical outcome of this observed reduction of boceprevir trough concentrations has not been directly assessed.
Telaprevir/Efavirenz (1,125 mg q8h/600 mg once daily)	Telaprevir (relative to 750 mg q8h): AUC: ↓ 18% (↓ 8 to ↓ 27) Cmax: ↓ 14% (↓ 3 to ↓ 24) Cmin: ↓ 25% (↓ 14 to ↓ 34)% Efavirenz: AUC: ↓ 18% (↓ 10 to ↓ 26) Cmax: ↓ 24% (↓ 15 to ↓ 32) Cmin: ↓ 10% (↑ 1 to ↓ 19)% (CYP3A induction by efavirenz)	If efavirenz and telaprevir are co-administered, telaprevir 1,125mg every 8 hours should be used.
Simeprevir/Efavirenz (150 mg once daily/600 mg once daily)	Simeprevir: AUC: ↓ 71% (↓ 67 to ↓ 74) Cmax: ↓ 51% (↓ 46 to ↓ 56) Cmin: ↓ 91% (↓ 88 to ↓ 92) Efavirenz: AUC: ↔ Cmax: ↔ Cmin: ↔ No effect (↔) equals a decrease in mean ratio estimate of ≤20% or increase in mean ratio estimate of ≤25% (CYP3A4 enzyme induction)	Concomitant administration of simeprevir with efavirenz resulted in significantly decreased plasma concentrations of simeprevir due to CYP3A induction by efavirenz, which may result in loss of therapeutic effect of simeprevir. Co-administratio n of simeprevir with efavirenz is not recommended.
Sofosbuvir/velpatasvir	↔sofosbuvir ↓velpatasvir ↔efavirenz	Concomitant administration of sofosbuvir/velpatasvir with efavirenz resulted in a reduction (approximately 50%) in the systemic exposure of velpatasvir. The mechanism of the effect on velpatasvir is induction of CYP3A and CYP2B6 by efavirenz. Co-administration of sofosbuvir/velpatasvir with efavirenz is not recommended. Refer to the prescribing information for sofosbuvir/velpatasvir for more information.
Velpatasvir/ sofosbuvir/ voxilaprevir	↓velpatasvir ↓voxilaprevir	Concomitant administration of velpatasvir/sofosbuvir/ voxilaprevir with efavirenz is not recommended, as it may decrease concentrations of velpatasvir and voxilaprevir. Refer

		to the prescribing information for velpatasvir/sofosbuvir/ voxilaprevir for more information
Protease inhibitor: Elbasvir/Grazoprevir	↓elbasvir ↓grazoprevir ↔efavirenz	Concomitant administration of efavirenz with elbasvir/grazoprevir is contraindicated because it may lead to loss of virologic response to elbasvir/grazoprevir. This loss is due to significant decreases in elbasvir and grazoprevir plasma concentrations caused by CYP3A4 induction. Refer to the prescribing information for elbasvir/grazoprevir for more information.
Glecaprevir/pibrentasvir	↓ Glecaprevir ↓ Pibrentasvir	Concomitant administration of glecaprevir/pibrentasvir with efavirenz may significantly decrease plasma concentrations of glecaprevir and pibrentasvir, leading to reduced therapeutic effect. Co-administration of glecaprevir/pibrentasvir with efavirenz is not recommended. Refer to the prescribing information for glecaprevir/pibrentasvir for more information.
Antibiotics		
Azithromycin/Efavirenz (600 mg single dose/400 mg once daily)	No clinically significant pharmacokinetic interaction.	No dose adjustment is necessary for either medicinal product.
Clarithromycin/Efavirenz (500 mg q12h/400 mg once daily)	Clarithromycin: AUC: ↓ 39% (↓ 30 to ↓ 46) Cmax: ↓ 26% (↓ 15 to ↓ 35) Clarithromycin 14-hydroxymetabolite: AUC: ↑ 34% (↑ 18 to ↑ 53) Cmax: ↑ 49% (↑ 32 to ↑ 69) Efavirenz: AUC: ↔ Cmax: ↑ 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. No dose adjustment is necessary for efavirenz.
Other macrolide antibiotics (e.g.,erythromycin)/Efavirenz	Interaction not studied.	No data are available to make a dose recommendation.
Antimycobacterials		
Rifabutin/Efavirenz (300 mg once daily/600 mg once daily)	Rifabutin: AUC: ↓ 38% (↓ 28 to ↓ 47) Cmax: ↓ 32% (↓ 15 to ↓ 46) Cmin: ↓ 45% (↓ 31 to ↓ 56) Efavirenz: AUC: ↔ Cmax: ↔ Cmin: ↓ 12% (↓ 24 to ↑ 1) (CYP3A4 induction)	The daily dose of rifabutin should be increased by 50% when administered with efavirenz. Consider doubling the rifabutin dose in regimens where rifabutin is given 2 or 3 times a week in combination with efavirenz. The clinical effect of this dose adjustment has not been adequately evaluated. Individual tolerability and virological response should be considered when making the dose adjustment (see section 5.2).
Rifampicin/Efavirenz	Efavirenz:	When taken with rifampicin in patients weighing 50 kg or

(600 mg once daily/600 mg once daily)	AUC: ↓ 26% (↓ 15 to ↓ 36) Cmax: ↓ 20% (↓ 11 to ↓ 28) Cmin: ↓ 32% (↓ 15 to ↓ 46) (CYP3A4 and CYP2B6 induction)	greater, increasing efavirenz daily dose to 800 mg may provide exposure similar to a daily dose of 600 mg when taken without rifampicin. The clinical effect of this dose adjustment has not been adequately evaluated. Individual tolerability and virological response should be considered when making the dose adjustment (see section 5.2). No dose adjustment is necessary for rifampicin.
Antifungals		
Itraconazole/Efavirenz (200 mg q12h/600 mg once daily)	Itraconazole: AUC: ↓ 39% (↓ 21 to ↓ 53) Cmax: ↓ 37% (↓ 20 to ↓ 51) Cmin: ↓ 44% (↓ 27 to ↓ 58) (decrease in itraconazole concentrations: CYP3A4 induction) Hydroxyitraconazole: AUC: ↓ 37% (↓ 14 to ↓ 55) Cmax: ↓ 35% (↓ 12 to ↓ 52) Cmin: ↓ 43% (↓ 18 to ↓ 60) Efavirenz: No clinically significant pharmacokinetic change.	Since no dose recommendation for itraconazole can be made, alternative antifungal treatment should be considered.
Posaconazole/Efavirenz --/400 mg once daily	Posaconazole: AUC: ↓ 50% Cmax: ↓ 45% (UDP-G induction)	Concomitant use of posaconazole and efavirenz should be avoided unless the benefit to the patient outweighs the risk.
Voriconazole/Efavirenz (200 mg twice daily/400 mg once daily)	Voriconazole: AUC: ↓ 77% Cmax: ↓ 61% Efavirenz: AUC: ↑ 44% Cmax: ↑ 38%	When efavirenz is co-administered with voriconazole, the voriconazole maintenance dose must be increased to 400 mg twice daily and the efavirenz dose must be reduced by 50%, i.e., to 300 mg once daily. When treatment with voriconazole is stopped, the initial dose of efavirenz should be restored.
Voriconazole/Efavirenz (400 mg twice daily/300 mg once daily)	Voriconazole: AUC: ↓ 7% (↓ 23 to ↑ 13) * Cmax: ↑ 23% (↓ 1 to ↑ 53) * Efavirenz: AUC: ↑ 17% (↑ 6 to ↑ 29) ** Cmax: ↔** *compared to 200 mg twice daily alone ** compared to 600 mg once daily alone (competitive inhibition of oxidative metabolism)	
Fluconazole/Efavirenz (200 mg once daily/400 mg once	No clinically significant pharmacokinetic	No dose adjustment is necessary for either medicinal product.

daily)	interaction	
Ketoconazole and other imidazole antifungals	Interaction not studied	No data are available to make a dose recommendation.
Antimalarials		
Artemether/lumefantrine (20/120 mg tablet, 6 doses of 4 tablets each over 3 days/600 mg once daily)	Artemether: AUC: ↓ 51% Cmax: ↓ 21% Dihydroartemisinin: AUC: ↓ 46% Cmax: ↓ 38% Lumefantrine: AUC: ↓ 21% Cmax: ↔ Efavirenz: AUC: ↓ 17% Cmax: ↔ (CYP3A4 induction)	Since decreased concentrations of artemether, dihydroartemisinin, or lumefantrine may result in a decrease of antimalarial efficacy, caution is recommended when efavirenz and artemether/lumefantrine tablets are co-administered.
Atovaquone and proguanil hydrochloride/efavirenz (250/100 mg single dose/600 mg once daily)	Atovaquone: AUC: ↓ 75% (↓ 62 to ↓ 84) Cmax: ↓ 44% (↓ 20 to ↓ 61) Proguanil: AUC: ↓ 43% (↓ 7 to ↓ 65) Cmax: ↔	Concomitant administration of atovaquone/proguanil with efavirenz should be avoided whenever possible.
Praziquantel/efavirenz(single-dose)	Praziquantel: AUC: ↓ 77%	Concomitant use with efavirenz is not recommended due to significant decrease in plasma concentrations of praziquantel, with risk of treatment failure due to increased hepatic metabolism by efavirenz. In case the combination is needed, an increased dose of praziquantel could be considered.
ACID REDUCING AGENTS		
Aluminium hydroxide-magnesium hydroxide-simethicone antacid/Efavirenz (30 mL single dose/400 mg single dose) Famotidine/Efavirenz (40 mg single dose/400 mg single dose)	Neither aluminium/magnesium hydroxide antacids nor famotidine altered the absorption of efavirenz.	Co-administration of efavirenz with medicinal products that alter gastric pH would not be expected to affect efavirenz absorption.
ANTIANXIETY AGENTS		
Lorazepam/Efavirenz (2 mg single dose/600 mg once daily)	Lorazepam: AUC: ↑ 7% (↑ 1 to ↑ 14) Cmax: ↑ 16% (↑ 2 to ↑ 32) These changes are not considered clinically significant.	No dose adjustment is necessary for either medicinal product.
ANTICOAGULANTS		
Warfarin/Efavirenz Acenocoumarol/Efavirenz	Interaction not studied. Plasma concentrations and effects of warfarin are potentially increased or decreased by efavirenz.	Dose adjustment of warfarin may be required.
ANTICONVULSANTS		
Carbamazepine/Efavirenz (400 mg once daily/600 mg once daily)	Carbamazepine: AUC: ↓ 27% (↓ 20 to ↓ 33) Cmax: ↓ 20% (↓ 15 to ↓	No dose recommendation can be made. An alternative anticonvulsant should be considered. Carbamazepine plasma levels should be monitored periodically.

	24) Cmin: ↓ 35% (↓ 24 to ↓ 44) Efavirenz: AUC: ↓ 36% (↓ 32 to ↓ 40) Cmax: ↓ 21% (↓ 15 to ↓ 26) Cmin: ↓ 47% (↓ 41 to ↓ 53) (decrease in carbamazepine concentrations: CYP3A4 induction; decrease in efavirenz concentrations: CYP3A4 and CYP2B6 induction) The steady-state AUC, Cmax and Cmin of the active carbamazepine epoxide metabolite remained unchanged. Co-administration of higher doses of either efavirenz or carbamazepine has not been studied.	
Phenytoin, Phenobarbital, and other anticonvulsants that are substrates of CYP450 isoenzymes	Interaction not studied. There is a potential for reduction or increase in the plasma concentrations of phenytoin, phenobarbital and other anticonvulsants that are substrates of CYP450 isoenzymes when co-administered with efavirenz.	When efavirenz is co- administered with an anticonvulsant that is a substrate of CYP450 isoenzymes, periodic monitoring of anticonvulsant levels should be conducted.
Valproic acid/Efavirenz (250 mg twice daily/600 mg once daily)	No clinically significant effect on efavirenz pharmacokinetics. Limited data suggest there is no clinically significant effect on valproic acid pharmacokinetics.	No dose adjustment is necessary for efavirenz. Patients should be monitored for seizure control.
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	No dose adjustment is necessary for any of these medicinal products.

	as efavirenz.	
ANTIDEPRESSANTS		
Selective Serotonin Reuptake Inhibitors (SSRIs)		
Sertraline/Efavirenz (50 mg once daily/600 mg once daily)	Sertraline: AUC: ↓ 39% (↓ 27 to ↓ 50) Cmax: ↓ 29% (↓ 15 to ↓ 40) Cmin: ↓ 46% (↓ 31 to ↓ 58) Efavirenz: AUC: ↔ Cmax: ↑ 11% (↑ 6 to ↑ 16) Cmin: ↔ (CYP3A4 induction)	Sertraline dose increases should be guided by clinical response. No dose adjustment is necessary for efavirenz.
Paroxetine/Efavirenz (20 mg once daily/600 mg once daily)	No clinically significant pharmacokinetic interaction	No dose adjustment is necessary for either medicinal product.
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.	No dose adjustment is necessary for either medicinal product.
NOREPINEPHRINE AND DOPAMINE REUPTAKE INHIBITOR		
Bupropion/efavirenz [150 mg single dose (sustained release)/600 mg once daily]	Bupropion: AUC: ↓ 55% (↓ 48 to ↓ 62) Cmax: ↓ 34% (↓ 21 to ↓ 47) Hydroxybupropion: AUC: ↔ Cmax: ↑ 50% (↑ 20 to ↑ 80) (CYP2B6 induction)	Increases in bupropion dose should be guided by clinical response, but the maximum recommended dose of bupropion should not be exceeded. No dose adjustment is necessary for efavirenz.
ANTIHISTAMINES		
Cetirizine/Efavirenz (10 mg single dose/600 mg once daily)	Cetirizine: AUC: ↔ Cmax: ↓ 24% (↓ 18 to ↓ 30) These changes are not considered clinically significant. Efavirenz: No clinically significant pharmacokinetic interaction	No dose adjustment is necessary for either medicinal product.
CARDIOVASCULAR AGENTS		
Calcium Channel Blockers		
Diltiazem/Efavirenz (240 mg once daily/600 mg once daily)	Diltiazem: AUC: ↓ 69% (↓ 55 to ↓ 79) Cmax: ↓ 60% (↓ 50 to ↓	Dose adjustments of diltiazem should be guided by clinical response (refer to the Summary of Product Characteristics for diltiazem). No dose adjustment is necessary for efavirenz.

	68) Cmin: ↓ 63% (↓ 44 to ↓ 75) Desacetyl diltiazem: AUC: ↓ 75% (↓ 59 to ↓ 84) Cmax: ↓ 64% (↓ 57 to ↓ 69) Cmin: ↓ 62% (↓ 44 to ↓ 75) N-monodesmethyl diltiazem: AUC: ↓ 37% (↓ 17 to ↓ 52) Cmax: ↓ 28% (↓ 7 to ↓ 44) Cmin: ↓ 37% (↓ 17 to ↓ 52) Efavirenz: AUC: ↑ 11% (↑ 5 to ↑ 18) Cmax: ↑ 16% (↑ 6 to ↑ 26) Cmin: ↑ 13% (↑ 1 to ↑ 26) (CYP3A4 induction) The increase in efavirenz pharmacokinetic parameters is not considered clinically significant.	
Verapamil, Felodipine, Nifedipine and Nicardipine	Interaction not studied. 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 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 mg once daily/600 mg once daily)	Atorvastatin: AUC: ↓ 43% (↓ 34 to ↓ 50) Cmax: ↓ 12% (↓ 1 to ↓ 26) 2-hydroxy atorvastatin: AUC: ↓ 35% (↓ 13 to ↓ 40) Cmax: ↓ 13% (↓ 0 to ↓ 23) 4-hydroxy atorvastatin: AUC: ↓ 4% (↓ 0 to ↓ 31) Cmax: ↓ 47% (↓ 9 to ↓ 51)	Cholesterol levels should be periodically monitored. Dose adjustment of atorvastatin may be required (refer to the Summary of Product Characteristics for atorvastatin). No dose adjustment is necessary for efavirenz.

	Total active HMG Co-A reductase inhibitors: AUC: ↓ 34% (↓ 21 to ↓ 41) Cmax: ↓ 20% (↓ 2 to ↓ 26)	
Pravastatin/Efavirenz (40 mg once daily/600 mg once daily)	Pravastatin: AUC: ↓ 40% (↓ 26 to ↓ 57) Cmax: ↓ 18% (↓ 59 to ↑ 12)	Cholesterol levels should be periodically monitored. Dose adjustment of pravastatin may be required (refer to the Summary of Product Characteristics for pravastatin). No dose adjustment is necessary for efavirenz.
Simvastatin/Efavirenz (40 mg once daily/600 mg once daily)	Simvastatin: AUC: ↓ 69% (↓ 62 to ↓ 73) Cmax: ↓ 76% (↓ 63 to ↓ 79) Simvastatin acid: AUC: ↓ 58% (↓ 39 to ↓ 68) Cmax: ↓ 51% (↓ 32 to ↓ 58) Total active HMG Co-A reductase inhibitors: AUC: ↓ 60% (↓ 52 to ↓ 68) Cmax: ↓ 62% (↓ 55 to ↓ 78) (CYP3A4 induction) Co-administration of efavirenz with atorvastatin, pravastatin, or simvastatin did not affect efavirenz AUC or Cmax values.	Cholesterol levels should be periodically monitored. Dose adjustment of simvastatin may be required (refer to the Summary of Product Characteristics for simvastatin). No dose adjustment is necessary for efavirenz.
Rosuvastatin/Efavirenz	Interaction not studied. Rosuvastatin is largely excreted unchanged via the faeces, therefore interaction with efavirenz is not expected.	No dose adjustment is necessary for either medicinal product.
HORMONAL CONTRACEPTIVES		
Oral: Ethinyloestradiol + Norgestimate/ Efavirenz (0.035 mg + 0.25 mg once daily/600 mg once daily)	Ethinyloestradiol: AUC: ↔ Cmax: ↔ Cmin: ↓ 8% (↑ 14 to ↓ 25) Norelgestromin (active metabolite): AUC: ↓ 64% (↓ 62 to ↓ 67) Cmax: ↓ 46% (↓ 39 to ↓ 52) Cmin: ↓ 82% (↓ 79 to ↓ 85) Levonorgestrel (active metabolite): AUC: ↓ 83% (↓ 79 to ↓	A reliable method of barrier contraception must be used in addition to hormonal contraceptives (see section 4.6).

	87) Cmax: ↓ 80% (↓ 77 to ↓ 83) Cmin: ↓ 86% (↓ 80 to ↓ 90) (induction of metabolism) Efavirenz: no clinically significant interaction. The clinical significance of these effects is not known.	
Injection: Depomedroxyprogesterone acetate (DMPA)/Efavirenz (150 mg IM single dose DMPA)	In a 3-month drug interaction study, no significant differences in MPA pharmacokinetic parameters were found between subjects receiving efavirenz-containing antiretroviral therapy and subjects receiving no antiretroviral therapy. Similar results were found by other investigators, although the MPA plasma levels were more variable in the second study. In both studies, plasma progesterone levels for subjects receiving efavirenz and DMPA remained low consistent with suppression of ovulation.	Because of the limited information available, a reliable method of barrier contraception must be used in addition to hormonal contraceptives (see section 4.6).
Implant: Etonogestrel/Efavirenz	Decreased exposure of etonogestrel may be expected (CYP3A4 induction). There have been occasional post-marketing reports of contraceptive failure with etonogestrel in efavirenz-exposed patients.	A reliable method of barrier contraception must be used in addition to hormonal contraceptives (see section 4.6).
IMMUNOSUPPRESSANTS		
Immunosuppressants metabolized by CYP3A4 (eg, cyclosporine, tacrolimus, sirolimus)/Efavirenz	Interaction not studied. Decreased exposure of the immunosuppressant may be expected (CYP3A4 induction). These immunosuppressants are not anticipated to affect exposure of efavirenz.	Dose adjustments of the immunosuppressant may be required. Close monitoring of immunosuppressant concentrations for at least 2 weeks (until stable concentrations are reached) is recommended when starting or stopping treatment with efavirenz.

NON-OPIOID ANALGESICS		
Metamizole/Efavirenz	Co-administration of efavirenz with metamizole, which is an inducer of metabolising enzymes including CYP2B6 and CYP3A4 cause a reduction in plasma concentrations of efavirenz with potential decrease in clinical efficacy.	Therefore, caution is advised when metamizole and efavirenz. are administered concurrently; clinical response and/or drug levels should be monitored as appropriate.
OPIOIDS		
Methadone/Efavirenz (stable maintenance, 35-100 mg once daily/600 mg once daily)	Methadone: AUC: ↓ 52% (↓ 33 to ↓ 66) Cmax: ↓ 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 should be monitored for signs of withdrawal and their methadone dose increased as required to alleviate withdrawal symptoms.
Buprenorphine/naloxone/Efavirenz	Buprenorphine: AUC: ↓ 50% Norbuprenorphine: AUC: ↓ 71% Efavirenz: No clinically significant pharmacokinetic interaction	Despite the decrease in buprenorphine exposure, no patients exhibited withdrawal symptoms. Dose adjustment of buprenorphine or efavirenz may not be necessary when co-administered.

[a] 90% confidence intervals unless otherwise noted.
[b] 95% confidence intervals.
Other interactions: Efavirenz does not bind to cannabinoid receptors. False-positive urine cannabinoid test results have been reported with some screening assays in uninfected and HIV-infected subjects receiving efavirenz. Confirmatory testing by a more specific method such as gas chromatography/mass spectrometry is recommended in such cases.

4.6 Fertility, pregnancy and lactation

Contraception in males and females
Barrier contraception should always be used in combination with other methods of contraception (for example, oral or other hormonal contraceptives, see section 4.5). Because of the long half-life of efavirenz, use of adequate contraceptive measures for 12 weeks after discontinuation of efavirenz is recommended.

Pregnancy:
Efavirenz should not be used during pregnancy, unless the patient's clinical condition requires such treatment. Women of childbearing potential should undergo pregnancy testing before initiation of efavirenz (see section 5.3).

There have been seven retrospective reports of findings consistent with neural tube defects, including meningomyelocele, all in mothers exposed to efavirenz-containing regimens (excluding any efavirenz containing fixed-dose combination tablets) in the first trimester.
Two additional cases (1 prospective and 1 retrospective) including events consistent with neural tube defects have been reported with the fixed-dose combination tablet containing efavirenz, emtricitabine, and tenofovir disoproxil fumarate. A causal relationship of these events to the use of efavirenz has not been established, and the denominator is unknown. As neural tube defects occur within the first 4 weeks of foetal development (at which time neural tubes are sealed), this potential risk would concern women exposed to efavirenz during the first trimester of pregnancy.
As of July 2013, the Antiretroviral Pregnancy Registry (APR) has received prospective reports of 904 pregnancies with first trimester exposure to efavirenz-containing regimens, resulting in 766 live births. One child was reported to have a neural tube defect, and the frequency and pattern of other birth defects were similar to those seen in children exposed to non-efavirenz-containing regimens, as well as those in HIV negative controls. The incidence of neural tube defects in the general population ranges from 0.5-1 case per 1,000 live births.

Malformations have been observed in foetuses from efavirenz-treated monkeys (see section 5.3).

Breast-feeding:
Efavirenz has been shown to be excreted in human milk.
There is insufficient information on the effects of efavirenz in newborns/infants. Risk to the infant can not be excluded. Breastfeeding should be discontinued during treatment with Efavirenz Rowex. It is recommended that women living with HIV do not breast-feed their infants in order to avoid transmission of HIV.

Fertility:
The effect of efavirenz on male and female fertility in rats has only been evaluated at doses that achieved systemic drug exposures equivalent to or below those achieved in humans given recommended doses of efavirenz. In these studies, efavirenz did not impair mating or fertility of male or female rats (doses up to 100 mg/kg/bid), and did not affect sperm or offspring of treated male rats (doses up to 200 mg/bid). The reproductive performance of offspring born to female rats given efavirenz was not affected.

4.7 Effects on ability to drive and use machines

Efavirenz may cause dizziness, impaired concentration, and/or somnolence. Patients should be instructed that if they experience these symptoms they should avoid potentially hazardous tasks such as driving or operating machinery.

4.8 Undesirable effects

Summary of the safety profile
Efavirenz has been studied in over 9,000 patients. In a subset of 1,008 adult patients who received 600 mg efavirenz daily in combination with PIs and/or NRTIs in controlled clinical studies, the most frequently reported adverse reactions of at least moderate severity reported in at least 5% of patients were rash (11.6%), dizziness (8.5%), nausea (8.0%), headache (5.7%) and fatigue (5.5%). The most notable adverse reactions associated with efavirenz are rash and nervous system symptoms. Nervous system symptoms usually begin soon after therapy onset and generally resolve after the first 2 – 4 weeks. Severe skin reactions such as Stevens-Johnson syndrome and erythema multiforme; psychiatric adverse reactions including severe depression, death by suicide, and psychosis like behaviour; and seizures have been reported in patients treated with efavirenz. The administration of Efavirenz Rowex with food may increase efavirenz exposure and may lead to an increase in the frequency of adverse reactions (see section 4.4).
The long-term safety profile of efavirenz-containing regimens was evaluated in a controlled trial (006) in which patients received efavirenz + zidovudine + lamivudine (n = 412, median duration 180 weeks), efavirenz + indinavir (n = 415, median duration 102 weeks), or indinavir + zidovudine + lamivudine (n = 401, median duration 76 weeks). Long-term use of efavirenz in this study was not associated with any new safety concerns.
Tabulated list of adverse reactions
Adverse reactions of moderate or greater severity with at least possible relationship to treatment regimen (based on investigator attribution) reported in clinical trials of efavirenz at the recommended dose in combination therapy (n = 1,008) are listed below. Also listed in italics are adverse reactions observed post-marketing in association with efavirenz-containing antiretroviral treatment regimens. Frequency is defined using the following convention: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); very rare (< 1/10,000)

Immune system disorders	

uncommon	hypersensitivity
Metabolism and nutrition disorders	
common	hypertriglyceridaemia*
uncommon	hypercholesterolaemia*
Psychiatric disorders	
common	abnormal dreams, anxiety, depression, insomnia*
uncommon	affect lability, aggression, confusional state, euphoric mood, hallucination, mania, paranoia, *psychosis†*, suicide attempt, suicide ideation, catatonia*
rare	*delusion ‡, neurosis ‡, completed suicide‡,**
Nervous system disorders	
common	*cerebellar coordination and balance disturbances†,* disturbance in attention (3.6%), dizziness (8.5%), headache (5.7%), somnolence (2.0%)*
uncommon	agitation, amnesia, ataxia, coordination abnormal, convulsions, thinking abnormal,* *tremor†*
Not known	Encephalopathy
Eye disorders	
uncommon	vision blurred
Ear and labyrinth disorders	
uncommon	*tinnitus†,* vertigo
Vascular disorders	
uncommon	*flushing†*
Gastrointestinal disorders	
common	abdominal pain, diarrhoea, nausea, vomiting
uncommon	pancreatitis
Hepatobiliary disorders	
common	aspartate aminotransferase (AST) increased*, alanine aminotransferase (ALT) increased*, gamma-glutamyltransferase (GGT) increased*
uncommon	hepatitis acute
rare	*hepatic failure‡,**
Skin and subcutaneous tissue disorders	
very common	rash (11.6%)*
common	pruritus
uncommon	erythema multiforme, Stevens-Johnson syndrome*
rare	*photoallergic dermatitis†*
Reproductive system and breast disorders	
uncommon	gynaecomastia
General disorders and administration site conditions	
common	fatigue

* †,‡ See section. *Description of selected adverse reactions* for more details.

* †,‡ See section. *Description of selected adverse reactions* for more details.
Description of selected adverse reactions
Information regarding post-marketing surveillance
†These adverse reactions were identified through post-marketing surveillance; however, the frequencies were determined using data from 16 clinical trials (n=3,969).
‡These adverse reactions were identified through post-marketing surveillance but not reported as medicinal product-related events for efavirenz-treated patients in 16 clinical trials. The frequency category of "rare" was defined per A Guideline on Summary of Product Characteristics (SmPC) (rev. 2, Sept 2009) on the basis of an estimated upper bound of the 95% confidence interval for 0 events given the number of patients treated with efavirenz in these clinical trials (n=3,969).
Rash
In clinical studies, 26% of patients treated with 600 mg of efavirenz experienced skin rash compared with 17% of patients treated in control groups. Skin rash was considered treatment related in 18% of patients treated with efavirenz. Severe rash occurred in less than 1% of patients treated with efavirenz, and 1.7% discontinued therapy because of rash. The incidence of erythema multiforme or Stevens-Johnson syndrome was approximately 0.1%.
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. 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 NNRTI class is limited. Reported rates of recurrent rash following a switch from nevirapine to efavirenz therapy, primarily based on retrospective cohort data from published literature, range from 13 to 18%, comparable to the rate observed in patients treated with efavirenz in clinical studies. (See section 4.4.)
Psychiatric symptoms
Serious psychiatric adverse reactions have been reported in patients treated with efavirenz. In controlled trials, the frequency of specific serious psychiatric events were:

	Efavirenz regimen	Control regimen
	(n=1,008)	(n=635)
- severe depression	1.6%	0.6%
- suicidal ideation	0.6%	0.3%
- non-fatal suicide attempts	0.4%	0%
- aggressive behaviour	0.4%	0.3%
- paranoid reactions	0.4%	0.3%
- manic reactions	0.1%	0%

Patients with a history of psychiatric disorders appear to be at greater risk of these serious psychiatric adverse reactions with frequencies of each of the above events ranging from 0.3% for manic reactions to 2.0% for both severe depression and suicidal ideation. There have also been post-marketing reports of death by suicide, delusions, psychosis-like behaviour and catatonia.
Nervous system symptoms
In clinical controlled trials, frequently reported adverse reactions included, but were not limited to dizziness, insomnia, somnolence, impaired concentration and abnormal dreaming. Nervous system symptoms of moderate-to-severe intensity were experienced by 19% (severe 2%) of patients compared to 9% (severe 1%) of patients receiving control regimens. In clinical studies 2% of patients treated with efavirenz discontinued therapy due to such symptoms.
Nervous system symptoms usually begin during the first one or two days of therapy and generally resolve after the first 2 - 4 weeks. In a study of uninfected volunteers, a representative nervous system symptom had a median time to onset of 1 hour post-dose and a median duration of 3 hours. 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 and can be recommended during the first weeks of therapy and in patients who continue to experience these symptoms (see section 4.2). Dose reduction or splitting the daily dose has not been shown to provide benefit.
Analysis of long-term data 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.

Ataxia and encephalopathy associated with high levels of efavirenz, occurring months to years after beginning efavirenz therapy have been reported post-marketing (see section 4.4).
Hepatic failure
A few of the post marketing reports of hepatic failure, including cases in patients with no pre-existing hepatic disease or other identifiable risk factors, were characterized by a fulminant course, progressing in some cases to transplantation or death.
Immune reactivation syndrome

*I*n HIV infected patients with severe immune deficiency at the time of initiation of combination antiretroviral therapy (CART), an inflammatory reaction to asymptomatic or residual opportunistic infections may arise. Autoimmune disorders (such as Graves' disease and autoimmunie hepatitis) have also been reported; however, the reported time to onset is more variable and these events can occur many months after initiation of treatment (see section 4.4).
Osteonecrosis
Cases of osteonecrosis have been reported, particularly in patients with generally acknowledged risk factors, advanced HIV disease or long-term exposure to combination antiretroviral therapy (CART). The frequency of this is unknown (see section 4.4).
Laboratory test abnormalities:
Liver enzymes: elevations of AST and ALT to greater than five times the upper limit of the normal range (ULN) were seen in 3% of 1,008 patients treated with 600 mg of efavirenz (5-8% after long-term treatment in study 006). Similar elevations were seen in patients treated with control regimens (5% after long- term treatment). Elevations of GGT to greater than five times ULN were observed in 4% of all patients treated with 600 mg of efavirenz and 1.5-2% of patients treated with control regimens (7% of efavirenz-treated patients and 3% of control-treated patients after long-term treatment). Isolated elevations of GGT in patients receiving efavirenz may reflect enzyme induction. In the long-term study (006), 1% of patients in each treatment arm discontinued because of liver or biliary system disorders.

Amylase: in the clinical trial subset of 1,008 patients, asymptomatic increases in serum amylase levels greater than 1.5 times the upper limit of normal 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.
Metabolic parameters
Weight and levels of blood lipids and glucose may increase during antiretroviral therapy (see section 4.4).
Paediatric population
Undesirable effects in children were generally similar to those of adult patients. Rash was reported more frequently in children (in a clinical study including 57 children who received efavirenz during a 48-week period, rash was reported in 46 %) and was more often of higher grade than in adults (severe rash was reported in 5.3 % of children). Prophylaxis with appropriate antihistamines prior to initiating
therapy with efavirenz in children may be considered. Although nervous system symptoms are difficult for young children to report, they appear to be less frequent in children and were generally mild. In the study of 57 children, 3.5 % of patients experienced nervous system symptoms of moderate intensity, predominantly dizziness. No child had severe symptoms or had to discontinue because of nervous system symptoms.
Other special populations
Liver enzymes in hepatitis B or C co-infected patients: in the long-term data set from study 006, 137 patients treated with efavirenz-containing regimens (median duration of therapy, 68 weeks) and 84 treated with a control regimen (median duration, 56 weeks) were seropositive at screening for hepatitis B (surface antigen positive) and/or C (hepatitis C antibody positive). Among co-infected patients in study 006, elevations in AST to greater than five times ULN developed in 13% of efavirenz-treated patients and in 7% of controls, and elevations in ALT to greater than five times ULN developed in 20% and 7%, respectively. Among co-infected patients, 3% of those treated with efavirenz and 2% in the control arm discontinued because of liver disorders (see section 4.4).
Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system: HPRA Pharmacovigilance; website: www.hpra.ie.

4.9 Overdose

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

Treatment of overdose with efavirenz should consist of general supportive measures, including monitoring of vital signs and observation of the patient's clinical status. 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.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antivirals for systemic use, non-nucleoside reverse transcriptase inhibitors.

ATC code: J05AG03

Mechanism of action

Efavirenz is a NNRTI of HIV-1. Efavirenz is a non-competitive inhibitor of HIV-1 reverse transcriptase (RT) and does not significantly inhibit HIV-2 RT or cellular DNA polymerases (α, β, γ or δ).

Cardiac electrophysiology

The effect of efavirenz on the QTc interval was evaluated in an open-label, positive and placebo controlled, fixed single sequence 3-period, 3-treatment crossover QT study in 58 healthy subjects enriched for CYP2B6 polymorphisms. The mean Cmax of efavirenz in subjects with CYP2B6 *6/*6 genotype following the administration of 600 mg daily dose for 14 days was 2.25-fold the mean Cmax observed in subjects with CYP2B6 *1/*1 genotype. A positive relationship between efavirenz concentration and QTc prolongation was observed. Based on the concentration-QTc relationship, the mean QTc prolongation and its upper bound 90% confidence interval are 8.7 ms and 11.3 ms in subjects with CYP2B6*6/*6 genotype following the administration of 600 mg daily dose for 14 days (see section 4.5).

Antiviral activity:

*T*he free concentration of efavirenz required for 90 to 95% inhibition of wild type or zidovudine-resistant laboratory and clinical isolates *in vitro* ranged from 0.46 to 6.8 nM in lymphoblastoid cell lines, peripheral blood mononuclear cells (PBMCs) and macrophage/monocyte cultures.

Resistance:

The potency of efavirenz in cell culture against viral variants with amino acid substitutions at positions 48, 108, 179, 181 or 236 in RT or variants with amino acid substitutions in the protease was similar to that observed against wild type viral strains. The single substitutions which led to the highest resistance to efavirenz in cell culture correspond to a leucine-to-isoleucine change at position 100 (L100I, 17 to 22-fold resistance) and a lysine-to-asparagine at position 103 (K103N, 18 to 33-fold resistance). Greater than 100-fold loss of susceptibility was observed against HIV variants expressing K103N in addition to other amino acid substitutions in RT.

K103N was the most frequently observed RT substitution in viral isolates from patients who experienced a significant rebound in viral load during clinical studies of efavirenz in combination with indinavir or zidovudine + lamivudine. This mutation was observed in 90% of patients receiving efavirenz with virological failure. 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. The pattern of amino acid substitutions in RT associated with resistance to efavirenz was independent of the other antiviral medications used in combination with efavirenz.

Cross resistance:

Cross resistance profiles for efavirenz, nevirapine and delavirdine in cell culture demonstrated that the K103N substitution confers loss of susceptibility to all three NNRTIs. Two of three delavirdine-resistant clinical isolates examined were cross-resistant to efavirenz and contained the K103N substitution. A third isolate which carried a substitution at position 236 of RT was not cross-resistant to efavirenz.

Viral isolates recovered from PBMCs of patients enrolled in efavirenz clinical studies who showed evidence of treatment failure (viral load rebound) were assessed for susceptibility to NNRTIs. Thirteen isolates previously characterised as efavirenz-resistant were also resistant to nevirapine and delavirdine. Five of these NNRTI-resistant isolates were found to have K103N or a valine-to-isoleucine substitution at position 108 (V108I) in RT. Three of the efavirenz treatment failure isolates tested remained sensitive to efavirenz in cell culture and were also sensitive to nevirapine and delavirdine.

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

Clinical efficacy:

Efavirenz has not been studied in controlled studies in patients with advanced HIV disease, namely with CD4 counts < 50 cells/mm3, or in PI or NNRTI experienced patients. Clinical experience in controlled studies with combinations including didanosine or zalcitabine is limited.

Two controlled studies (006 and ACTG 364) of approximately one year duration with efavirenz in combination with NRTIs and/or PIs, have demonstrated reduction of viral load below the limit of quantification of the assay and increased CD4 lymphocytes in antiretroviral therapy-naive and NRTI-experienced HIV-infected patients. Study 020 showed similar activity in NRTI-experienced patients over 24 weeks. In these studies the dose of efavirenz was 600 mg once daily; the dose of indinavir was 1,000 mg every 8 hours when used with efavirenz and 800 mg every 8 hours when used without efavirenz. The dose of nelfinavir was 750 mg given three times a day. The standard doses of NRTIs given every 12 hours were used in each of these studies.

Study 006, a randomized, open-label trial, compared efavirenz + zidovudine + lamivudine or efavirenz + indinavir with indinavir + zidovudine + lamivudine in 1,266 patients who were required to be efavirenz-, lamivudine-, NNRTI-, and PI-naive at study entry. The mean baseline CD4 cell count was 341 cells/mm3 and the mean baseline HIV-RNA level was 60,250 copies/mL. Efficacy results for study 006 on a subset of 614 patients who had been enrolled for at least 48 weeks are found in Table 2. In the analysis of responder rates (the non-completer equals failure analysis [NC = F]), patients who terminated the study early for any reason, or who had a missing HIV-RNA measurement that was either preceded or followed by a measurement above the limit of assay quantification were considered to have HIV-RNA above 50 or above 400 copies/mL at the missing time points.

Table 2 Efficacy results for study 006

Responder rates (NC = F[a]) Plasma HIV-RNA < 400 copies/mL (95% C.I.[b])		< 50 copies/mL (95% C.I.[b])		Mean change from baseline-CD4 cell count cells/mm^3 (S.E.M.[c])
Treatment Regimen[d]	n	48 weeks	48 weeks	48 weeks
EFV + ZDV + 3TC	202	67% (60%, 73%)	62% (55%, 69%)	187 (11.8)
EFV + IDV	206	54% (47%, 61%)	48% (41%, 55%)	177 (11.3)
IDV + ZDV + 3TC	206	45% (38%, 52%)	40% (34%, 47%)	153 (12.3)

[a] NC = F, noncompleter = failure.
[b] C.I., confidence interval.
[c] S.E.M., standard error of the mean.
[d] EFV, efavirenz; ZDV, zidovudine; 3TC, lamivudine; IDV, indinavir.

Long-term results at 168 weeks of study 006 (160 patients completed study on treatment with EFV+IDV, 196 patients with EFV+ZDV+3TC and 127 patients with IDV+ZDV+3TC, respectively), suggest durability of response in terms of proportions of patients with HIV RNA < 400 copies/mL, HIV RNA < 50 copies/mL and in terms of mean change from baseline CD4 cell count. Efficacy results for studies ACTG 364 and 020 are found in Table 3. Study ACTG 364 enrolled 196 patients who had been treated with NRTIs but not with PIs or NNRTIs. Study 020 enrolled 327 patients who had been treated with NRTIs but not with PIs or NNRTIs. Physicians were allowed to change their patient's NRTI regimen upon entry into the study. Responder rates were highest in patients who switched NRTIs.

Table 3 Efficacy results for studies ACTG 364 and 020

Responder rates (NC = F[a]) Plasma HIV-RNA						Mean change from baseline-CD4 cell count	
Study Number/ Treatment Regimens[b]	n	%	(95% C.I.[c])	%	(95% C.I.)	cells/mm^3	(S.E.M.[d])
Study ACTG 364 48 weeks		< 500 copies/mL		< 50 copies/mL			
EFV + NFV + NRTIs	65	70	(59, 82)			107	(17.9)
EFV + NRTIs	65	58	(46, 70)			114	(21.0)
NFV + NRTIs	66	30	(19, 42)			94	(13.6)
Study 020			< 400 copies/mL	< 50 copies/mL			
24 weeks							
EFV + IDV + NRTIs	157	60	(52, 68)	49	(41, 58)	104	(9.1)
IDV + NRTIs	170	51	(43, 59)	38	(30, 45)	77	(9.9)

[a] NC = F, noncompleter = failure.
[b] EFV, efavirenz; ZDV, zidovudine; 3TC, lamivudine; IDV, indinavir; NRTI, nucleoside reverse transcriptase inhibitor; NFV, nelfinavir.
[c] C.I., confidence interval for proportion of patients in response.
[d] S.E.M., standard error of the mean.
---, not performed.

Paediatric population:

ACTG 382 is an ongoing uncontrolled study of 57 NRTI-experienced paediatric patients (3 - 16 years) which characterises the pharmacokinetics, antiviral activity and safety of efavirenz in combination with nelfinavir (20 - 30 mg/kg given three times a day) and one or more NRTIs. The starting dose of efavirenz was the equivalent of a 600 mg dose (adjusted from calculated body size based on weight). The response rate, based on the NC = F analysis of the percentage of patients with plasma HIV-RNA < 400 copies/mL at 48 weeks was 60 % (95 %, C.I. 47, 72), and 53 % (C.I. 40, 66) based on percentage of patients with plasma HIV-RNA < 50 copies/mL. The mean CD4 cell counts were increased by 63 ± 34.5 cells/mm3 from baseline. The durability of the response was similar to that seen in adult patients.

5.2 Pharmacokinetic properties

Absorption
Peak efavirenz plasma concentrations of 1.6 - 9.1 µM were attained by 5 hours following single oral doses of 100 mg to 1,600 mg administered to uninfected volunteers. Dose related increases in C_{max} and AUC were seen for doses up to 1,600 mg; the increases were less than proportional suggesting diminished absorption at higher doses. Time to peak plasma concentrations (3 - 5 hours) did not change following multiple dosing and steady-state plasma concentrations were reached in 6 - 7 days.

In HIV infected patients at steady state, mean C_{max}, mean C_{min}, and mean AUC were linear with 200 mg, 400 mg, and 600 mg daily doses. In 35 patients receiving efavirenz 600 mg once daily, steady state C_{max} was 12.9 ± 3.7 µM (29%) [mean ± S.D. (% C.V.)], steady state C_{min} was 5.6 ± 3.2 µM (57%), and AUC was 184 ± 73 µM·h (40%).

Effect of food
The AUC and C_{max} of a single 600 mg dose of efavirenz film-coated tablets in uninfected volunteers was increased by 28% (90% CI: 22-33%) and 79% (90% CI: 58-102%), respectively, when given with a high fat meal, relative to when given under fasted conditions (see section 4.4).

Distribution
*E*favirenz is highly bound (approximately 99.5 - 99.75%) to human plasma proteins, predominantly albumin. In HIV-1 infected patients (n = 9) who received efavirenz 200 to 600 mg once daily for at least one month, cerebrospinal fluid concentrations ranged from 0.26 to 1.19% (mean 0.69%) of the corresponding plasma concentration. This proportion is approximately 3-fold higher than the non-protein-bound (free) fraction of efavirenz in plasma.

Biotransformation
*S*tudies 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 isozymes responsible for efavirenz metabolism and that it inhibited P450 isozymes 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 the 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 CYP3A4 and CYP2B6, resulting in the induction of its own metabolism, which may be clinically relevant in some patients. In uninfected volunteers, multiple doses of 200 - 400 mg per day for 10 days resulted in a lower than predicted extent of accumulation (22 - 42% lower) and a shorter terminal half-life compared with single dose administration (see below). Efavirenz has also been shown to induce UGT1A1. Exposures of raltegravir (a UGT1A1 substrate) are reduced in the presence of efavirenz (see section 4.5, table 1).

Although *in vitro* data suggest that efavirenz inhibits CYP2C9 and CYP2C19, there have been contradictory reports of both increased and decreased exposures to substrates of these enzymes when co-administered with efavirenz *in vivo*. The net effect of co-administration is not clear.

Elimination
*E*favirenz has a relatively long terminal half-life of at least 52 hours after single doses and 40 - 55 hours after multiple doses. Approximately 14 - 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.

Hepatic impairment
In a single-dose study, half-life was doubled in the single patient with severe hepatic impairment (Child Pugh Class C), indicating a potential for a much greater degree of accumulation. A multiple-dose study showed no significant effect on efavirenz pharmacokinetics in patients with mild hepatic impairment (Child-Pugh Class A) compared with controls. There were insufficient data to determine whether moderate or severe hepatic impairment (Child-Pugh Class B or C) affects efavirenz pharmacokinetics.

Gender, race, elderly:
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 in the elderly.

Paediatric population
In 49 paediatric patients receiving the equivalent of a 600 mg dose of efavirenz (dose adjusted from calculated body size based on weight), steady state Cmax was 14.1 mM, steady state Cmin was 5.6 mM, and AUC was 216 mM ·h. The pharmacokinetics of efavirenz in paediatric patients were similar to adults.

5.3 Preclinical safety data

Efavirenz was not mutagenic or clastogenic in conventional genotoxicity assays.

Efavirenz induced foetal resorptions in rats. 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, microophthalmia was observed in another foetus, and cleft palate was observed in a third foetus. No malformations were observed in foetuses from efavirenz-treated rats and rabbits.

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).

Carcinogenicity studies 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 in male mice, 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.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

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

Film-coating:
Hypromellose (E464)
Quinoline yellow aluminium lake (E104)
Titanium dioxide (E171)
Macrogol
Iron oxide red (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years.

After first opening of the bottle: 2 months.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

- HDPE bottles with a child-resistant polypropylene closure sealed with liner and containing a silica gel packet
- White opaque PVC/Aclar/Al blisters

Pack sizes:
- Bottle packs: 30 or 90 (3x30) film-coated tablets.
- Blister packs: 10, 28, 30, 84 or 90 film-coated tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

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

7 MARKETING AUTHORISATION HOLDER

Rowex Ltd
Newtown
Bantry
Co. Cork
Ireland

8 MARKETING AUTHORISATION NUMBER

PA0711/207/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 25th October 2013
Date of last renewal: 2nd July 2018

10 DATE OF REVISION OF THE TEXT

January 2024