PROFESSIONAL INFORMATION MAY 2023

SCHEDULING STATUS: S4

1. NAME OF THE MEDICINE

MACLEODS EFAVIRENZ 600 mg tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 600 mg of efavirenz.

Contains sugar (lactose monohydrate – 400 mg).

Excipients:

This medicine contains less than 1 mmol sodium (23mg) per tablet that is to say is essentially 'sodium free'.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Yellow capsule shaped, biconvex, film coated tablets engraved with "ML 12" on one side and plain on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

MACLEODS EFAVIRENZ 600 mg tablets are indicated in combination with other antiretroviral agents for treatment of HIV-1 infected adults, adolescents and children weighing greater than or equal to 40 kg.

4.2 Posology and method of administration

Posology

Adults

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

It is recommended that MACLEODS EFAVIRENZ 600 mg be taken on an empty stomach, preferably at bedtime. A high fat meal may increase the absorption of MACLEODS EFAVIRENZ 600 mg and should be avoided.

Concomitant antiretroviral therapy

MACLEODS EFAVIRENZ 600 mg must be given in combination with other antiretroviral medications (see **INTERACTIONS**).

Adolescents and children (17 years and under)

The recommended dosage of **MACLEODS EFAVIRENZ 600 mg** in combination with a protease inhibitor and/or nucleoside analogue reverse transcriptase inhibitors (NRTIs) is 600 mg orally, once daily and can only be used in adults and children who weigh greater than or equal to 40 kg.

MACLEODS EFAVIRENZ 600 mg should only be administered to children who are able to reliably swallow tablets.

Method of administration

Oral use

4.3 Contraindications

- **MACLEODS EFAVIRENZ 600 mg** is contra-indicated in patients with previously demonstrated clinically significant hypersensitivity to efavirenz or to any of the excipients of **MACLEODS EFAVIRENZ 600 mg**.
- Pregnancy and Lactation **(see section 4.6).**
- **MACLEODS EFAVIRENZ 600 mg** should not be administered concurrently with terfenadine ,astemizole, cisapride, midazolam, triazolam, pimozide, bepridil 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] and St John's wort, as it may lead to loss of virologic response and possible resistance.

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- Patients with severe hepatic impairment (Child Pugh Class C) see section 4.4
- Patients with a history of previous liver injury/failure with efavirenz-containing antiretroviral treatment (ART). (section 4.4)
- **MACLEODS EFAVIRENZ 600 mg** is contraindicated in adults and children who weigh less than 40 kg.

4.4 Special warnings and precautions for use

Resistant virus emerges rapidly when NNRTIs such as **MACLEODS EFAVIRENZ 600 mg** are administered as monotherapy. **MACLEODS EFAVIRENZ 600 mg** must therefore not be used as a single agent to treat HIV or added on as a sole agent to a failing regimen. The choice of new antiretroviral agents to be used in combination with efavirenz should take into consideration the potential for viral cross-resistance.

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)

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

Concomitant use of Gingko biloba extract is not recommended (see section 4.5). Serious nervous system and psychiatric symptoms have been reported (see Nervous system symptoms)

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.

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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 it 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 **MACLEODS EFAVIRENZ 600 mg** 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 **MACLEODS EFAVIRENZ 600 mg**, does not prevent the risk of transmission of HIV to others through sexual contact or blood contamination. Appropriate precautions should continue to be employed.

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MACLEODS EFAVIRENZ 600 mg must not be used as a single agent to treat HIV or added on as a sole agent to a failing regimen.

When prescribing medications concomitantly with **MACLEODS EFAVIRENZ 600 mg**, medical practitioners should refer to the corresponding manufacturer's product package insert.

If any antiretroviral medication in a combination regimen is interrupted because of 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 agents is not advisable because of the increased potential for selection of drug-resistant mutant virus.

Skin Rash: Mild-to-moderate rash has been reported with **MACLEODS EFAVIRENZ 600 mg** 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 and erythema multiforme or Stevens-Johnson syndrome has been reported. **MACLEODS EFAVIRENZ 600 mg** should be discontinued in patients developing severe rash associated with blistering desquamation, mucosal involvement or fever. If therapy with **MACLEODS EFAVIRENZ 600 mg** is discontinued, consideration should also be given to interrupting therapy with other antiretroviral agents to avoid development of drug resistant virus (see **SIDE EFFECTS**).

Rash was reported in children treated with **MACLEODS EFAVIRENZ 600 mg** and was severe in some patients. Prophylaxis with appropriate antihistamines prior to initiating therapy with **MACLEODS EFAVIRENZ 600 mg** in children may be considered.

Nervous System Symptoms: Nervous system symptoms have been reported (see **SIDE EFFECTS**). In addition, there have been reports of psychosis- like reactions, such as delusions and inappropriate behaviour (including aggressive reactions) predominantly in patients with a history of mental illness or substance abuse. Severe acute depression (including suicidal ideation/attempts) has also been infrequently reported, particularly in patients with a previous history of depression. Patients should be advised that if they experience these symptoms they should contact their doctor immediately because discontinuation of **MACLEODS EFAVIRENZ 600 mg** may be required.

Psychiatric symptoms

Psychiatric adverse reactions have been reported in patients treated with efavirenz. Patients with a prior history of psychiatric disorders appear to be at greater risk of these serious psychiatric adverse

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reactions. In particular, severe depression was more common in those with a history of depression. There have also been post-marketing reports of severe depression, death by suicide, delusions and psychosis-like behaviour 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 **MACLEODS EFAVIRENZ600 mg**, and if so, to determine whether the risks of continued therapy outweigh the benefits (see section 4.8).

Seizures

Convulsions have been observed in adult and paediatric patients receiving efavirenz, generally in the presence of known medical history of seizures. Patients who are receiving concomitant anticonvulsant medicines 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 section4.5). Caution must be taken in any patient with a history of seizures.

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.

Special Populations:

Hepatic impairment

Because of the extensive cytochrome P450-mediated metabolism of **MACLEODS EFAVIRENZ 600 mg** and limited clinical experience in patients with chronic liver disease, caution should be exercised in administering **MACLEODS EFAVIRENZ 600 mg** to patients with liver disease.

Patients with mild liver disease may be treated with their normally recommended dose of **MACLEODS EFAVIRENZ 600 mg**. Patients should be monitored carefully for dose-related adverse reactions, especially nervoussystem symptoms.

Efavirenz-induced liver injury (see section 4.3): There is some evidence that efavirenz 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/mortality risk and may present many months after therapy has been initiated or even stopped. Risk factors include

younger age, CD4+ counts > 350 cells/µL and female gender. Patients on **MACLEODS EFAVIRENZ 600 mg** or efavirenz-containing antiretroviral treatment (ART) should be regularly monitored for jaundice (including a laboratory bilirubin and liver enzymes) and bleeding tendencies.

Early detection and treatment of the liver failure and the immediate discontinuation of **MACLEODS EFAVIRENZ 600 mg** or efavirenz-containing medicines should be stressed. Patients who discontinue treatment with **MACLEODS EFAVIRENZ 600 mg** should be followed up for symptoms/signs of liver failure for up to 12 months.

MACLEODS EFAVIRENZ 600 mg is not recommended in patients with moderate to severe hepatic impairment because there are insufficient data to determine whether dose adjustments are required.

Liver Enzymes: In patients with known or suspected history of Hepatitis 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 **MACLEODS EFAVIRENZ 600 mg** needs to be weighed against the unknown risks of significant liver toxicity (see section 4.8)

The safety and efficacy of **MACLEODS EFAVIRENZ 600 mg** in patients with both HIV and hepatitis B virus infection have not been established.

Hepatic events: A few of the post-marketing reports of hepatic failure occurred in patients with no pre-existing 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.

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 characterised by a fulminant course, progressing in some cases to transplantation or death.

The pharmacokinetics of **MACLEODS EFAVIRENZ 600 mg** have not been studied in patients with renal insufficiency: however, less than 1 % of a **MACLEODS EFAVIRENZ 600 mg** dose is excreted unchanged in the urine, so the impact of renal impairment on **MACLEODS EFAVIRENZ 600 mg** elimination should be minimal.

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

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

Consider alternatives to efavirenz when co-administered with a medicine with a known risk of Torsade de Pointes or when administered to patients at higher risk of Torsade de Pointes.

Weight and metabolic parameters: Weight and levels of blood lipids and glucose may increase during antiretroviral therapy. Such changes may in part be linked to disease control and lifestyle. 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.

Elderly patients:

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

Lactose intolerance

MACLEODS EFAVIRENZ 600 mg contains lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take **MACLEODS EFAVIRENZ 600 mg**.

Cholesterol: Monitoring of cholesterol should be considered in patients treated with **MACLEODS EFAVIRENZ 600 mg**.

Paediatric use

MACLEODS EFAVIRENZ 600 mg has not been studied in paediatric patients below 3 years of age or who weigh less than 13 kg.

4.5 Interaction with other medicines and other forms of interaction

MACLEODS EFAVIRENZ 600 mg is an inducer of CYP3A4. The **MACLEODS EFAVIRENZ 600 mg** plasma concentrations may be altered by substrates, inhibitors, or inducers of CYP3A. **MACLEODS EFAVIRENZ 600 mg** in return may alter plasma concentrations of medicines metabolised by CYP3A.

QT Prolonging Drugs

Efavirenz is contraindicated with concomitant use of medicines (they may cause prolonged QTc interval and *Torsade de Pointes*) such as: antiarrhythmics of classes IA and III,neuroleptics and antidepressant

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agents, certain antibiotics including some medicines of the following classes: macrolides, fluoroquinolones, imidazole, and triazole antifungal medicines, certain non-sedating antihistaminics (terfenadine, astemizole), cisapride, flecainide, certain antimalarials and methadone (see section4.3).

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).

Elbasvir/grazoprevir

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. (see section 4.3).

Concurrent antiviral medicines

Indinavir

Indinavir (800 mg every 8 hours) given with **MACLEODS EFAVIRENZ 600 mg:** the indinavir AUC and C_{max} decrease by approximately 31% and 16%, respectively as a result of enzyme induction. Therefore, the dose of indinavir should be increased from 800 mg to 1000 mg every 8 hours when **MACLEODS EFAVIRENZ 600 mg** and indinavir are co-administered. No adjustment of the dose of **MACLEODS EFAVIRENZ 600 mg** is necessary when given with indinavir.

Ritonavir

MACLEODS EFAVIRENZ 600 mg (given once daily at bedtime) and ritonavir 500 mg (given every 12 hours) is not well tolerated and is associated with a higher frequency of adverse clinical experiences (e.g., dizziness, nausea, paraesthesia) and laboratory abnormalities (elevated liver enzymes). Monitoring of liver enzymes is recommended when **MACLEODS EFAVIRENZ 600 mg** is used in combination with ritonavir.

Saquinavir

Saquinavir (1200 mg given 3 times a day)given with **MACLEODS EFAVIRENZ 600 mg:** the saquinavir AUC and C_{max} are decreased by 62% and 45 to 50% respectively. Use of **MACLEODS EFAVIRENZ 600 mg** in combination with saquinavir as the sole protease inhibitor is not recommended.

Rifamycins

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Rifampicin reduces **MACLEODS EFAVIRENZ 600 mg** AUC by 26% and C_{max} by 20%. The dose of **MACLEODS EFAVIRENZ 600 mg** should be increased to 800 mg/day when taken with rifampicin. No dose adjustment of rifampicin is recommended when given with **MACLEODS EFAVIRENZ 600 mg**. Rifabutin has not been studied in combination with **MACLEODS EFAVIRENZ 600 mg**.

Macrolide antibiotics

Clarithromycin

Co-administration of **MACLEODS EFAVIRENZ 600 mg** once daily with clarithromycin results in a significant effect of efavirenz on the pharmacokinetics of clarithromycin. The AUC and C_{max} of clarithromycin decrease by 39% and 26% respectively, while the AUC and C_{max} of the clarithromycin hydroxymetabolite are increased 34% and 49% respectively, when used in combination with **MACLEODS EFAVIRENZ 600 mg**. The clinical significance of these changes in clarithromycin plasma levels is not known. No dose adjustment of **MACLEODS EFAVIRENZ 600 mg** is recommended when given with clarithromycin. Alternatives to clarithromycin should be considered.

Anticonvulsants

Carbamazepine: the effect on both carbamazepine and efavirenz may be decreased. There are insufficient data to make a dose recommendation for efavirenz. Alternative anticonvulsant treatment should be used.

Phenytoin/phenobarbital: There is a potential for reduction in the anticonvulsant and/or efavirenz plasma levels; periodic monitoring of anticonvulsant plasma levels should be conducted.

HMG-CoA reductase inhibitors

Atorvastatin, pravastatin, simvastatin: Plasma levels of atorvastatin, pravastatin, simvastatin may be decreased.

Oral contraceptives

The AUC following a single dose of ethinylestradiol is increased (37%) by **MACLEODS EFAVIRENZ 600 mg**. No significant changes are observed in C_{max} of ethinylestradiol. The clinical significance of these effects is not known. No effect of a single dose of ethinylestradiol on **MACLEODS EFAVIRENZ 600 mg**C_{max}, or AUC is observed. Because the potential interaction of **MACLEODS EFAVIRENZ 600 mg** with oral contraceptives has not been fully characterised, a reliable method of barrier contraception should be used in addition to oral contraceptives.

Methadone

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Co-administration of **MACLEODS EFAVIRENZ 600 mg** with methadone results in decreased plasma levels of methadone and signs of opiate withdrawal. Patients should be monitored for signs of withdrawal and their methadone dose increased as required to alleviate withdrawal symptoms.

St. John's wort (*Hypericum perforatum*)

Patients on **MACLEODS EFAVIRENZ 600 mg** should not use products containing St John's wort (*Hypericum perforatum*) since it may reduce plasma concentrations of **MACLEODS EFAVIRENZ 600 mg**. This effect is due to an induction of CYP3A4 and may result in loss of therapeutic effect and development of resistance.

Table 1: Interactions between efavirenz and other medicines in adults

Medicine by therapeutic areas (dose)	**Effects on medicine 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		
Atazanavir/ritonavir/ Efavirenz (400 mg once daily/100 mg once daily/600 mg once daily, administered with food	Atazanivir (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 dose of both atazanavir and ritonavir to 400 mg and 200 mg, respectively, in combination with efavirenz could be considered with close clinical monitoring.
	Atazanivir (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 C_{min}. 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 medicines. See also ritonavir row below.

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Fosamprenavir/Nelfinavir/ Efavirenz	Interaction not studied.	No dose adjustment is necessary for any of these medicines
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 q8hwas 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 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	

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	efavirenz was higher than the mean historical C_{min}(0,15 mg/l) when indinavir was given alone at 800 mg q8h. In HIV-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 or oral solution doses by 33% should be considered (4 capsules/~6.5 ml twice daily instead of 3 capsules/5ml 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)	No dose adjustment is necessary for either medicine.

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	The combination was generally well tolerated.	
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	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 pharmcodynamic interaction.

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	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: AUC_{12}: ↓ 45% (↓ 38 to ↓ 51) C_{max}: ↓ 51% (↓ 37 to ↓ 62) Efavirenz concentrations not measured, no effect is expected.	Refer to the Professional Information for the medicine containing maraviroc.
Integrase strand transfer inhibitor		
Raltegravir/Efavirenz (400 mg single dose/ -)	Raltegravir: AUC: ↓ 36% C12: ↓ 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 fumarate. Clinically significant	No dose adjustment is necessary for either medicine.

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	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.	
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 increase	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.

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	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	Concomitant administration of sofosbuvir/velpatasvir with

	↔efavirenz	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 medicine.

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Clarithromycin/ Efavirenz (500 mg q12h/400 mg once daily)	Clarithromycin: AUC: ↓ 39 % (↓ 30 to ↓ 46) C_{max}: ↓ 26 % (↓ 15 to ↓ 35) Clarithromycin 14-hydroxymetabolite: AUC: ↑ 34 % (↑ 18 to ↑ 53) C_{max}: ↑ 49 % (↑ 32 to ↑ 69) Efavirenz: AUC: ↔ C_{max}: ↑ 11% (↑ 3 to ↑ 19) (CYP3A4 induction) Rash developed in 46 % of uninfected volunteers receiving efavirenz and clarithromycin.	The clinical significance of these changes in clarithromycin plasma levels is not known. Alternatives to clarithromycin (e.g. azithromycin) may be considered. 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.
Antimicrobials		
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

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		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 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

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		necessary for rifampicin, including 600 mg.
Antifungals		
Itraconazole/ Efavirenz (200 mg q12h/600 mg once daily)	Itraconazole: AUC: ↓ 39 % (↓ 21 to ↓ 53) C_{max}: ↓ 37 % (↓ 20 to ↓ 51) C_{min}: ↓ 44 % (↓ 27 to ↓ 58) (decrease in itraconazole concentrations: CYP3A4 induction) Hydroxyitraconazole: AUC: ↓ 37 % (↓ 14 to ↓ 55) C_{max}: ↓ 35 % (↓ 12 to ↓ 52) C_{min}: ↓ 43 % (↓ 18 to ↓ 60) Efavirenz: 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% 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	Voriconazole: AUC: ↓ 77 % C_{max}: ↓ 61 % Efavirenz: AUC: ↑ 44 % C_{max}: ↑ 38 % Voriconazole:	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

(400 mg twice daily/300 mg once daily)	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 twice daily alone (competitive inhibition of oxidative mechanism).	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 medicine.
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/600 mg once daily)	Artemether: AUC: ↓51 % C_{max}: ↓21 % Dihydroartemisinin: AUC: ↓46 % C_{max}: ↓38 % Lumefantrine: AUC: ↓21 % C_{max}: ↔ Efavirenz: AUC: ↓ 17 %	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.

	C_{max}: ↔ (CYP3A4 induction)	
Atovaquone and proguanil hydrochloride/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.
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.
ANTI-ANXIETY 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 medicine.
ANTICOAGULANTS		
Warfarin/Efavirenz Acenocoumarol/ Efavirenz	Interaction not studied. Plasma concentrations and effects of warfarin or acenocoumarol are	Dose adjustment of warfarin or acenocoumarol may be required.

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	potentially increased or decreased by efavirenz.	
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) Cmin: ↓ 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 unchanged. Co-administration of higher doses of either efavirenz or carbamazepine has not been studied.	No dose recommendation can be made. An alternative anticonvulsant should be considered. Carbamazepine plasma levels should be monitored periodically.
Phenytoin, Phenobarbital, and other anticonvulsants that are	Interaction not studied. There is a potential for reduction or increase in the	When efavirenz is co-administered with an anticonvulsant that is a substrate

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substrates of CYP450 isoenzymes	plasma concentrations of phenytoin, phenobarbital and other anticonvulsants that are substrates of CYP450 isoenzymes when co-administered with efavirenz.	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 and 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 medicines.
ANTIDEPRESSANTS **Selective serotonin Reuptake inhibitors (SSRis)**		
Sertraline/Efavirenz	Sertraline: AUC: ↓ 39 % (↓ 27 to ↓ 50)	Sertraline dose increases should be guided by clinical

(50 mg once daily/600 mg once daily)	C_{max}: ↓ 29 % (↓ 15 to ↓ 40) C_{min}: ↓ 46 % (↓ 31 to ↓ 58) Efavirenz: AUC: ↔ C_{max}: ↑ 11 % (↑ 6 to ↑ 16) C_{min}: ↔ (CYP3A4 induction)	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 medicine.
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 medicine.
CARDIOVASCULAR MEDICINES		

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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 Professional Information 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 that is a substrate of the CYP3A4 enzyme, there is a potential for reduction in the	Dose adjustments of calcium channel blockers should be guided by clinical response (refer to the Professional Information for the calcium channel blocker).

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	plasma concentrations of the calcium channel blocker.	
LIPID LOWERING MEDICINE **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 Professional Information 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 Professional Information 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.	
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 medicine.
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)	A reliable method of barrier contraception must be used in addition to hormonal contraceptives (see section 4.6).

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	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.	
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	A reliable method of barrier contraception must be used in addition to hormonal

	have been occasional postmarketing reports of contraceptive failure with etonogestrel in efavirenz-exposed patients.	contraceptives (see section 4.6).
IMMUNOSUPPRESSANTS		
Immunosuppressants metabolized by CYP3A4 (eg, cyclosporine, tacrolimus, sirolimus)/ Efavirenz	Decreased exposure of etonogestrel may be expected (CYP3A4 induction). There have been occasional postmarketing 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 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.
OPIODS		
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)	Concomitant administration with efavirenz should be avoided due to the risk for QTc prolongation (see section 4.3).

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	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.	
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.

Cannabinoid test interaction

MACLEODS EFAVIRENZ 600 mg does not bind to cannabinoid receptors. False positive urine cannabinoid test results have been reported in volunteers who received **MACLEODS EFAVIRENZ 600 mg**. 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.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential

Barrier contraception should always be used in combination with other methods of contraception (e.g. oral or other hormonal contraceptives) (see section 4.5). Women of childbearing potential should undergo pregnancy testing prior to initiation of **MACLEODS EFAVIRENZ 600 mg** (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

MACLEODS EFAVIRENZ 600 mg may cause foetal harm when administered during the first trimesterof pregnancy to a pregnant woman. Pregnancy should be avoided in women receiving **MACLEODS EFAVIRENZ 600 mg.**

Foetal neural tube defects

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.

Breastfeeding

The safety of **MACLEODS EFAVIRENZ 600 mg** in lactation has not been established. Efavirenz may pass into breast milk. Mothers taking **MACLEODS EFAVIRENZ 600 mg** should not breastfeed their infants. HIV-infected women should not breastfeed their infants under any circumstances in order to avoid transmission of HIV.

4.7 Effects on ability to drive and use machines

MACLEODS EFAVIRENZ 600 mg 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

The most frequently reported treatment-related undesirable effects of at least moderate severity reported in at least 5% of patients were rash (11,6%), dizziness (8,5 %), nausea (8,0%), headache

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(5,7%), and fatigue (5,5%). The most notable undesirable effects associated with **MACLEODS EFAVIRENZ 600 mg** are rash and nervous system symptoms (see **WARNINGS ANDSPECIAL PRECAUTIONS**).

Tabulated list of adverse reactions

MedDRA System organ class	**Frequency**	**Adverse reactions**
Immune system disorders	Less frequent	Hypersensitivity
	Frequency unknown	Immuno-allergic liver injury/failure
Metabolism and nutrition disorders	Frequent	Hypertriglyceridaemia
	Less frequent	Hypercholesterolaemia
	Frequency unknown	Weight gain and weight loss
Psychiatric disorders	Frequent	Abnormal dreams, anxiety, depression, insomnia
	Less frequent	Aggressive reactions, agitation, emotional lability, mania, paranoia, psychosis, euphoria, stupor, confusion, apathy, hallucinations, suicide ideation and attempt, nervousness.
	Frequency unknown	delusions, neurosis, completed suicide.
Nervous system disorders	Frequent	Dizziness, impaired concentration, headache, somnolence.
	Less frequent	Amnesia, ataxia, cerebellar coordination and balance disturbances, convulsions, hypoesthesia, paraesthesia, tremors, anorexia, agitation, increased appetite, impotence, decreased libido, neuralgia, speech disorder, vertigo

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	Frequency unknown	Neuropathy
Eye disorders	Less frequent	Abnormal vision
Ear and labyrinth disorders	Less frequent	Tinnitus, vertigo
Cardiac disorders	Less frequent	Flushing, palpitations and tachycardia
Respiratory, thoracic and mediastinal disorders	Less frequent	Asthma
	Frequency unknown	Upper respiratory tract infections, sinusitis, dyspnoea.
Gastrointestinal disorders	Frequent	Nausea, vomiting, diarrhoea, dyspepsia, abdominal pain
	Less frequent	Taste perversion, pancreatitis
	Frequency unknown	Gastritis, gastroenteritis, gastro-oesophageal reflux, constipation and malabsorption.
Hepatobiliary disorders	Less frequent	Hepatitis
	Frequency unknown	Increased hepatic enzymesand hepatic failure
Skin and subcutaneous disorders	Frequent	Rash, including erythema, diffuse maculopapular rash, dry desquamation, pruritus, increased sweating.
	Less frequent	Rash, including vesiculation, moist desquamation, ulceration,erythema multiforme, Stevens-Johnson Syndrome, toxic epidermal necrolysis, necrosis requiring surgery, exfoliative dermatitis, eczema, alopecia, urticaria.
	Frequency unknown	Acne, seborrhoea, photoallergic dermatitis, nail disorders
	Less frequent	Arthralgia, myalgia

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Musculoskeletal, connective tissue and bone disorders	Frequency unknown	Myopathy
Reproductive system and breast disorders	Less frequent	Gynaecomastia
	Frequency unknown	
General disorders and administrative site conditions	Frequent	Fatigue, pain
	Less frequent	Asthenia, malaise, syncope
	Frequency unknown	Influenza-like symptoms, redistribution/accumulation of body fat.
Investigations	Frequent	ALT >5 ULN; AST >5 ULN; GGT > 5 x ULN; amylase > 2 x ULN, glucose > 250 mg/dl, neutrophils <750/mm^3. Raised liver enzyme values.
	Less frequent	Increased serum cholesterol and triglyceride concentrations.

The type and frequency of undesirable effects in children was generally similar to that of adult patients, with the exception that rash was reported more frequently in children and was more often of higher grade that in adults.

Rashes are usually mild-to-moderate maculopapular skin eruptions that occur within the first two weeks of initiating therapy with **MACLEODS EFAVIRENZ 600 mg**. In most patients rash resolves with continuing therapy with **MACLEODS EFAVIRENZ 600 mg** within one month. **MACLEODS EFAVIRENZ 600 mg** can be reinitiated in patients interrupting therapy because of rash. Use of appropriate antihistamines and/or corticosteroids is recommended when **MACLEODS EFAVIRENZ 600 mg** is restarted (see section 4.3).

Patients receiving **MACLEODS EFAVIRENZ 600 mg** should be alerted to the potential for additive central nervous system effects when **MACLEODS EFAVIRENZ 600 mg** is used concomitantly with alcohol or psychoactive medicines.

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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. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the "**6.04 Adverse Drug Reactions Reporting Form**", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8.

4.9 Overdose

Symptoms of overdose

Increased nervous system symptoms, involuntary muscle contractions (see section 4.8).

Treatment of overdose

Treatment of overdose with **MACLEODS EFAVIRENZ 600 mg** 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 **MACLEODS EFAVIRENZ 600 mg**. Since **MACLEODS EFAVIRENZ 600 mg** is highly protein bound, dialysis is unlikely to significantly remove efavirenz from the blood.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

A.20.2.8 Antiviral agents

Efavirenz is a selective non-nucleoside reverse transcriptase inhibitor 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 well in excess of those achieved clinically.

***In vitro* HIV susceptibility**

Efavirenz demonstrated synergistic activity in cell culture in combination with the nucleoside analogue reverse transcriptase inhibitors (NRTIs), zidovudine (ZDV) or didanosine (ddI), or the protease inhibitor, indinavir.

Resistance VR

HIV-1 isolates with reduced susceptibility to efavirenz (greater than 380-fold increase in IC_{90}.) compared to baseline can emerge *in vitro*. Phenotypic changes in evaluable HIV-1 isolates and genotypic changes in plasma virus from selected patients treated with efavirenz in combination with IDV or with ZDV plus lamivudine were monitored. One or more RT mutations at amino acid positions 100, 101, 103, 108, 190 and 225, were observed in all patients with a frequency of at least 10 % compared to baseline. The mutation at RT amino acid position 103 (lysine to asparagines) was the most frequently observed (greater or equal to 90 %). A mean loss in susceptibility (IC_{90}) to efavirenz of 47 fold was observed. Five clinical isolates were evaluated for both genotypic and phenotypic changes from baseline. Decreases in efavirenz susceptibility (range from 9 to greater than 312-fold increase in IC_{90}) were observed for these isolates *in vitro* compared to baseline. All 5 isolates possessed at least one of the efavirenz-associated RT mutations. The clinical relevance of phenotypic and genotypic changes associated with efavirenz therapy has not been established.

Cross-resistance

Rapid emergence of HIV-1 strains that are cross-resistant to non nucleoside RT inhibitors has been observed *in vitro*.

5.2 Pharmacokinetic properties

Absorption

Peak efavirenz plasma concentrations of 1,6 to 9,1 µM are attained by 5 hours following singe oral doses of 100 mg to 1600 mg administered to uninfected volunteers. Dose-related increases in C_{max} and AUC were seen for doses up to 1600 mg; the increases are 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 are linear with 200 mg, 400 mg, and 600 mg daily doses and steady state is reached in 6 to 10 days.

Distribution

Efavirenz is highly bound (approximately 99,5 to 99,75 %) to human plasma proteins, predominantly albumin. In HIV-1 infected patients receiving efavirenz 200 to 600 mg once daily for at least one month, cerebrospinal fluid concentrations range from 0,26 to 1,19 % (mean 0,69 %) of the corresponding

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plasma concentration. This proportion is approximately 3-fold higher than the non-protein-bound (free) fraction of efavirenz in plasma.

Metabolism

Studies in humans and *in vitro* studies using human liver microsomes have demonstrated that efavirenz is principally metabolized 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. Efavirenz has been shown to induce P450 enzymes, resulting in the induction of its own metabolism. Multiple doses of 200 to

400 mg per day for 10 days resulted in a lower than predicted extent of accumulation (22 to 42 % lower) and a shorter terminal half-life of 40 to 55 hours (single dose half-life 52 to 76 hours).

Elimination

Efavirenz has a relatively long terminal half-life of 52 to 76 hours after single doses and 40 to 55 hours after multiple doses. Approximately 14 to 34 % of a radiolabeled dose of efavirenz was recovered in the urine and less than 1 % of the dose was excreted in urine as unchanged efavirenz.

Special Populations

Hepatic impairment

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

Renal impairment

The pharmacokinetics of efavirenz have 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

Clinical studies of efavirenz did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects.

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Paediatric use

Efavirenz has not been studied in paediatric patients below 3 years of age or who weigh less than 13 kg. The type and frequency of adverse experiences was generally similar to that of adult patients with the exception of a higher incidence of new onset rash in children (46 %) (see section 4.8). The pharmacokinetics of efavirenz in paediatric patients were similar to adults

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

croscarmellose sodium

hydroxypropylcellulose,

lactose monohydrate,

microcrystalline cellulose,

magnesium stearate,

sodium laurel sulfate

Film coating:

Opadry Yellow 03B52055 (contains hydroxypropyl methyl cellulose, iron oxide yellow (E172), polyethylene glycol 400, titanium dioxide (CI 77891)).

Contains sugar (lactose).

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months

6.4 Special precautions for storage

MACLEODS EFAVIRENZ 600 mg tablets should be stored at or below 30 °C. Keep well closed and protect from light.

KEEP OUT OF REACH OF CHILDREN.

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6.5 Nature and contents of container

Round, white HDPE containers, and a white closure (cap), with 28 or 30 tablets.

7. HOLDER OF CERTIFICATE OF REGISTRATION

MACLEODS PHARMACEUTICALS SA (PTY) LTD

GROUND FLOOR, BLOCK 1,

BASSONIA ESTATE OFFICE PARK (EAST),

1 CUSSONIA DRIVE,

BASSONIA ROCK EXT 12

ALBERTON

GAUTENG

8. REGISTRATION NUMBER:

45/20.2.8/0537

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

29 July 2012

10. DATE OF REVISION OF THE TEXT

13 June 2023

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