PROFESSIONAL INFORMATION

SCHEDULING STATUS: S4

1. NAME OF THE MEDICINE

SONKE EFAVIRENZ 200 Capsules

SONKE EFAVIRENZ 600 Film-coated Tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

SONKE EFAVIRENZ 200:

Each capsule contains efavirenz 200 mg.

Contains sugar: Lactose monohydrate 62,50 mg.

SONKE EFAVIRENZ 600:

Each film-coated tablet contains efavirenz 600 mg.

Contains sugar: Lactose monohydrate 237,60 mg.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

CAPSULE

SONKE EFAVIRENZ 200: White/white, opaque, hard gelatine, self-locked capsules of size 0 elongated, imprinted twice with RD38 in black ink on cap and body and containing a white to pale yellow free flowing granular powder.

Film-coated tablet

SONKE EFAVIRENZ 600: Peach coloured, capsule shaped, biconvex, film-. coated tablets, debossed with RC68 on one side and plain on other side with intact coating

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

SONKE EFAVIRENZ 200 capsules are indicated in combination with other antiretroviral medicines for the

treatment of HIV-1 infected adults, adolescents and children, greater than 3 years of age and 13 kg weight.

SONKE EFAVIRENZ 600 tablets are indicated in combination with other antiretroviral medicines for the 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:

The recommended dosage of SONKE EFAVIRENZ 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

SONKE EFAVIRENZ must be given in combination with other antiretroviral medicines (see section 4.5).

Adolescents and children (17 years and younger)

The recommended dose of SONKE EFAVIRENZ in combination with a protease inhibitor and/or NRTI's for patients 17 years of age and under is described below. SONKE EFAVIRENZ should only be administered to children who are able to reliably swallow capsules or tablets. SONKE EFAVIRENZ has not been adequately studied in children under the age of 3 years or children weighing less than 13 kg. SONKE EFAVIRENZ must not be used in children less than 3 years of age or less than 13 kg weight.

Paediatric doses to be administered once daily:

Body weight (kg)	**SONKE EFAVIRENZ dose (mg)**
13 to less than 15	200
15 to less than 20	250*

20 to less than 25	300*
25 to less than 32.5	350*
32.5 to less than 40	400
Greater than or equal to 40	600

*The formulation of SONKE EFAVIRENZ is not suitable to provide this dosage

Dose adjustment

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

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

Special populations

Renal impairment

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

Hepatic impairment

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

Paediatric population

SONKE EFAVIRENZ 600 tablets are not suitable for children weighing less than 40 kg.

SONKE EFAVIRENZ 200 capsules are available for these patients.

Method of administration

SONKE EFAVIRENZ may be taken with or without food as desired. A high fat meal may increase the absorption of SONKE EFAVIRENZ and should be avoided.

4.3 Contraindications

- Hypersensitivity to efavirenz or to any of the excipients of SONKE EFAVIRENZ.
- Patients with severe hepatic impairment (Child Pugh Class C) (see section 4.4).
- Pregnancy and lactation (see section 4.6).
- Patients with a history of previous liver injury/failure with efavirenz-containing antiretroviral treatment (ART). (see section 4.4).
- SONKE EFAVIRENZ 200 capsules is contraindicated in children less than 3 years or weighing less than 13 kg and adults weighing less than 13 kg. SONKE EFAVIRENZ 600 tablets is contraindicated in adults and children who weigh less than 40 kg.
- SONKE EFAVIRENZ 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).

4.4 Special warnings and precautions for use

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

The choice of new antiretroviral agent(s) to be used in combination with efavirenz should take into consideration the potential for viral cross-resistance (see section 5.1).

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

Coadministration 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 with

efavirenz is not recommended (see section 4.5).

Concomitant use of Ginkgo biloba extracts 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.

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, cryptococcal meningitis and pneumonia caused by *Pneumocystis jiroveci* (formerly known *as Pneumocystis carinii*).

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

Concomitant use

When prescribing medicines concomitantly with SONKE EFAVIRENZ, medical practitioners should refer to the corresponding manufacturer's medicine professional information. If any antiretroviral medicine in a combination regimen is interrupted because of suspected intolerance, serious consideration should be given to simultaneous discontinuation of all antiretroviral medicines. The antiretroviral medicines 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 drug- resistant mutant virus.

Skin rash

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

Severe rash associated with blistering, moist desquamation or ulceration has been reported in less than 1 % of

patients treated with efavirenz. The incidence of erythema multiforme or Stevens-Johnson syndrome was approximately 0,1 %. Experience with efavirenz in patients who discontinued other antiretroviral medicines of the NNRTI class is limited (see section 4.8). SONKE EFAVIRENZ is not recommended for patients who have had a life-threatening cutaneous reaction (e.g. Stevens-Johnson syndrome) while taking another NNRTI.
Prophylaxis with appropriate antihistamines prior to initiating therapy with SONKE EFAVIRENZ in children may be considered.

Nervous system symptoms

Symptoms including, but not limited to, dizziness, insomnia, somnolence, impaired concentration and abnormal dreaming are frequently reported adverse reactions in patients receiving efavirenz 600 mg daily in clinical studies (see section 4.8). Nervous system symptoms usually begin during the first one or two days of therapy and generally resolve after the first 2 – 4 weeks. Patients should be informed that if they do occur, these common symptoms are likely to improve with continued therapy and are not predictive of subsequent onset of any of the less frequent psychiatric symptoms.

Psychiatric symptoms

Psychiatric adverse reactions have been reported in patients treated with efavirenz. Patients with a prior history of psychiatric disorders appear to be at greater risk of these serious psychiatric adverse reactions. In particular, severe depression was more common in those with a history of depression. There have also been post-marketing reports of severe depression, death by suicide, delusions and psychosis-like behaviour 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 SONKE EFAVIRENZ, 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: Patients with mild liver disease may be treated with their normally recommended dose of SONKE EFAVIRENZ. Patients should be monitored carefully for dose-related adverse reactions, especially nervous system 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 SONKE EFAVIRENZ 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 SONKE EFAVIRENZ or efavirenz-containing medicines should be stressed. Patients who discontinue treatment with SONKE EFAVIRENZ should be followed up for symptoms/signs of liver failure for up to 12 months.
SONKE EFAVIRENZ is not recommended in patients with moderate to severe hepatic impairment because there are insufficient data to determine whether dose adjustments are required.
The safety and efficacy of SONKE EFAVIRENZ 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.

Liver disease: SONKE EFAVIRENZ is contraindicated in patients with severe hepatic impairment (see sections 4.3 and 5.2) and not recommended in patients with moderate hepatic impairment because of insufficient data to determine whether dose adjustment is necessary. Because of the extensive cytochrome P450-mediated metabolism of efavirenz and limited clinical experience in patients with chronic liver disease, caution must be exercised in administering SONKE EFAVIRENZ to patients with mild hepatic impairment. Patients should be monitored carefully for dose-related adverse reactions, especially nervous system symptoms. Laboratory tests should be performed to evaluate their liver disease at periodic intervals (see section 4.2). The safety and efficacy of SONKE EFAVIRENZ has not been established in patients with significant underlying liver disorders. Patients with chronic hepatitis B or C and treated with combination antiretroviral therapy are at increased risk for severe and potentially fatal hepatic adverse reactions. Patients with pre-existing liver dysfunction including chronic active hepatitis have an increased frequency of liver function abnormalities during combination antiretroviral therapy and should be monitored according to standard practice. If there is evidence of worsening liver disease or persistent elevations of serum transaminases to greater than 5 times the upper limit of the normal range, the benefit of continued therapy with efavirenz needs to be weighed against the potential risks of significant liver toxicity. In such patients, interruption or discontinuation of treatment must be considered (see section 4.8).
In patients treated with other medicines associated with liver toxicity, monitoring of liver enzymes is also recommended. In case of concomitant antiviral therapy for hepatitis B or C, please refer also to the relevant professional information for these medicines.

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

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

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

Paediatric population:

Efavirenz film-coated tablets are not suitable for children weighing less than 40 kg. Rash was reported in 59 of 182 children (32%) treated with efavirenz and was severe in six patients. Prophylaxis with appropriate antihistamines prior to initiating therapy with efavirenz in children may be considered.

4.5 Interaction with other medicines and other forms of interaction

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

Efavirenz exposure may be increased when given with medicinal products (for example, ritonavir) or food (for

example, grapefruit juice) which inhibit CYP3A4 or CYP2B6 activity. Compounds or herbal preparations (for example Ginkgo biloba extracts and St. John's wort) which induce these enzymes may give rise to decreased plasma concentrations of efavirenz. Concomitant use of St. John's wort is contraindicated (see section 4.3). Concomitant use of Ginkgo biloba extracts is not recommended (see section 4.4).
Co-administration of efavirenz with metamizole, which is an inducer of metabolising enzymes including CYP2B6 and CYP3A4 may cause a reduction in plasma concentrations of efavirenz with potential decrease in clinical efficacy. Therefore, caution is advised when metamizole and efavirenz are administered concurrently; clinical response and/or drug levels should be monitored as appropriate.

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 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).

St. John’s Wort (*Hypericum perforatum*)

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

Other interactions

Interactions between efavirenz and protease inhibitors, antiretroviral medicines other than protease inhibitors and other non-antiretroviral medicines are listed in Table 1 below (increase is indicated as "↑", decrease as "↓", no change as"↔", and once every 8 or 12 hours as "q8h" or "q12h"). If available, 90% or 95% confidence intervals are shown in parentheses. Studies were conducted in healthy subjects unless otherwise noted.

Table 1: Interactions between efavirenz and other 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 (PI)		
Atazanavir/ ritonavir/Efavirenz (400 mg once daily/100 mg oncedaily/600 mg once daily, alladministered 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

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 300mg/ritonavir 100 mg once daily in the evening without efavirenz. This decrease in atazanavir Cmin might negatively impact the efficacy of atazanavir. ** based on historical comparison	be considered with close clinical monitoring.
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.

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) Cmin: ↓ 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 necessaryfor efavirenz when given withindinavir or indinavir/ritonavir.
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}	See also ritonavir row below.

	(0.15 mg/l) when indinavir was given alone at 800 mg q8h. In HIV-1infected 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) The combination was generally well tolerated.	No dose adjustment is necessary for either medicine.
Ritonavir/Efavirenz (500 mg twice daily/600 mg once daily)	Ritonavir: Morning AUC: ↑ 18% (↑ 6 to ↑ 33) Evening AUC: ↔	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

	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.	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 Professional Information for the medicine 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 fumarate. Clinically significant interactions are not expected since the NRTIs are metabolised via a different route than efavirenz and would be unlikely to compete for the same metabolic enzymes and elimination pathways.	No dose adjustment is necessary for either medicine.

NNRTIs/Efavirenz	Interaction not studied.	Since use of two NNRTIs proved not beneficial in terms of efficacyand 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 in mean ratio estimate of ≤25 %	Plasma trough concentrations of boceprevir were decreased when administered with efavirenz. The clinical outcome of this observed reduction of boceprevir trough concentrations has not been directly assessed.
Telaprevir/Efavirenz (1,125 mg q8h/600 mg once daily)	Telaprevir (relative to 750 mg q8h): AUC: ↓ 18% (↓ 8 to ↓ 27) 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)%	If efavirenz and telaprevir are co-administered, telaprevir 1,125 mg every 8 hours should be used.

	(CYP3A induction by efavirenz)	
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 medicine.
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.
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)	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

	(CYP3A4 induction)	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 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 (200 mg q12h/600 mg once daily)	Itraconazole: AUC: ↓ 39 % (↓ 21 to ↓ 53)	Since no dose recommendation for itraconazole can be made, alternative

	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.	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	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.

	** compared to 600 mg once daily alone (competitive inhibition of oxidative metabolism)	
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 % C_{max}: ↔ (CYP3A4 induction)	Since decreased concentrations of artemether, dihydroartemisinin, or lumefantrine may result in a decrease of antimalarial efficacy, caution is recommended when efavirenz and artemether/lumefantrine tablets are coadministered.
Atovaquone and proguanil hydrochloride/Efavirenz (250/100 mg single dose/600 mg once daily)	Atovaquone: AUC: ↓ 75 % (↓ 62 to ↓ 84) Cmax: ↓ 44 % (↓ 20 to ↓ 61) Proguanil: AUC: ↓ 43 % (↓ 7 to ↓ 65) Cmax: ↔	Concomitant administration of atovaquone/proguanil with efavirenz should be avoided.
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 MEDICNES		
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 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)	No dose recommendation can be made. An alternative anticonvulsant should be considered. Carbamazepine plasma levels should be monitored periodically.

	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 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	No dose adjustment is necessary for efavirenz. Patients should be monitored for seizure control.

	valproic acid pharmacokinetics.	
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 (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 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: ↔ Cmax: ↓ 24 % (↓ 18 to ↓ 30) These changes are not considered clinically significant. Efavirenz: No clinically significant pharmacokinetic interaction	No dose adjustment is necessary for either medicine
CARDIOVASCULAR MEICINES		
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)	Dose adjustments of diltiazem should be guided by clinical response (refer to the Professional Information for diltiazem). No dose adjustment is necessary for efavirenz

	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.	
Verapamil, Felodipine, Nifedipine and Nicardipine	Interaction not studied. When efavirenz is co-administered with a calcium channel blocker that is a substrate of the CYP3A4 enzyme, there is a potential for reduction in the plasma concentrations of the calcium channel blocker.	Dose adjustments of calcium channel blockers should be guided by clinical response (refer to the Professional Information for the calcium channel blocker**).**
LIPID LOWERING MEDICINES		
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)	Cholesterol levels should be periodically monitored. Dose adjustment of atorvastatin may be required (refer to the Professional Information for atorvastatin). No dose adjustmentis necessary for efavirenz.

	Total active HMG Co-A reductase inhibitors: AUC: ↓ 34 % (↓ 21 to ↓ 41) C_{max}: ↓ 20 % (↓ 2 to ↓ 26)	
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.	Cholesterol levels should be periodically monitored. Dose adjustment of simvastatin may be required (refer to the Professional Information for simvastatin). No dose adjustment is necessary for efavirenz.
Rosuvastatin/Efavirenz	Interaction not studied. Rosuvastatin is largely excreted unchanged via the	No dose adjustment is necessary for either medicine.

	faeces, therefore 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	Because of the limited information available, a reliable method of barrier contraception must be used in addition to hormonal contraceptives (see section 4.6).

	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.	
Implant: Etonogestrel/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		
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 administration with efavirenz should be avoided due to the risk for QTc prolongation (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.

Cannabinoid test interaction

SONKE EFAVIRENZ does not bind to cannabinoid receptors. False positive urine cannabinoid test results have been reported in uninfected volunteers who received efavirenz. False positive test results have only been observed with 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 SONKE EFAVIRENZ (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

SONKE EFAVIRENZ should not be used during pregnancy as teratogenicity has been reported. 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 SONKE EFAVIRENZ.

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

Since animal data suggest that the substance may be passed into breast milk, mothers taking SONKE EFAVIRENZ should not breastfeed their infants (see section 4.3). It is recommended that HIV-infected women do not breastfeed their infants under any circumstances in order to avoid transmission of HIV.

4.7 Effects on ability to drive and use machines

SONKE EFAVIRENZ 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

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	Aggravated depression, emotional lability, euphoria, hallucination.
	Less frequent	Mania, paranoia, psychosis, suicide attempt, suicide ideation, delusion, neurosis, completed suicide.
Nervous system disorders	Frequent	Dizziness, impaired concentration, headache, somnolence, insomnia.
	Less frequent	Abnormal dreams, anorexia, hypoesthesia, abnormal coordination, ataxia, convulsions, paraesthesia, neuropathy, tremors, agitation, amnesia, anxiety, apathy, increased appetite, confusion, impaired coordination, impotence, decreased libido, increased libido, neuralgia, peripheral neuropathy, speech disorder, vertigo.
Eye disorders	Less frequent	Blurred vision.
Ear and labyrinth disorders	Less frequent	Tinnitus.

Cardiac disorders	Less frequent	Flushing, palpitations, tachycardia.
Respiratory, thoracic and mediastinal disorders	Less frequent	Asthma.
	Frequency unknown	Sinusitis, dyspnoea, upper respiratory tract infections.
Gastrointestinal disorders	Frequent	Nausea, vomiting, diarrhoea.
	Less frequent	Dyspepsia, abdominal pain, pancreatitis.
	Frequency unknown	Gastritis, gastroenteritis, gastroesophageal reflux, constipation, malabsorption.
Hepatobiliary disorders	Less frequent	Hepatitis, hepatic enzyme increase.
	Frequency unknown	Hepatic failure.
Skin and subcutaneous tissue disorders	Frequent	Rash, pruritus, increased sweating.
	Less frequent	Eczema, skin exfoliation, alopecia, erythema multiforme, Stevens-Johnson Syndrome, urticaria, folliculitis.
	Frequency unknown	Acne, seborrhoea, nail disorders, skin discolouration.
Musculoskeletal and connective tissue disorders	Less frequent	Arthralgia, myalgia.
	Frequency unknown	Myopathy.
Reproductive system and breast disorders	Less frequent	Gynaecomastia.
General disorders and administration site conditions	Frequent	Fatigue, allergic reaction, asthenia.
	Less frequent	Taste perversion, malaise, syncope.
	Frequency unknown	Alcohol intolerance, hot flushes, influenza-like symptoms, pain, redistribution/accumulation of body fat.

Investigations

Laboratory abnormalities

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

Liver enzymes

Elevations of AST and ALT to greater than five times the upper limit of the normal range were seen in 3 % of patients treated with 600 mg of SONKE EFAVIRENZ.

Lipids

Increases in total cholesterol of 10 to 20 % have been observed in some uninfected volunteers receiving SONKE 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 SONKE EFAVIRENZ + IDV. The effects of SONKE EFAVIRENZ on triglycerides and LDL were not well characterized. The clinical significance of these findings is unknown (see section 4.4).

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

In overdose, side effects will be exacerbated and exaggerated (see section 4.8). Some patients accidentally taking 600 mg twice daily have reported increased nervous system symptoms and involuntary muscle contractions. Treatment of overdose with SONKE EFAVIRENZ should consist of general supportive measures, including monitoring of vital signs and observation of the patient's clinical status. Administration of activated charcoal may be used to aid removal of unabsorbed drug. There is no specific antidote for overdose with SONKE EFAVIRENZ. Since SONKE EFAVIRENZ is highly protein bound, dialysis is unlikely to significantly remove the drug from the blood. See section 4.8.

Treatment is symptomatic and supportive.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

A 20.2.8 Antiviral agents

Mechanism of action

Efavirenz is a selective non-nucleoside reverse transcriptase inhibitor (NNRTI) of Human Immunodeficiency Virus type 1 HIV-1. Efavirenz diffuses into the cell where it binds adjacent to the active site of reverse transcriptase. This produces a conformational change in the enzyme and inhibits its function. 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.

In vitro HIV susceptibility

The clinical significance of in vitro susceptibility of HIV-1 to efavirenz has not been established. The in vitro antiviral activity of efavirenz was assessed in lymphoblastoid cell lines, peripheral blood mononuclear cells (PBMCs) and macrophage/monocyte cultures enriched from PBMCs. The 90 to 95 % inhibitor concentration (IC_{90-95}) of efavirenz for wild type laboratory adapted strains and clinical isolates ranged from 1,7 to 25 nM.
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 (IDV).

Resistance

HIV-1 isolates with reduced susceptibility to efavirenz (greater than 380-fold increase in IC90) 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 62 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 than or equal to 90 %). A mean loss in susceptibility (IC_{90}) to efavirenz of 47-fold was observed in 26 clinical isolates. 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*. Clinical isolates previously characterized as efavirenz-resistant were also phenotypically resistant to nevirapine and delavirdine *in vitro* compared to baseline. Clinically derived ZDV-resistant HIV-1 isolated and tested *in vitro* retained susceptibility to efavirenz. Cross-resistance between efavirenz and HIV protease inhibitors is unlikely because of the different enzyme targets involved.

5.2 Pharmacokinetic properties

Absorption

Peak efavirenz plasma concentrations of 1,6 – 9,1 µM were attained by 5 hours following single oral doses of 100 mg to 1 600 mg administered to uninfected volunteers. Dose- related increases in C_{max} and AUC were seen for doses up to 1 600 mg; the increases were less than proportional suggesting diminished absorption at higher doses.

Distribution

Efavirenz is very 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. Steady state plasma concentrations are reached in 6 – 7 days.

Biotransformation

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.

The in vitro studies suggest that CYP3A4 and CYP2B6 are the major isozymes responsible for efavirenz metabolism and that it inhibited P450 isozymes 2C9, 2C19, and 3A4. In in vitro studies, efavirenz did not inhibit CYP2E1 and inhibited CYP2D6 and CYP1A2 only at concentrations well above those achieved clinically. Efavirenz plasma exposure may be increased in patients with the homozygous G516T genetic variant of the CYP2B6 isoenzyme. The clinical implications of such an association are unknown; however, the potential for an increased frequency and severity of efavirenz-associated adverse events cannot be excluded.

Efavirenz has been shown to induce CYP3A4 and CYP2B6, resulting in the induction of its own metabolism, which may be clinically relevant in some patients. In uninfected volunteers, multiple doses of 200 – 400 mg per day for 10 days resulted in a lower than predicted extent of accumulation (22 – 42 % lower) and a shorter terminal half-life compared with single dose administration.

Elimination

Efavirenz has a long terminal half-life of 52 – 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 the faeces, mainly in the form of metabolites.

Special populations

Hepatic impairment

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

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

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.

Gender and race

Pharmacokinetics of efavirenz in patients appear to be similar between men and women and among the racial groups studied.

Geriatric use

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

Paediatric population

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

SONKE-EFAVIRENZ 200

Capsule content

Lactose monohydrate

Magnesium stearate

Sodium lauryl sulphate

Sodium starch glycollate

Capsule shell

Gelatine

Sodium lauryl sulphate

Titanium dioxide

Printing ink

Black iron oxide

Butyl alcohol

Dehydrated alcohol

Isopropyl alcohol

Propylene glycol

Potassium hydroxide

Purified water

Shellac

Strong ammonia solution

SONKE EFAVIRENZ 600

Tablet core

Croscarmellose sodium

Hydroxypropyl cellulose

Lactose monohydrate

Magnesium stearate

Microcrystalline cellulose

Sodium lauryl sulphate

Film-coat

Hypromellose

Iron oxide red

Iron oxide yellow

Macrogol/polyethylene glycol 400

Titanium dioxide

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

SONKE-EFAVIRENZ 200: 24 months.

SONKE EFAVIRENZ 600: 24 months.

6.4 Special precautions for storage

Store at or below 25 °C.

6.5 Nature and contents of container

SONKE-EFAVIRENZ 200: Cold form blister strips or Aclar laminated PVC blister strips contain 10 capsules each. Cold form blister strips comprise of cold forming aluminium foil (one side bright, soft tempered, plain; dull side lacquered to oriented polyamide film; bright side lacquer laminated to PVC film) with a backing of aluminium foil. PVC blister strips comprise of clear transparent PVC film laminated with Aclar film having backing of hard tempered aluminium foil coated with heat seal lacquer on inner side. Cartons contain 10, 30, 60, 90 or 100 capsules. Alternatively, 84 or 90 capsules are packed in a securitainer or in a white, opaque, HDPE bottle.

SONKE EFAVIRENZ 600: Cold form blister strips or PVdC/PE/PVC blister strips contain10 tablets each. Cold form blister strips comprise of cold forming aluminium foil (one side bright, soft tempered, plain; dull side lacquered to oriented polyamide film; bright side lacquer laminated to PVC film) with a backing of aluminium foil. PVdC/PE/PVC blister strips comprise of clear transparent PVC film laminated with polyethylene and coated with PVdC on inner side having backing of hard tempered aluminium foil coated with heat seal lacquer. Cartons contain 10, 30, 60 or 100 tablets. Alternatively, 28 or 30 tablets are packed in a securitainer or in a white, opaque, HDPE bottle.

6.6 Special precautions for disposal

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

SONKE PHARMACEUTICALS (PTY) LTD

Ground Floor, Tugela House

Riverside Office Park

1303 Heuwel Avenue

Centurion

8. REGISTRATION NUMBERS

SONKE EFAVIRENZ 200: A40/20.2.8/0507

SONKE EFAVIRENZ 600: A40/20.2.8/0508

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

SONKE EFAVIRENZ 200: 05 October 2007

SONKE EFAVIRENZ 600: 05 October 2007

10. DATE OF REVISION OF THE TEXT

September 2022

This medicine is not for resale outside of the following countries: Angola, Democratic Republic of Congo, Lesotho, Madagascar, Mauritius, Namibia, Seychelles, South Africa, Swaziland, Zimbabwe and Botswana.

Use of Efavirenz patents with the consent of Merck & Co, Inc.

BOTSWANA: S2

SONKE EFAVIRENZ 200 – Reg. No.: BOT0801208

SONKE EFAVIRENZ 600 – Reg. No.: BOT0801209

NAMIBIA: NS2

SONKE EFAVIRENZ 200 – Reg. No.: 07/20.2.8/0176

SONKE EFAVIRENZ 600 – Reg. No.: 07/20.2.8/0177