SUMMARY OF PRODUCT CHARACTERISTICS
1. NAME OF THE MEDICINAL PRODUCT

Aspen Efavirenz 600 mg *

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 600 mg of efavirenz.

Each tablet contains about 295.5 mg of lactose monohydrate.

For a full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Film-coated tablet

White to off-white, oval, biconvex, film-coated tablet.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Aspen Efavirenz 600 mg is indicated for the treatment of HIV-1 infection in combination with other antiretroviral agents in adults and adolescents.

Consideration should be given to official treatment guidelines for HIV-1 infection (e.g. by WHO).

4.2 Posology and method of administration

Oral use.

Therapy should be prescribed by a physician experienced in the management of HIV-1 infection.

Adults and adolescents over 40 kg

The recommended dosage of efavirenz is 600 mg orally, once daily.

Efavirenz should be taken on an empty stomach. Food may increase efavirenz exposure and may lead to an increase in the frequency of adverse events (see section 4.8).

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

For patients who cannot reliably swallow tablets, liquid efavirenz formulations are available.

Children

Aspen Efavirenz 600 mg are not indicated for children weighing less than 40 kg as appropriate dose reductions for the weight of the child cannot be made.

Efavirenz is not recommended for use in patients younger than 3 years and weighing less than 10 kg due to a lack of data on safety and efficacy.

Dose adjustments

Hepatic impairment

No dose adjustment is necessary for mild to moderate liver impairment. The pharmacokinetics of efavirenz in severe liver impairment have not been studied; however data from one patient indicate a substantially prolonged half-life (see section 4.4).

* Trade names are not prequalified by WHO. This is the national medicines regulatory authority’s (NMRA) responsibility. Throughout this WHOPAR the proprietary name is given as an example only.
Renal impairment
No dose modification is necessary.

Co-administration of voriconazole
If Aspen Efavirenz 600 mg is coadministered with voriconazole, the efavirenz dose must be reduced by 50%; (the voriconazole dose must be increased to 400 mg every 12 hours, see also section 4.5). When treatment with voriconazole is stopped, the initial efavirenz dose should be restored.

Co-administration of rifampicin
If Aspen Efavirenz 600 mg is coadministered with rifampicin, an increase in the efavirenz dose by 33% (i.e. for example from 600 mg to 800 mg/day) may be considered (see section 4.5).

4.3 Contraindications
Efavirenz is contraindicated in patients with clinically significant hypersensitivity to efavirenz or to any of the excipients contained in the formulation.

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

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

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

4.4 Special warnings and precautions for use
Rash: a mild-to-moderate rash very commonly develops within two weeks after starting efavirenz and does not require treatment discontinuation. The rash usually resolves within two weeks. Severe rash or erythema, including Stevens-Johnson syndrome, requires immediate discontinuation (see section 4.8).

Central nervous system and psychiatric effects: central nervous system and psychiatric side effects are very common after starting efavirenz. These symptoms typically occur within the first week of treatment and usually resolve within 4 weeks of treatment. There is a potential additive effect with alcohol and other psychoactive drugs. Patients should be advised that if they experience symptoms such as severe depression, psychosis or suicidal ideation they should contact their doctor immediately to determine whether the benefits outweigh the risks of continued therapy. Patients with a history of psychiatric disorders may be at greater risk of serious psychiatric adverse reactions.

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 medicinal products primarily metabolised by the liver, such as phenytoin, carbamazepine and phenobarbital, may require periodic monitoring of plasma levels. In a drug interaction study, carbamazepine plasma concentrations were decreased when carbamazepine was co-administered with efavirenz (see section 4.5). Caution must be taken in any patient with a history of seizures.

Liver disease: Transaminase levels may increase months after starting efavirenz and may be more frequent in patients with HBV or HCV co-infection. Discontinuation is recommended if hepatotoxicity is symptomatic, or if the transaminase level is more than 10 times the upper limit of normal. Hepatic failure has 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.
Efavirenz is contraindicated in patients with severe hepatic impairment (see sections 4.3 and 5.2) and not recommended in patients with moderate hepatic impairment because of insufficient data to determine whether dose adjustment is necessary. Because of the extensive cytochrome P450-mediated metabolism of efavirenz and limited clinical experience in patients with chronic liver disease, caution must be exercised in administering efavirenz to patients with mild hepatic impairment. Patients should be monitored carefully for dose-related adverse reactions, especially nervous system symptoms. Laboratory tests should be performed to evaluate their liver disease at periodic intervals (see section 4.2).

The safety and efficacy of efavirenz has not been established in patients with significant underlying liver disorders. Patients with chronic hepatitis B or C and treated with combination antiretroviral therapy are at increased risk for severe and potentially fatal hepatic adverse reactions. Patients with pre-existing liver dysfunction including chronic active hepatitis have an increased frequency of liver function abnormalities during combination antiretroviral therapy and should be monitored according to standard practice. If there is evidence of worsening liver disease or persistent elevations of serum transaminases to greater than 5 times the upper limit of the normal range, the benefit of continued therapy with efavirenz needs to be weighed against the potential risks of significant liver toxicity. In such patients, interruption or discontinuation of treatment must be considered (see section 4.8).

In patients treated with other medicinal products associated with liver toxicity, monitoring of liver enzymes is also recommended. In case of concomitant antiviral therapy for hepatitis B or C, please refer also to the relevant product information for these medicinal products.

**Discontinuation of efavirenz-containing antiretroviral therapy:** due to the long half-life of efavirenz, discontinuation of the antiretroviral regimen containing Aspen Efavirenz 600 mg without immediate institution of another effective antiretroviral therapy may result in a period of de facto monotherapy with efavirenz, which may result in high-level efavirenz resistance (see section 5.1). A new regimen should be immediately instituted when efavirenz is stopped, with consideration of the possibility of a period of continued enzyme induction by efavirenz and consequent decrease of drug levels of the new therapy.

**Opportunistic infections:** patients receiving antiretroviral therapy may continue to develop opportunistic infections and other complications of HIV infection. Therefore patients should remain under close clinical observation by physicians experienced in the treatment of HIV infection.

**Transmission of HIV:** Effective antiviral therapy can substantially reduce the risk of HIV transmission. However, the risk may not be eliminated entirely. It is therefore essential to take precautions according to national and other authoritative guidelines to prevent transmission through sexual contact or blood contamination.

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

**Immune Reactivation Syndrome:** in HIV-infected patients with severe immune deficiency, typically in the first few weeks or months after initiation of combination ART, an inflammatory reaction to asymptomatic or residual opportunistic pathogens (e.g. CMV retinitis, mycobacterial infections, Pneumocystis pneumonia) may arise and cause serious clinical conditions or aggravation of symptoms. Treatment should be instituted when necessary. Autoimmune disorders (such as Graves’ disease) have also been reported to occur in the setting of immune reactivation; however, the reported time to onset is more variable and these events can occur many months after initiation of treatment.

**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 (adult) patients with advanced HIV-disease and/or long-term
exposure to combination antiretroviral therapy. Patients should be advised to seek medical advice if they experience joint aches and pain, joint stiffness or difficulty in movement.

Excipients: Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption may experience symptoms of intolerance.

4.5 Interaction with other medicinal products and other forms of interaction

Efavirenz is eliminated through hepatic metabolism, mainly through the genetically polymorphic cytochrome (CYP) 450 isoform CYP2B6, but also by CYP3A. Therefore, agents that alter the activity of CYP2B6 or CYP3A may alter the plasma concentration of efavirenz.

Efavirenz is a clinically important inducer of cytochrome P450 enzymes, such as CYP3A4; therefore interactions with medicinal products metabolised by this pathway may occur. In vitro, efavirenz is also an inhibitor of UDP-glucuronosyl transferases, CYP3A4, CYP2C9 and CYP2C19. In the great majority of cases where efavirenz interacts in vivo with CYP3A substrates, the net result after multiple doses is decreased systemic exposure of the drug interacting with efavirenz. Though efavirenz might act in vivo as a net inhibitor of CYP3A4 after the first doses, it has not been demonstrated that this happens once CYP3A4 induction has set in.

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.

Efavirenz should not be administered concurrently with terfenadine, astemizole, cisapride, midazolam, triazolam, pimozide, bepridil or ergot derivatives, since this may result in altered plasma concentration of these drugs.

Table of drug interactions

The following list of interactions should not be considered exhaustive, but as representative of the classes of medicinal products where caution should be exercised (“↑” indicates increased exposure, “↓” indicates decreased exposure, “↔” as no change).

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<td>Nucleoside analogues</td>
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<td>Zidovudine</td>
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<td>stavudine</td>
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<td>Didanosine</td>
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<td>Lamivudine</td>
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<td>Emtricitabine</td>
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<td>Tenofovir</td>
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<tr>
<td>Abacavir</td>
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<td>Concomitant use not recommended because of additive toxicity and no benefit in terms of efficacy.</td>
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<tr>
<td>Non-nucleoside inhibitors of reverse transcriptase</td>
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<td>Nevirapine</td>
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<td>Etravirine</td>
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<td>Rilpivirine</td>
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<tr>
<td><strong>Protease inhibitors</strong></td>
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<tr>
<td><strong>Fosamprenavir/ritonavir (700/100 mg twice daily)</strong></td>
<td>Fosamprenavir $C_{min} \downarrow 17%$ No significant interaction with twice daily regimen at steady state.</td>
<td>No dose adjustment for any of these products necessary.</td>
</tr>
<tr>
<td><strong>Fosamprenavir/ritonavir (1400/200 mg once daily)</strong></td>
<td>Amprenavir $C_{min} \downarrow 36%$ at steady state</td>
<td>Avoid concomitant use with once-daily fosamprenavir regimen.</td>
</tr>
<tr>
<td><strong>Saquinavir (hard gelatin capsules)/ritonavir (1000/100 mg twice daily)</strong></td>
<td>No clinically relevant interaction was noted.</td>
<td></td>
</tr>
<tr>
<td><strong>Indinavir (800 mg three times daily)</strong></td>
<td>Indinavir AUC $\downarrow 31%$, $C_{min} \downarrow 40%$</td>
<td>Concomitant use with unboosted indinavir is not recommended.</td>
</tr>
<tr>
<td><strong>Indinavir/ritonavir (800/100 mg twice daily)</strong></td>
<td>Indinavir AUC$<em>{ss} \downarrow 25%$, $C</em>{min} \downarrow 50%$</td>
<td>Concomitant use with boosted indinavir is only recommended when the plasma concentration of indinavir can be monitored.</td>
</tr>
<tr>
<td><strong>Ritonavir (500 mg twice daily)</strong></td>
<td>Interaction studies have shown moderate increase in the AUC for both ritonavir and efavirenz.</td>
<td>Avoid concomitant use with full-dose ritonavir, due to low tolerability.</td>
</tr>
<tr>
<td><strong>Nelfinavir (various doses)</strong></td>
<td>Interaction studies have shown variable results, including 20% increase in nelfinavir AUC and $C_{min}$, as well as 25% decrease in AUC and 45% decrease in $C_{min}$.</td>
<td>Concomitant use is recommended only if the plasma concentration of nelfinavir can be monitored.</td>
</tr>
<tr>
<td><strong>Lopinavir/ritonavir soft capsules or oral solution</strong></td>
<td>Substantial decrease in lopinavir exposure.</td>
<td>With efavirenz, increasing the lopinavir/ritonavir soft capsule or oral solution dose by 33% should be considered. Caution is warranted since this dosage adjustment might be insufficient in some patients. Lopinavir/ritonavir tablets dose should be increased to 500/125 mg twice daily when given with efavirenz 600 mg once daily.</td>
</tr>
<tr>
<td><strong>Lopinavir/ritonavir tablets (400/100 mg twice daily)</strong></td>
<td>Lopinavir $C_{min} \downarrow \approx 40%$</td>
<td></td>
</tr>
<tr>
<td><strong>Lopinavir/ritonavir tablets (500/125 mg twice daily)</strong></td>
<td>Lopinavir concentrations: similar to lopinavir/ritonavir 400/100 mg twice daily without efavirenz</td>
<td></td>
</tr>
<tr>
<td><strong>Atazanavir 400 mg</strong></td>
<td>Atazanavir AUC$<em>{ss} \downarrow 74%$, $C</em>{min} \downarrow 93%$</td>
<td>Concomitant use of efavirenz and unboosted atazanavir is not recommended.</td>
</tr>
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### Medicinal products by therapeutic areas

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| **Atazanavir/ritonavir**<br>(400/100 mg once daily, all drugs administered with food)<br>(400/200 mg once daily) | Atazanavir AUC unchanged, $C_{\text{min}} \downarrow 42\%$
AUC unchanged, $C_{\text{min}} \uparrow 12\%$
(Data compared with atazanavir/ritonavir 300/100 mg without efavirenz) | Co-treatment with ritonavir-boosted atazanavir should be avoided. If co-treatment is deemed necessary plasma concentrations should be monitored if possible. The initial atazanavir dose should be increased from 300 mg to 400 mg once daily, and an increase of the ritonavir dose from 100 mg to 200 mg should be considered. |
| **Tipranavir/ritonavir** | Appropriate data on the interaction between the approved tipranavir regimen and efavirenz are lacking. | The combination should be used with caution. |
| **Darunavir/ritonavir**<br>(300/100 mg twice daily) | Darunavir AUC at steady state $\downarrow 13\%$, $C_{\text{min}} \downarrow 31\%$. Efavirenz AUC $\uparrow 21\%$, $C_{\text{min}} \uparrow 17\%$ | The combination should be used with caution in patients harbouring virus with significantly reduced sensitivity to darunavir. Clinical monitoring for central nervous system toxicity associated with increased exposure to efavirenz may be indicated. |
| **CCR-5 antagonists** | Maraviroc AUC: $\downarrow 45\%$
Maraviroc $C_{\text{max}}$: $\downarrow 51\%$ | When co-treating with maraviroc and efavirenz in the absence of a boosted PI, the maraviroc dose should be increased to 600 mg twice daily. The SmPC for the medicinal product containing maraviroc should be consulted, when co-treating in addition with a boosted PI. |
| **Integrase inhibitors** | Raltegravir AUC $\downarrow 36\%$
Raltegravir AUC $\downarrow 14\%$ | No dose adjustment necessary. |
| Raltegravir (400 mg single dose)<br>Raltegravir (1200 mg single dose) | | |
| **Elvitegravir/cobicistat/emtricitabine/TDF or TAF** | Dolutegravir: $\downarrow AUC 57\%$
$\downarrow C_{\text{max}} 39\%$
$\downarrow C_{\text{trough}} 75\%$ | A dose increase of dolutegravir to 50 mg twice daily is recommended. |
<p>| <strong>Dolutegravir</strong> | | |</p>
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<th>Medicinal products by therapeutic areas</th>
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<tr>
<td><strong>Hepatitis B antivirals</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adefovir, entecavir, lamivudine, tenofovir, telbivudine</td>
<td>No interaction expected.</td>
<td></td>
</tr>
<tr>
<td><strong>Hepatitis C Antivirals</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Daclatasvir</td>
<td>Daclatasvir: ↓ AUC 32%  ↓ Cmax 17%  ↓ Cmin 59%</td>
<td>The dose of daclatasvir should be increased to 90 mg once daily when coadministered with efavirenz.</td>
</tr>
<tr>
<td>Elbasvir/Grazoprevir</td>
<td>Decreased elbasvir and grazoprevir AUCs by 54% and 83%, respectively.</td>
<td>Coadministration is contraindicated.</td>
</tr>
<tr>
<td>Ombitasvir/Paritaprevir/r + Dasabuvir</td>
<td>Decreased plasma concentrations of ombitasvir/paritaprevir/ritonavir + dasabuvir are expected.</td>
<td>Coadministration is contraindicated. Subjects had severe tolerability issues and the study was discontinued due to ALT elevations.</td>
</tr>
<tr>
<td>Ribavirin</td>
<td>No interaction expected.</td>
<td></td>
</tr>
<tr>
<td>Simeprevir 150 mg once daily</td>
<td>Simeprevir: ↓ AUC: 71% (↓ 67 to ↓ 74)  ↓ Cmax: 51% (↓ 46 to ↓ 56)  ↓ Cmin: 91% (↓ 88 to ↓ 92) Efavirenz: no effect</td>
<td>Co-administration of simeprevir with efavirenz is not recommended.</td>
</tr>
<tr>
<td>Sofosbuvir</td>
<td>No interaction expected</td>
<td></td>
</tr>
<tr>
<td>Sofosbuvir/velpatasvir</td>
<td>Velpatasvir: ↓ AUC 53%  ↓ Cmax 47%  ↓ Cmin 57%</td>
<td>Coadministration of sofosbuvir/velpatasvir with efavirenz-containing regimens is not recommended.</td>
</tr>
<tr>
<td>Sofosbuvir/ledipasvir</td>
<td>Not studied.</td>
<td>No information.</td>
</tr>
<tr>
<td><strong>Antifungals</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ketoconazole (400 mg single dose; efavirenz 600 mg to steady state)</td>
<td>Ketoconazole AUC ↓ 72%</td>
<td>Consider alternative antifungal agent, or use therapeutic drug monitoring if available.</td>
</tr>
<tr>
<td>Itraconazole (200 mg twice daily)</td>
<td>Itraconazole AUC&lt;sub&gt;ss&lt;/sub&gt; ↓ 39%, &lt;br&gt; C&lt;sub&gt;max&lt;/sub&gt; ↓ 44%</td>
<td>Consider alternative antifungal agent, or use therapeutic drug monitoring if available.</td>
</tr>
<tr>
<td>Posaconazole (400 mg twice daily/400 mg daily)</td>
<td>Posaconazole AUC ↓ 50%  C&lt;sub&gt;max&lt;/sub&gt; ↓ 45%</td>
<td>Concomitant use of posaconazole and efavirenz should be avoided.</td>
</tr>
<tr>
<td>Fluconazole (200 mg once daily)</td>
<td>No significant interaction</td>
<td></td>
</tr>
<tr>
<td>Voriconazole (200 mg twice daily + efavirenz 600mg)</td>
<td>No data available</td>
<td>Efavirenz and voriconazole at standard doses must not be co-administered.</td>
</tr>
<tr>
<td>Medicinal products by therapeutic areas</td>
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<td>Recommendations on co-administration</td>
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</tr>
<tr>
<td><strong>Voriconazole</strong> (200 mg twice daily + efavirenz 400 mg once daily)</td>
<td>Voriconazole AUC&lt;sub&gt;ss&lt;/sub&gt; ↓77%; efavirenz AUC&lt;sub&gt;ss&lt;/sub&gt; ↑44%</td>
<td>The dose reduction for efavirenz with voriconazole at standard dose significantly alters the pharmacokinetics of both drugs and must thus not be used.</td>
</tr>
<tr>
<td><strong>Voriconazole</strong> (400 mg twice daily + efavirenz 300 mg once daily)</td>
<td>Voriconazole AUC&lt;sub&gt;ss&lt;/sub&gt; ↓7%; efavirenz AUC&lt;sub&gt;ss&lt;/sub&gt; ↑17%; both compared with standard doses of voriconazole and efavirenz (200 mg twice daily and 600 mg once daily, respectively)</td>
<td>If co-administration is considered necessary, voriconazole should be dosed 400 mg twice daily and efavirenz dosed at 300 mg once daily.</td>
</tr>
</tbody>
</table>

**Antibacterials/Antituberculosis**

| **Clarithromycin** (500 mg twice daily, multiple doses) | Clarithromycin AUC ↓39%; 14-OH-clarithromycin AUC ↑34% | The clinical significance of these alterations in clarithromycin exposure is not known. A high frequency of rash was seen when the drugs were co-administered in healthy volunteers; consider azithromycin instead, if possible. |

| **Azithromycin** (600 mg single dose; 400 mg efavirenz once daily) | No clinically significant pharmacokinetic interaction | No dosage adjustment is necessary for either medicinal product |

| **Rifampicin** (600 mg once daily, multiple doses) | Efavirenz AUC ↓26%, C<sub>max</sub> ↓32% | When co-treating, increasing the efavirenz dose by 33% (e.g. from 600 mg to 800 mg once daily) should be considered. |

| **Rifabutin** (300 mg once daily) | Rifabutin AUC<sub>ss</sub> ↓38% | Increase rifabutin dose by 50%. |

**Antimalarials**

| **Chloroquine** | No formal interaction studies available. Drug interactions and safety in co-administration with efavirenz has not been systematically evaluated; on a theoretical basis, clinically significant drug interactions with efavirenz are unlikely |

| **Mefloquine** | |

| **Sulfadoxine** | |

| **Pyrimethamine** | |

| **Amodiaquine/Artesunate** (600/250 mg once daily) | An interaction study (EFV at steady-state) was terminated after the first two subjects developed asymptomatic but significant hepatic enzyme elevations after a three-day course of amodiaquine. Amodiaquine AUC ↑114 and 302% respectively | Possibly increased hepatic toxicity. Avoid combination. |
### Medicinal products by therapeutic areas

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| Artemether/lumefantrine (80/480 mg 6 times daily for 3 days) | Artemether AUC ↓ 51%  
Dihydroartemisinin  
AUC ↓ 46%  
C<sub>max</sub> ↓ 21%  
Lumefantrine AUC ↓ 21%  
Efavirenz AUC ↓ 17% | Since reduced concentration of artemether, dihydroartemisinin, or lumefantrine may reduce antimalarial efficacy, efavirenz and artemether/lumefantrine tablets should be co-administered cautiously. |
| Lumefantrine Halofantrine | No formal interaction studies available. These agents are metabolised by CYP3A; hence, co-treatment with efavirenz may decrease exposure. | Co-treatment is not recommended. |
| Atovaquone/proguanil (250/100 mg single dose) | Atovaquone AUC ↓ 75%  
C<sub>max</sub> ↓ 44%  
Proguanil AUC ↓ 43% | Co-administration of atovaquone/proguanil with efavirenz should be avoided whenever possible. |
| **ANTICONVULSANTS** | | |
| Carbamazepine (400 mg once daily) | Carbamazepine AUC<sub>ss</sub> ↓ 27%,  
C<sub>min</sub> ↓ 35%;  
efavirenz AUC<sub>ss</sub> ↓ 36%,  
C<sub>min</sub> ↓ 47% | Co-administration should be avoided unless plasma concentrations of carbamazepine and efavirenz can be monitored. |
| Phenytoin | No interaction study available. Phenytoin and efavirenz clearance is likely to be increased. | Co-administration should be avoided unless plasma concentrations of phenytoin and efavirenz can be monitored. |
| Valproic acid (250 mg twice daily) | No significant interaction is likely. | |
| **CARDIOVASCULAR AGENTS** | | |
| Calcium channel blockers | | |
| Diltiazem (240 mg once daily) | Diltiazem AUC ↓ 69%  
Desacetyldiltiazem AUC↓ 75%  
N-monodesmethyldiltiazem  
AUC ↓ 37% | Monitor the clinical effect of diltiazem and increase dose if necessary. |
| Verapamil, felodipine, nifedipine, nicardipine | Interaction not studied. Calcium channel blocker exposure is likely to be lowered when given with efavirenz. | Monitor clinical efficacy and increase calcium channel blocker dose if necessary. |
| **LIPID-LOWERING AGENTS** | | |
| Atorvastatin (10 mg once daily) | Atorvastatin AUC ↓ 43%  
Total active moiety AUC ↓ 34% | Cholesterol levels should be periodically monitored and the dose of atorvastatin increased in case of insufficient efficacy. |
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<td><strong>Pravastatin</strong> (40 mg once daily)</td>
<td>Pravastatin: AUC: ↓ 40%</td>
<td>Cholesterol levels should be periodically monitored and the dose of pravastatin increased in case of insufficient efficacy.</td>
</tr>
<tr>
<td><strong>Simvastatin 40 mg once daily)</strong></td>
<td>Simvastatin AUC ↓ 69% Total active moiety AUC: ↓ 60%</td>
<td>Cholesterol levels should be periodically monitored and the dose of simvastatin increased in case of insufficient efficacy.</td>
</tr>
<tr>
<td><strong>Rosuvastatin</strong></td>
<td>Interaction not studied. Rosuvastatin is largely excreted unchanged via the faeces; therefore metabolic drug interaction with efavirenz is not expected.</td>
<td></td>
</tr>
</tbody>
</table>

**HORMONAL CONTRACEPTIVES**

| Ethinylestradiol/norgestimate (32.5 micrograms + 250 micrograms once daily) | No change in ethinylestradiol exposure. Levonorgestrel AUC ↓ 83%, norelgestromin AUC ↓ 64% (active metabolites). | A reliable method of barrier contraception should be used in addition to oral contraceptives. |
| Medroxyprogesterone acetate (150-mg single-dose depot injection) | The pharmacokinetics and efficacy of medroxyprogesterone acetate was not altered by co-treatment with efavirenz | Because of the limited information available, a reliable method of barrier contraception must be used in addition to hormonal contraception. |
| Etonogestrel (implant) | Interaction not studied. Decreased exposure of etonogestrel may be expected due to the CYP3A induction by efavirenz. 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 contraception. |
| **Levonorgestrel implants** | ↓ levonorgestrel levels≈50% | Levonorgestrel implants are not recommended in women on long-term treatment with hepatic enzyme-inducing drugs such as efavirenz. |

**IMMUNOSUPPRESSANTS**

| Tacrolimus, ciclosporin, sirolimus | Interaction not formally studied. Decreased exposure of these immunosuppressants may be expected when co-treating with efavirenz. | Dose adjustments of the immunosuppressants may be needed. Close monitoring of immunosuppressant drug concentrations for at least 2 weeks (until steady-state concentrations are reached) is recommended when starting or stopping therapy with efavirenz. |
### Medicinal products by therapeutic areas

<table>
<thead>
<tr>
<th>Medicinal products by therapeutic areas</th>
<th>Interaction</th>
<th>Recommendations on co-administration</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>OThERS</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Methadone</td>
<td>Methadone AUC ↓ 57%</td>
<td>Monitor for withdrawal symptoms and increase methadone dose if necessary.</td>
</tr>
<tr>
<td>Buprenorphine</td>
<td>Buprenorphine AUC ↓ 50%; norbuprenorphine AUC ↓ 71% (active metabolite) Despite these decreases in exposure, no patients in the study exhibited withdrawal symptoms</td>
<td>Monitor for withdrawal symptoms and increase buprenorphine dose if necessary.</td>
</tr>
<tr>
<td>Warfarin</td>
<td>No interaction study available Co-administration may decrease (and less likely increase) warfarin exposure.</td>
<td>Monitor INR. Dose adjustments of warfarin may be necessary.</td>
</tr>
<tr>
<td>Lorazepam (2 mg single dose)</td>
<td>Lorazepam: AUC: ↑ 7% (↑ 1 to ↑ 14)</td>
<td>No dose adjustment necessary.</td>
</tr>
<tr>
<td>Midazolam, Triazolam</td>
<td>No interaction study available</td>
<td>These benzodiazepines are metabolised by CYP3A. While efavirenz is an inducer of CYP3A in vivo, it acts as an inhibitor in vitro. The impact of co-administration on midazolam and triazolam pharmacokinetics is unknown. Co-administer with caution.</td>
</tr>
<tr>
<td>St. John’s wort (Hypericum perforatum)</td>
<td>No interaction study available</td>
<td>Concomitant treatment contraindicated. Co-administration likely to decrease efavirenz levels and to precipitate virological failure.</td>
</tr>
</tbody>
</table>

### 4.6 Fertility, pregnancy and breastfeeding

**Fertility**

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

**Pregnancy**

WHO HIV Treatment guidelines recommend efavirenz-containing therapy for pregnant women and women of childbearing potential. Recent data on the safety of efavirenz during pregnancy are reassuring, with no evidence of an increased risk of congenital anomalies with efavirenz compared to other antiretroviral drugs. Also, a large body of clinical and programmatic evidence representing an estimated 15 million person-years of experience supports the use of efavirenz in a range of settings, including during pregnancy.
Breastfeeding
It is not known if efavirenz appears in human milk. Current recommendations on HIV and breastfeeding (e.g. those from the WHO) should be consulted before advising patients on this matter. Preferred options may vary depending on the local circumstances.

4.7 Effects on ability to drive and use machines
Efavirenz may cause central nervous system side effects such as dizziness, impaired concentration, and somnolence. Patients should be instructed that if they experience these symptoms they should avoid potentially hazardous tasks such as driving or operating machinery.

4.8 Undesirable effects
The following adverse events have been reported in controlled clinical trials and case series during treatment of HIV-1 infection with efavirenz.

Adverse reactions of moderate or greater severity with at least a possible relationship to treatment regimen (based on investigator attribution) reported in clinical trials of efavirenz at the recommended dose in combination therapy (n = 1008) are listed below. Also listed in italics are adverse reactions observed post-marketing in association with efavirenz-containing antiretroviral treatment regimens.

Frequency is defined using the following convention: very common (≥ 1/10); common (1/100 to 1/10); uncommon (1/1000 to 1/100); rare (1/10 000 to 1/1000); or very rare (< 1/10 000).

Immune system disorders
Uncommon: hypersensitivity

Psychiatric disorders
Common: abnormal dreams, anxiety, depression (severe in 1.6%), insomnia
Uncommon: affect lability, aggression, confusional state, euphoric mood, hallucination, mania, paranoia, psychosis*, suicide attempt, suicide ideation
Rare: delusion*, neurosis*, completed suicide*

Nervous system disorders
Common: cerebellar coordination and balance disturbances*, disturbance in attention (3.6%), dizziness (8.5%), headache (5.7%), somnolence (2.0%).
Uncommon: agitation, amnesia, ataxia, coordination abnormal, convulsions, thinking abnormal, tremor*

Nervous system symptoms of moderate-to-severe intensity were experienced by 19% (severe 2%) of patients compared to 9% (severe 1%) of patients receiving control regimens. In clinical studies 2% of patients treated with efavirenz discontinued therapy due to such symptoms.

Nervous system symptoms usually begin during the first one or two days of therapy and generally resolve after the first 2–4 weeks.

Eye disorders
Uncommon: vision blurred

Ear and labyrinth disorders
Uncommon: tinnitus*, vertigo

Metabolism and nutrition disorders
Common: hypertriglyceridaemia
Uncommon: hypercholesterolaemia

Vascular disorders
Uncommon: flushing*

Gastrointestinal disorders
Common: abdominal pain, diarrhoea, nausea, vomiting, asymptomatic increase of amylase
Uncommon: pancreatitis
Hepatobiliary disorders
Common: elevation of liver enzymes
Uncommon: acute hepatitis
Rare: hepatic failure*

Skin and subcutaneous tissue disorders
Very common: rash (11.6%)
Common: pruritus
Uncommon: erythema multiforme, Stevens-Johnson syndrome
Rare: photoallergic dermatitis*

Reproductive system and breast disorders
Uncommon: gynaecomastia.

General disorders and administration site disorders
Common: fatigue

*These adverse reactions were identified through post-marketing surveillance; however, the frequencies were determined using data from 16 clinical trials (n=3,969).

*These adverse reactions were identified through post-marketing surveillance but not reported as drug-related events for efavirenz-treated patients in 16 clinical trials. The frequency category of "rare" was defined on the basis of an estimated upper bound of the 95% confidence interval for 0 events given the number of patients treated with efavirenz in these clinical trials (n=3,969).

Immune Reactivation Syndrome: when initiating combination antiretroviral therapy (CART) in HIV-infected patients with severe immune deficiency, an inflammatory reaction to asymptomatic or residual opportunistic infections may arise (see section 4.4). Autoimmune disorders (such as Graves' disease) have also been reported; however, the reported time to onset is more variable and these events can occur many months after initiation of treatment (see section 4.4).

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

Rash: Rashes are usually mild-to-moderate maculopapular skin eruptions that occur within the first two weeks of initiating therapy with efavirenz. In most patients rash resolves with continuing therapy with efavirenz within one month. Efavirenz can be reinitiated in patients interrupting therapy because of rash. Use of antihistamines and/or corticosteroids is recommended when efavirenz is restarted. Experience with efavirenz in patients who discontinued other antiretroviral agents of the NNRTI class is limited. Reported rates of recurrent rash following a switch from nevirapine to efavirenz therapy, primarily based on retrospective cohort data from published literature, range from 13 to 18%, comparable to the rate observed in patients treated with efavirenz in clinical studies.

Children
Adverse reactions in children were generally similar to those in adult patients. However, in a study with 57 children, who received efavirenz for 48 weeks, rash was reported more frequently and was more often of higher grade than in adults (severe in 5.3%). Prophylaxis with appropriate antihistamines prior to initiating therapy with efavirenz in children may be considered. No child had severe nervous system symptoms or discontinued because of nervous system symptoms.

Other special populations
Liver enzymes in hepatitis B or C co-infected patients:
137 patients treated with efavirenz-containing regimens (median duration of therapy, 68 weeks) and 84 treated with a control regimen (median duration, 56 weeks) were seropositive at screening for hepatitis B (surface antigen positive) and/or C (hepatitis C antibody positive). Among these co-infected patients, AST was elevated more than five times the upper limit of normal in 13% of
Efavirenz-treated patients and in 7% of controls, and ALT was raised to more than five times the upper limit of normal in 20% and 7%, respectively. Among co-infected patients, 3% of those treated with efavirenz and 2% in the control arm discontinued because of liver disorders (see section 4.4).

4.9 Overdose

Some patients accidentally having taken 600 mg twice daily reported increased nervous system symptoms. One patient experienced involuntary muscle contractions. Treatment of overdose with efavirenz should consist of general supportive measures, including monitoring of vital signs and observation of the patient’s clinical status. Activated charcoal may be used to aid removal of unabsorbed efavirenz. There is no specific antidote for overdose with efavirenz. Since efavirenz is highly protein-bound, dialysis is unlikely to remove significant quantities of it from blood.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Non-nucleoside reverse transcriptase inhibitors.
ATC code: J05AG03

Mechanism of action

Efavirenz is a non-nucleoside reverse transcriptase inhibitor (NNRTI) of HIV-1. Efavirenz binds directly to reverse transcriptase and blocks the RNA-dependent and DNA-dependent DNA polymerase activities. The activity of efavirenz does not compete with template or nucleoside triphosphates. HIV-2 reverse transcriptase and eukaryotic DNA polymerases (such as human DNA polymerases α, β, γ, or δ) are not inhibited by efavirenz.

Resistance

A large proportion of patients experiencing virological failure while receiving efavirenz will develop resistance to efavirenz. The main mutations occurring are K103N, G190S/A/E and Y188L; a single one of these mutations is sufficient to cause high-grade resistance. The cross resistance between efavirenz and nevirapine or delavirdine is extensive; therefore patients who have experienced virological failure with either of these drugs, are likely to harbour virus not susceptible to efavirenz, and vice versa. With accumulating number of NNRTI mutations, the susceptibility to etravirine will also be compromised. Due to the long half-life of efavirenz, a period of functional monotherapy with efavirenz may follow discontinuation of effective efavirenz-containing antiretroviral therapy. This may cause significant resistance, and compromise the efficacy of future efavirenz, nevirapine or delavirdine therapy (see section 4.4)

Clinical efficacy

Efavirenz has been investigated in several randomized, prospective clinical trials combined with other antiretroviral drugs. These studies have demonstrated significant decrease in plasma HIV RNA and increase in CD4 cell counts when used in combination with nucleoside analogue(s) and/or a PI. In recent studies by intention-to-treat analysis > 70% of subjects have achieved plasma HIV RNA < 50 copies/ml after 48 weeks of combination treatment that included efavirenz with other antiretroviral drugs. In a randomized controlled trial studying antiretroviral therapy with efavirenz plus either stavudine and lamivudine, or tenofovir and lamivudine in treatment-naïve patients, 62.5% and 67.9% of the patients in each arm had plasma HIV RNA <50 copies after 144 weeks of therapy.

5.2 Pharmacokinetic properties

Absorption and Bioavailability

Bioavailability is 40% to 45% without food. Food increases absorption significantly. Following single dose of administration of Aspen Efavirenz 600 mg in healthy volunteers, mean (± SD) efavirenz C\text{max} value was 2476 (± 711) ng/ml and the corresponding value for AUC\text{0-72h} was 57722 (± 17055) ng·hour/ml. The mean efavirenz t\text{max} value was 3.58 ± 1.06 hours.
Time to peak plasma concentrations (3–5 hours) did not change following multiple dosing of the innovator product and steady-state plasma concentrations were reached in 6–7 days. In HIV-infected patients at steady state, mean $C_{\text{max}}$, mean $C_{\text{min}}$, and mean AUC were linear with 200-mg, 400-mg, and 600-mg daily doses. In 35 patients receiving efavirenz 600 mg (innovator product) once daily, steady state $C_{\text{max}}$ was 12.9 ± 3.7 µM, steady state $C_{\text{min}}$ was 5.6 ± 3.2 µM, and AUC was 184 ± 73 µM·h.

**Distribution**

Efavirenz is highly bound (more than 99%) to human plasma proteins, predominantly albumin. In HIV-1 infected patients who received efavirenz 200–600 mg once daily for at least one month, mean cerebrospinal fluid concentration was 0.69% of the corresponding plasma concentration. This proportion is approximately 3-fold higher than the unbound (free) fraction of efavirenz in plasma.

**Metabolism**

Efavirenz is principally metabolised by the cytochrome P450 system to hydroxylated metabolites. These metabolites are essentially inactive against HIV-1. *In vitro* studies, supported by *in vivo* observations, suggest that CYP3A4 and CYP2B6 are the major isoenzymes responsible for efavirenz metabolism. Efavirenz has been shown to induce cytochrome P450 enzymes, resulting in the induction of its own metabolism.

**Elimination**

Efavirenz has a relatively long terminal half-life of 17 to 154 hours after single doses, and 40–55 hours after multiple doses. In individuals with certain CYP2B6 genotypes (e.g. the T/T genotype at G516T) the terminal half-life may be substantially prolonged, and drug exposures higher. These genotypes are particularly common among Africans and African-Americans. In patients with liver impairment, lower efavirenz clearance and higher drug exposures have been reported. Approximately 14–34% of a radio-labelled dose of efavirenz was recovered in the urine and less than 1% of the dose was excreted in urine as unchanged efavirenz.

### 5.3 Preclinical safety data

Preclinical data revealed no special hazard for humans other than those observed in clinical studies based on conventional studies of safety, pharmacology, repeated dose toxicity, and genotoxicity. In reproductive toxicology studies, malformations were observed in 3 of 20 fetuses/newborns from efavirenz-treated cynomolgus monkeys given doses resulting in plasma efavirenz concentrations similar to those seen in humans. Carcinogenicity studies showed an increased incidence of hepatic and pulmonary tumours in female mice, but not in male mice.

### 6. PHARMACEUTICAL PARTICULARS

#### 6.1 List of Excipients

Core tablet: microcrystalline cellulose, croscarmellose sodium, hydroxypropyl cellulose, sodium lauryl sulphate, lactose monohydrate, magnesium stearate

Film coat: titanium dioxide, polyvinyl alcohol - part hydrolysed, macrogol / PEG 4000, talc, iron oxide yellow, iron oxide red, iron oxide black

#### 6.2 Incompatibilities

Not applicable.

#### 6.3 Shelf life

24 months

#### 6.4 Special precautions for storage

Do not store above 30 ºC. Protect from light.
Keep in a well-closed container.

For the patient ready pack: Keep the tablets in the layflat bag until required for use.

6.5 Nature and contents of container

HDPE bottles
The tablets are packed in a white opaque high density polyethylene (HDPE) plastic bottles sealed with a white polypropylene cap with induction sealing wad. Pack size: 30 tablets.

Patient-ready pack
The tablets are packed in a Layflat bag with Ziploc seal which is composed of laminate film 10 µm PET / 12 µm Aluminium / 30 µm mLLDPE with Ziploc. Pack size: 30 tablets.

6.6 Instructions for use and handling and disposal

No special requirements.

7. SUPPLIER

Pharmacare Limited
Building 12
Healthcare Park
Woodlands Drive
Woodmead
2191
South Africa

8. WHO REFERENCE NUMBER (PREQUALIFICATION PROGRAMME)

HA649

9. DATE OF FIRST PREQUALIFICATION/RENEWAL OF THE PREQUALIFICATION

7 December 2016

10. DATE OF REVISION OF THE TEXT

September 2017

Reference list

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