1.3.1.1 Proposed Professional Information for medicines for human use - clean

SCHEDULING STATUS

S4

1 NAME OF THE MEDICINE

EFRIN (film-coated tablet)

2 QUALITIVE AND QUANTITIVE COMPOSITION

Each film-coated tablet contains 600 mg efavirenz

Contains sugar: Lactose monohydrate 255, 60 mg

3 PHARMACEUTICAL FORM

Peach coloured, capsule shaped, film-coated tablets, debossed with “M109” on one side and plain on the other side.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

EFRIN in combination with other antiretroviral medicines is indicated for the treatment of HIV-1 infected adults and children weighing greater or equal to 40 kg.

4.2 Posology and method of administration

Posology

The therapy should be initiated by a medical practitioner experienced in the management of HIV infection.

Dosage:

Adults:

The recommended dosage of EFRIN in combination with a protease inhibitor, and/or nucleoside analogue reverse transcriptase inhibitors (NRTIs) is 600 mg orally, once daily.

In order to improve the tolerability of nervous system side effects, bedtime dosing is recommended during the first two to four weeks of therapy and in patients who continue to experience these symptoms (*see section 4.8*).

Concomitant Antiretroviral Therapy:

EFRIN must be given in combination with other antiretroviral medications (*see section 4.5*).

Special populations

Children weighing greater than or equal to 40 kg:

- The recommended dosage of EFRIN in combination with a protease inhibitor, and/or nucleoside analogue reverse transcriptase inhibitors (NRTIs) is 600 mg orally, once daily.
- EFRIN should only be administered to children who are able to reliably swallow tablets.
- EFRIN should not be used in adults and children weighing less than 40 kg.

Method of administration

For oral use.

EFRIN may be taken with or without food, preferably at bedtime *(see section 4.4).*

Contraindications

- EFRIN is contraindicated in patients with hypersensitivity to efavirenz or any of the excipients of EFRIN.
- EFRIN should not be administered concurrently with cisapride, midazolam, triazolam or ergot derivatives because competition for CYP3A4 by efavirenz could result in inhibition of metabolism of these medicines and create the potential for serious and/or life-threatening adverse events (e.g. cardiac dysrhythmias, prolonged sedation or respiratory depression).
- Pregnancy and lactation (*see section 4.6*).
- EFRIN is contraindicated in adults and children weighing less than 40 kg.
- A history of previous liver injury/ failure with efavirenz containing antiretroviral treatment (ART).

- Patients with severe hepatic impairment (Child Pugh Grade C) *(see section 5.2).*
- Co-administration with elbasvir (EBR) and grazoprevir (GZR) due to the potential for significant decreases in plasma concentrations of EBR and GZR (*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 dysrhythmia or with clinically relevant bradycardia or with congestive cardiac failure accompanied by reduced left ventricle ejection fraction.
    - severe disturbances of electrolyte balance e.g. hypokalemia or hypomagnesemia.
- Patients taking medicines that are known to prolong the QTc interval (prodysrhythmic). These medicines include:
    - antidysrhythmic of classes IA and III,
    - neuroleptics, antidepressive medicines,
    - certain antibiotics including some medicines of the following classes: macrolides, fluoroquinolones, imidazole and triazole antifungal medicines,
    - certain non-sedating antihistamines (terfenadine),
    - cisapride,
    - flecainide,
    - certain antimalarials,
    - methadone.

4.4 Special warnings and precautions for use

Resistant human immuno-virus (HIV) strains emerge rapidly when EFRIN is administered as monotherapy, therefore, EFRIN must not be used as a single medicine to treat HIV or added on as a sole medicine to a failing regimen.

When prescribing medications concomitantly with EFRIN, medical practitioners should refer to the corresponding manufacturer's medicine package insert.

If any antiretroviral medication in a combination regimen is interrupted because of e.g. suspected intolerance, serious consideration should be given to simultaneous discontinuation of all antiretroviral medications. The antiretroviral medications should be restarted at the same time upon resolution of the intolerance symptoms. Intermittent monotherapy and sequential reintroduction of antiretroviral medicines is not advisable because of the increased potential for selection of medicine-resistant mutant virus.

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

Coadministration of sofosbuvir/velpatasvir with efavirenz is not recommended *(see section 4.5).*
Concomitant administration of velpatasvir/sofosbuvir/ voxilaprevir with EFRIN is not recommended *(see section 4.5).*

Coadministration of glecaprevir/pibrentasvir with efavirenz may significantly decrease plasma concentrations of glecaprevir and pibrentasvir, leading to reduced therapeutic effect.
Coadministration 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).*

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

Skin Rash:

Mild-to-moderate rash has been reported with EFRIN use and usually resolves with continued therapy. Appropriate antihistamines and/or corticosteroids may improve the tolerability and hasten the resolution of rash. EFRIN should be discontinued in patients developing severe rash associated with blistering, desquamation, mucosal involvement or fever. If therapy with EFRIN is discontinued, consideration should also be given to interrupting therapy with other antiretroviral medicine to avoid development of resistant virus (*see section 4.8*).

Prophylaxis with appropriate antihistamines prior to initiating therapy with EFRIN in children may be considered.

EFRIN is not recommended for patients who have had a life-threatening cutaneous reaction (e.g., Stevens-Johnson syndrome) while taking another NNRTI.

Psychiatric symptoms:

Psychiatric adverse reactions have been reported in patients treated with EFRIN. 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 EFRIN, and if so, to determine whether the risks of continued therapy outweigh the benefits *(see section 4.8).*

Nervous System Symptoms:

Nervous system symptoms have been reported with EFRIN use (*see section 4.8*). In addition, there have been reports of inappropriate behaviour (including aggressive reactions), predominantly in patients with a history of mental illness or substance abuse.

Seizures:

Convulsions have been observed in adult and paediatric patients receiving EFRIN, 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 medicine interaction study, carbamazepine plasma concentrations were decreased when carbamazepine was coadministered with efavirenz as contained in EFRIN (*see section 4.5*). Caution must be taken in any patient with a history of seizures.

QTc Prolongation:

QTc prolongation has been observed with the use of EFRIN *(see sections 4.5 and 5.1).* Consider alternatives to efavirenz for coadministration with a medicine 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 EFRIN 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 EFRIN be taken on an empty stomach, preferably at bedtime.

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 lifestyle. For monitoring of blood lipids and glucose reference is made to established HIV treatment guidelines. Lipid disorders should be managed as clinically appropriate.

Lipodystrophy and metabolic abnormalities:

Combination antiretroviral therapy has been associated with the redistribution/accumulation of body fat, including central obesity, dorso-cervical fat, enlargement (buffalo hump), peripheral wasting, facial wasting, breast enlargement, and elevated serum lipid and glucose levels in HIV patients. Clinical examination should include evaluation for physical signs of fat redistribution. Patients with evidence of lipodystrophy should have a thorough cardiovascular risk assessment.

Immune Reconstitution Inflammatory Syndrome:

Immune reconstitution inflammatory syndrome (IRIS) is an immunopathological response resulting from the rapid restoration of pathogen-specific immune responses to pre-existing antigens combined with immune dysregulation, which occurs shortly after starting combination Anti-Retroviral Therapy (cART). Typically such reaction presents by paradoxical deterioration of opportunistic infections being treated or with unmasking of an asymptomatic opportunistic disease, often with an atypical inflammatory presentation. IRIS usually develops within the first three months of initiation of ART and occurs more commonly in patients with low CD4 counts. Common examples of IRIS reactions to opportunistic diseases are tuberculosis, cytomegalovirus retinitis, and cryptococcal meningitis. Appropriate treatment of the opportunistic disease should be instituted or continued and ART continued. Inflammatory manifestations generally subside after a few weeks. Severe cases may respond to glucocorticoids, but there is only limited evidence for this in patients with tuberculosis IRIS. Autoimmune disorders (such as Graves' disease) have also been reported as IRIS reactions; however, the reported time to onset is more variable and these events can occur many months after initiation of treatment.

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.

Opportunistic infections:

Patients receiving EFRIN should be advised that they may continue to develop opportunistic infections and other complications of HIV infection, and therefore they should remain under close observation by healthcare professionals experienced in the treatment of patients with associated HIV disease. Regular monitoring of viral load and CD4 counts needs to be done.

The risk of HIV transmission to others:

Patients should be advised that current antiretroviral therapy, including EFRIN, does not prevent the risk of transmission of HIV to others through sexual contact or blood contamination. Appropriate precautions should continue to be employed.

Cholesterol:

Monitoring of cholesterol and triglycerides should be considered in patients treated with EFRIN (*see section 4.8*).

Special Populations:

Because of the extensive cytochrome P450-mediated metabolism of EFRIN and limited clinical experience in patients with chronic liver disease, caution should be exercised in administering EFRIN to patients with liver disease.

Liver Enzymes:

In patients with known or suspected history of Hepatitis B or C infection and in patients treated with other medications associated with liver toxicity, monitoring of liver enzymes is recommended. In patients with persistent elevations of serum transaminases to greater than 5 times the upper limit of the normal range, the benefit of continued therapy with EFRIN needs to be weighed against the unknown risks of significant liver toxicity (*see section 4.8*).

Hepatic side effects:

There is some evidence that efavirenz that is associated with three clinical pathological patterns of drug induced liver failure in HIV positive patients of which the sub massive necrosis histological pattern seems to be associated with a high morbidity or mortality risk and may present many months after therapy has been initiated or even stopped. Risk factors include younger age, CD+ counts ≥ 350 cells/ µl and female gender. Patients on EFRIN or efavirenz containing antiretroviral treatment (ART should be regularly monitored for jaundice (including a laboratory bilirubin and liver enzymes) and bleeding tendencies.

EFRIN is not recommended in patients with moderate to severe hepatic impairment *(see section 4.3)*.

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 as contained in EFRIN 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:

EFRIN has not been studied in paediatric patients below 3 years of age or who weigh less than 13 kg *(see section 4.2).*

EFRIN contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp-lactase deficiency, or glucose-galactose malabsorption, should not take EFRIN.

4.5 Interaction with other medicines and other forms of Interaction

EFRIN is an inducer of CYP3A4. Other compounds that are substrates of CYP3A4 may have decreased plasma concentrations when co-administered with EFRIN.

EFRIN exposure may be increased when given with medicines (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 EFRIN. 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).*

QT Prolonging Drugs:

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

Saquinavir:

When saquinavir (1,200 mg given 3 times a day, soft capsule formulation) was given with efavirenz the saquinavir AUC and C_{max} were decreased by 62 % and 50 % respectively. Use of EFRIN in combination with saquinavir as the sole protease inhibitor is not recommended.

Oral contraceptives:

Only the ethinyl oestradiol component of oral contraceptives has been studied. The AUC following a single dose of ethinyl oestradiol was increased (37 %) after multiple dosing of efavirenz. No significant changes were observed in Cmax of ethinyl oestradiol. The clinical significance of these effects is not known. No effect of a single dose of ethinyl oestradiol on efavirenz Cmax or AUC was observed. Because the potential interaction of EFRIN with oral contraceptives has not been

fully characterised, a reliable method of barrier contraception must be used in addition to oral contraceptives *(see section 4.6).*

Contraindications of concomitant use:

EFRIN must not be administered concurrently with terfenadine, 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).*

Elbasvir/grazoprevir:

Concomitant administration of EFRIN 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. *(see section 4.3).*

St. John's Wort (Hypericum perforatum):

Patients on EFRIN should not concomitantly use products containing St. John's Wort *(Hypericum perforatum)* since it may be expected to result in reduced plasma concentrations of EFRIN. This effect is due to an induction of CYP3A4 and may result in loss of therapeutic effect and development of resistance.

Metamizole:

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

Cannabinoid Test interaction:

Efavirenz does not bind to cannabinoid receptors. False positive urine cannabinoid test results have been reported in uninfected volunteers who received EFRIN. 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.

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, C_{max} , C_{min} with confidence intervals if available[a] (mechanism)**	**Recommendation concerning co-administration with efavirenz**
ANTI-INFECTIVES		
HIV antivirals		
Protease inhibitors (PI)		
Atazanavir/ritonavir/Efavirenz (400 mg once daily/100 mg once daily/600 mg once daily, all administered with food)	Atazanavir (pm): AUC: ↔* (↓ 9 to ↑10) C_{max} : ↑17%* (↑8 to ↑27) C_{min} : ↓ 42%* (↓ 31 to ↓ 51)	Co-administration of efavirenz with atazanavir/ritonavir is not recommended. If the co-administration of atazanavir with an 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) C_{max} : ↔*/** (↓ 5 to ↑26) C_{min} : ↑ 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 C_{min} 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% C_{min} : ↓ 31% C_{max} : ↓ 15% (CYP3A4 induction) Efavirenz: AUC: ↑ 21% C_{min} : ↑ 17% C_{max} : ↑ 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) C_{min} : ↓ 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.
Indinavir/ritonavir/Efavirenz (800 mg twice daily/100 mg twice daily/600 mg once daily)	Indinavir: AUC: ↓ 25% (↓ 16 to ↓ 32) [b] C_{max} : ↓ 17% (↓ 6 to ↓ 26)[b] C_{min} : ↓ 50% (↓ 40 to ↓ 59)[b] Efavirenz: No clinically significant pharmacokinetic interaction The geometric mean C_{min} for indinavir (0.33 mg/l) when given with ritonavir and efavirenz was higher than the mean historical C_{min} (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	No dose adjustment is necessary for efavirenz when given with indinavir or indinavir/ritonavir. See also ritonavir row below.

	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 or oral 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 of lopinavir/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) C_{max} : ↑ 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 C_{max} : ↑ 24% (↑ 12 to ↑ 38) Evening C_{max} : ↔ Morning C_{min} : ↑ 42% (↑ 9 to ↑ 86) [b] Evening C_{min} : ↑ 24% (↑ 3 to ↑ 50) [b] Efavirenz: AUC: ↑ 21% (↑ 10 to ↑ 34) C_{max} : ↑ 14% (↑ 4 to ↑ 26) C_{min} : ↑ 25% (↑ 7 to ↑ 46) [b] (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.	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.
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: AUC_{12} : ↓45% (↓ 38 to ↓51) C_{max} : ↓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% C_{12} : ↓21% C_{max} : ↓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. 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%* C_{max}: ↔ 8% C_{min}: ↓44% Efavirenz: AUC: ↔ 20%* C_{max}: ↔ 11% CYP3A induction – effect on boceprevir *0 – 8 hours No effect (↔) equals a decrease in mean ratio estimate of ≤ 20% or	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.

	increase in mean ratio estimate of ≤ 25%	
Telaprevir/Efavirenz (1,125 mg q8h/600 mg once daily)	Telaprevir (relative to 750 mg q8h): AUC: ↓ 18% (↓ 8 to ↓ 27) C_{max}: ↓ 14% (↓ 3 to ↓ 24) C_{min}: ↓ 25% (↓ 14 to ↓ 34)% Efavirenz: AUC: ↓ 18% (↓ 10 to ↓ 26) C_{max}: ↓ 24% (↓ 15 to ↓ 32) C_{min}: ↓ 10% (↓ 1 to ↓ 19)% (CYP3A induction by efavirenz)	If efavirenz and telaprevir are co-administered, telaprevir 1,125 mg every 8 hours should be used.
Simeprevir/Efavirenz (150 mg once daily /600 mg once daily)	Simeprevir: AUC: ↓71% (↓67 to ↓74) C_{max}: ↓51% (↓46 to ↓56) C_{min}: ↓91% (↓88 to ↓92) Efavirenz: AUC: ↔ C_{max}: ↔ C_{min}: ↔ 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-administration 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. Coadministration 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. Coadministration 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) C_{max}: ↓26% (↓ 15 to ↓35) Clarithromycin 14 ⁻hydroxymetabolite:	The clinical significance of these changes in clarithromycin plasma levels is not known. Alternatives to clarithromycin (e.g.

	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.	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) 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 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 (600 mg once daily/600 mg once daily)	Efavirenz: AUC: ↓ 26% (↓ 15 to ↓ 36) C_{max} : ↓ 20% (↓ 11 to ↓ 28) C_{min} : ↓ 32% (↓ 15 to ↓ 46) (CYP3A4 and CYP2B6 induction)	When taken with rifampicin in patients weighing 50 kg or 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, including 600 mg.
Antifungals		
Itraconazole/Efavirenz	Itraconazole:	Since no dose

(200 mg q12h/600 mg once daily)	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: No clinically significant pharmacokinetic change.	recommendation for itraconazole can be made, alternative antifungal treatment should be considered.
Posaconazole/Efavirenz --/400 mg once daily	Posaconazole: AUC: ↓ 50% C_{max} : ↓ 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/Efavirenz (400 mg twice daily/300 mg once daily)	Voriconazole: AUC: ↓77% C_{max} : ↓ 61% Efavirenz: AUC: ↑ 44% C_{max} : ↑ 38% Voriconazole: AUC: ↓ 7% (↓ 23 to ↑ 13) * C_{max} : ↑ 23% (↓ 1 to ↑ 53) * Efavirenz: AUC: ↑ 17% (↑ 6 to ↑ 29) ** C_{max} : ↔** *compared to 200 mg twice daily alone ** compared to 600 mg once daily alone (competitive inhibition of oxidative metabolism)	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
Fluconazole/Efavirenz (200 mg once daily/400 mg once daily)	No clinically significant pharmacokinetic interaction	No dose adjustment is necessary for either medicinal product.
Ketoconazole and other imidazole antifungals	Interaction not studied	No data are available to make a dose recommendation.
ANTIMALARIALS		
Artemether/lumefantrine/ Efavirenz (20/120 mg tablet, 6 doses of 4 tablets each over 3 days/600mg once daily)	Artemether: AUC: ↓ 51% C_{max}: ↓ 21% Dihydroartemisinin: AUC: ↓ 46% C_{max}: ↓ 38% Lumefantrine: AUC: ↓ 21%	Since decreased concentrations of artemether, dihydroartemisinin, or lumefantrine may result in a decrease of antimalarial efficacy, caution is

	C_{max}: ↔ Efavirenz: AUC: ↓ 17% C_{max}: ↔ (CYP3A4 induction)	recommended when efavirenz and artemether/lumefantrine tablets are co-administered.
Atovaquone and proguanil hydrochlorothiazide/Efavirenz (250/100 mg single dose/600 mg once daily)	Atovaquone: AUC: ↓ 75% (↓ 62 to ↓ 84) C_{max}: ↓ 44% (↓ 20 to ↓ 61) Proguanil: AUC: ↓ 43% (↓ 7 to ↓ 65) C_{max}: ↔	Concomitant administration of atovaquone/proguanil with efavirenz should be avoided whenever possible.
ACID REDUCING MEDICINES		
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 MEDICINES		
Lorazepam/Efavirenz (2 mg single dose/600 mg once daily)	Lorazepam: AUC: ↑ 7% (↑ 1 to ↑ 14) C_{max} : ↑ 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 or acenocoumarol are potentially increased or decreased by efavirenz.	Dose adjustment of warfarin or acenocoumarol may be required.
ANTICONVULSANTS		
Carbamazepine/Efavirenz (400 mg once daily/600 mg once daily)	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) The steady-state AUC, C_{max} and C_{min} of the active carbamazepine epoxide metabolite remained	No dose recommendation can be made. An alternative anticonvulsant should be considered. Carbamazepine plasma levels should be monitored periodically.

	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 as efavirenz.	No dose adjustment is necessary for any of these medicinal products.
ANTIDEPRESSANTS		
Selective Serotonin Reuptake Inhibitors (SSRIs)		
Sertraline/Efavirenz (50 mg once daily/600 mg once daily)	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)	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	No dose adjustment is necessary for either medicinal product.

	expected for fluoxetine.	
NOREPINEPHRINE AND DOPAMINE REUPTAKE INHIBITOR		
Bupropion/Efavirenz [150 mg single dose (sustained release)/600 mg once daily]	Bupropion: AUC: ↓ 55% (↓ 48 to ↓ 62) C_{max}: ↓ 34% (↓ 21 to ↓ 47) Hydroxybupropion: AUC: ↔ C_{max}: ↑ 50% (↑ 20 to ↑ 80) (CYP2B6 induction)	Increases in bupropion dosage 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: ↔ C_{max} : ↓ 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 MEDICINES		
Calcium Channel Blockers		
Diltiazem/Efavirenz (240 mg once daily/600 mg once daily)	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 should be guided by clinical response (refer to the Summary of Product Characteristics for diltiazem). No dose adjustment is necessary for efavirenz.
Verapamil, Felodipine, Nifedipine and Nicardipine	Interaction not studied. When efavirenz is co-administered with a calcium channel blocker	Dose adjustments of calcium channel blockers should be guided by clinical

	that is a substrate of the CYP3A4 enzyme, there is a potential for reduction in the plasma concentrations of the calcium channel blocker.	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) 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. Dose adjustment of atorvastatin may be required (refer to the Summary of Product Characteristics for atorvastatin. No dose adjustment is necessary for efavirenz.
Pravastatin/Efavirenz (40 mg once daily/600 mg once daily)	Pravastatin: AUC: ↓40% (↓ 26 to ↓57) C_{max} : ↓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) 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) (CYP3A4 induction) Co-administration of efavirenz with atorvastatin, pravastatin, or simvastatin did not affect efavirenz AUC or C_{max} 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	No dose adjustment is necessary for either medicinal product.

	interaction with efavirenz is not expected.	
HORMONAL CONTRACEPTIVES		
Oral: Ethinyloestradiol + Norgestimate/ Efavirenz (0.035 mg + 0.25 mg once daily/600 mg once daily)	Ethinyloestradiol: AUC: ↔ C_{max} : ↔ C_{min} : ↓ 8% (↑ 14 to ↓ 25) Norelgestromin (active metabolite): AUC: ↓ 64% (↓ 62 to ↓ 67) C_{max} : ↓ 46% (↓ 39 to ↓ 52) C_{min} : ↓ 82% (↓ 79 to ↓ 85) Levonorgestrel (active metabolite): AUC: ↓ 83% (↓ 79 to ↓ 87) C_{max} : ↓ 80% (↓ 77 to ↓ 83) C_{min} : ↓ 86% (↓ 80 to ↓ 90) (induction of metabolism) Efavirenz: no clinically significant interaction. The clinical significance of these effects is not known.	A reliable method of barrier contraception must be used in addition to hormonal contraceptives (see section 4.6).
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.
OPIOIDS		
Methadone/Efavirenz (stable maintenance, 35-100 mg once daily/600 mg once daily)	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.	Concomitant use with methadone is contraindicated (*see section 4.3*).
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.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential/ Contraception in males and females

Women of childbearing potential should undergo pregnancy testing prior to initiation of EFRIN (*see section 4.3*). Barrier contraception should always be used in combination with other methods of contraception (oral or other hormonal contraceptives e.g. injectable or implant contraception)

(*see section 4.3*). Because of the long half-life of efavirenz, use of adequate contraceptive measures for 12 weeks after discontinuation of efavirenz is recommended.

Pregnancy

The use of EFRIN during pregnancy contraindicated as teratogenicity has been noted. Malformations have been observed in foetuses from efavirenz-treated monkeys that received doses, which resulted in plasma concentrations similar to those in humans given 600 mg/day; therefore pregnancy should be avoided in women receiving EFRIN.

Breastfeeding

The safety in lactation has not been established. Since animal data suggest that the substance may be passed into breast milk, it is recommended that mothers taking EFRIN do not breastfeed their infants.

4.7 Effects on ability to drive and use machines

EFRIN may cause dizziness, impaired concentration, and/or drowsiness. 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

a. Summary of the safety profile

The most frequently reported adverse reactions of EFRIN of at least moderate severity reported were rash, dizziness, nausea, headache and fatigue. The most notable adverse reactions associated with EFRIN 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 EFRIN. The administration of EFRIN with food may increase efavirenz exposure and may lead to an increase in the frequency of adverse reactions (*see section 4.4).*

357 **Tabulated list of adverse reactions**

Body System	**Undesirable effect**		
	Frequent	Less frequent	Frequency not known
Immune system disorders:		allergic reaction, erythema multiforme, Stevens-Johnson syndrome immuno-allergic reaction liver injury/failure [1]	
Endocrine disorders:		pancreatitis	
Metabolism and nutrition disorders:	Hypertriglyceridaemia[2]	anorexia hypercholesterolaemia[2]	increased appetite; redistribution/accumulation of body fat; weight gain and weight loss
Psychiatric disorders:	insomnia abnormal dreams, anxiety, depression[2]	abnormal thinking; agitation; aggravated depression; amnesia; anxiety; apathy; confusion; delirium; emotional lability; euphoria; hallucinations; psychosis; stupor; mania; suicide attempt; suicide ideation; catatonia[2]	neurosis; paranoid reactions; completed suicide[2]
Nervous system disorders:	dizziness; fatigue; headache; impaired concentration; somnolence	ataxia; convulsions; impaired co-ordination; malaise; neuralgia; peripheral neuropathy	abnormal co-ordination; hypo-aesthesia; neuropathy and pain; paraesthesia; speech disorder; tremor
Eye disorders:		abnormal vision	
Ear and labyrinth disorders:		tinnitus, vertigo	
Cardiac disorders:		palpitations and tachycardia	
Vascular disorders:		flushing	hot flushes
Respiratory, thoracic and mediastinal disorders:		asthma	dyspnoea; sinusitis; upper respiratory tract infections
Gastrointestinal disorders:	nausea; vomiting; taste perversion	abdominal pain and gastroesophageal reflux	constipation; diarrhoea; dyspepsia; gastritis; gastroenteritis;

			malabsorption pancreatitis[2]
Hepato-biliary disorders:	aspartate amino transferase (AST) increased, alanine aminotransferase (ALT) increased, gammaglutamyltransferase (GGT) increased	hepatitis and hepatic enzyme increase	hepatic failure
Skin and subcutaneous tissue disorders:	pruritus; rash	alopecia; eczema; folliculitis; skin exfoliation and urticarial; Stevens-Johnson syndrome[2]	acne; increased sweating; nail disorders; seborrhoea; skin discolouration
Musculoskeletal, connective tissue and bone disorders:	arthralgia and myalgia		Myopathy, osteonecrosis
Reproductive system and breast disorders:		gynaecomastia[2]	decreased libido; increased libido; impotence
Congenital and familial/genetic disorders:			
General disorders and administrative site conditions:	fatigue	asthenia	alcohol intolerance; influenza-like symptoms

Description of selected adverse reactions

Rashes are usually mild to moderate maculopapular skin eruptions that occur within the first two weeks of initiating therapy with EFRIN. In most patients rash resolves with continuing therapy with EFRIN within one month. EFRIN can be reinitiated in patients interrupting therapy because of rash. Use of appropriate antihistamines and/or corticosteroids is recommended when EFRIN is restarted.

Experience with EFRIN in patients who discontinued other antiretroviral medicines ~~medicines~~ 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 %.

Psychiatric symptoms:

Serious psychiatric adverse reactions have been reported in patients treated with EFRIN.

Specific serious psychiatric events:

- severe depression
- suicidal ideation
- non-fatal suicide attempts
- aggressive behaviour
- paranoid reactions
- manic reactions

Patients with a history of psychiatric disorders appear to be at greater risk of these serious psychiatric adverse reactions. 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 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.

Laboratory abnormalities:

Liver enzymes:

Raised liver enzyme values have occurred, particularly in patients with viral hepatitis. Raised serum-cholesterol and triglyceride concentrations have been reported.

Elevations of AST and ALT were seen in patients treated with 600 mg of EFRIN. Elevations of GGT to greater than 5 times the upper limit of the normal range were observed in patients treated with 600 mg EFRIN and in a greater percentage in patients seropositive for Hepatitis B or C.

Lipids:

An increase in total cholesterol of 10 to 20 % has been observed in uninfected volunteers receiving efavirenz. Increases in non-fasting total cholesterol and HDL of approximately 20 % and 25 % respectively were observed in patients treated with efavirenz+SDV+3TC, and of approximately 40 % and 35 % in patients treated with efavirenz+IDV. The effects of efavirenz on triglycerides and LDL were not well-characterised. The clinical significance of these findings is unknown (*see section 4.4*).

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 treated with EFRIN and was more often of higher grade than in adults. Prophylaxis with appropriate antihistamines prior to initiating therapy with EFRIN in children may be considered.

Other special populations:

Liver enzymes in hepatitis B or C co-infected patients:

Patients treated with efavirenz-containing regimens, as contained in EFRIN, were seropositive at screening for hepatitis B (surface antigen positive) and/or C (hepatitis C antibody positive).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions to SAHPRA via the “Report Drug Reaction Process”, found online under SAHPRA’s safety publications: https://www.sahpra.org.za/

4.9 Overdose

In overdose, side effects can be precipitated and/or be of increased severity *(see section 4.8).*

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

Administration of activated charcoal may be used to aid removal of unabsorbed substance. There is no specific antidote for overdose with EFRIN. Since EFRIN is highly protein bound, dialysis is unlikely to significantly remove the medicine from blood.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

A.20.2.8 Antiviral medicines

Pharmacotherapeutic group: Antivirals for systemic use, non-nucleoside reverse transcriptase inhibitors. ATC code: J05AG03

Mechanism of action:

Efavirenz is a selective non-nucleoside reverse transcriptase inhibitor (NNRTI) of human immunodeficiency virus type 1 HIV-1. Efavirenz is a non-competitive inhibitor of HIV-1 reverse transcriptase (RT) with respect to template, primer or nucleoside triphosphates, with a small

component of competitive inhibition. HIV-2 RT and human cellular DNA polymerases alpha, beta, gamma and delta are not inhibited by concentrations of efavirenz.

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 1600 mg administered to uninfected volunteers. Dose-related increases in Cmax and AUC were seen for doses up to 1600 mg; the increases were less than proportional suggesting diminished absorption at higher doses.

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 and steady state was reached in 6 to 10 days, in 35 patients receiving efavirenz 600 mg once daily, steady-state C_{max} was 12,9 µM, steady state C_{min} was 5,6 µM, and AUC was 184 µM•h.

Distribution:

Efavirenz is highly bound (approximately 99,5 – 99,75 %) to human plasma proteins, predominantly albumin. In HIV-1 infected patients 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 three-fold higher than the non-protein-bound (free) fraction of efavirenz in plasma.

Metabolism:

Efavirenz is principally metabolised by the cytochrome P450 system to hydroxylated metabolites with subsequent glucuronidation of these hydroxylated metabolites. These metabolites are inactive against HIV-1. CYP3A4 and CYP2B6 are the major isozymes responsible for efavirenz metabolism. Efavirenz has been shown to induce P450 enzymes, resulting in the induction of its own metabolism.

Elimination:

Efavirenz has a long terminal half-life of 52 to 76 hours after single doses, and 40-55 hours after multiple doses. Approximately 14 -34 % of a radio-labelled dose of efavirenz was recovered in the urine and 16-61 % was recovered in faeces, mainly in the form of metabolites.

Special populations:

Hepatic impairment:

The pharmacokinetics of efavirenz has not been adequately studied in patients with hepatic impairment (*see section 4.4*).

Renal impairment:

The pharmacokinetics of efavirenz has not been studied in patients with renal insufficiency. However, less than 1 % of efavirenz is excreted unchanged in the urine, so the impact of renal impairment on efavirenz elimination should be minimal.

Geriatric use:

Pharmacokinetics of efavirenz has not been studied in subjects aged 65 and over to establish whether they respond differently.

Paediatric use:

The pharmacokinetics of efavirenz in paediatric patients was similar to adults.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Cellulose microcrystalline, croscarmellose sodium, hydroxypropyl cellulose, sodium lauryl sulfate, lactose, magnesium stearate, film-coat {hypromellose, titanium dioxide, macrogol/PEG 400, iron oxide yellow, iron oxide red}.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

Store at or below 30 °C.

Store in the original container.

Do not remove from the carton until required for use.

Keep the bottle tightly closed.

6.5 Nature and contents of container

EFRIN is packed in high density polypropylene (HDPE) bottle pack (marketable pack) comprising of wide mouth white HDPE bottle with a white opaque polypropylene (PP) closure with induction sealing in pack sizes of 30's packed in a carton.

6.6 Special precautions for disposal of a used medicine or waste materials derived from such medicine and other handling of the product

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

7 THE HOLDER OF THE CERTIFICATE OF REGISTRATION

Viatris Healthcare (Pty) Ltd

4 Brewery Street, Isando,

Johannesburg, 1600,

Gauteng, South Africa

REGISTRATION NUMBERS

45/20.2.8/0169

DATE OF PACKAGE INSERT DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

20 April 2012

10 DATE OF REVISION OF TEXT

17 October 2022