WHO-PQ RECOMMENDED SUMMARY OF PRODUCT CHARACTERISTICS

This summary of product characteristics focuses on uses of the medicine covered by WHO's Prequalification Team - Medicines. The recommendations for use are based on WHO guidelines and on information from stringent regulatory authorities.[*]

The medicine may be authorised for additional or different uses by national medicines regulatory authorities.

[*]https://extranet.who.int/pqweb/sites/default/files/documents/75%20SRA%20clarification_Feb2017_newtempl.pdf

1. NAME OF THE MEDICINAL PRODUCT

[HA681 trade name]†

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 600 mg of efavirenz.

Excipients with potential clinical effect

Each tablet also contains about 255.6 mg of lactose monohydrate.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet.

Peach coloured, oblong, biconvex, film-coated tablet with one side marked "EZ 600" and plain on other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

[HA681 trade name] is indicated for the treatment of HIV-1 infection in combination with other antiretroviral agents in adults and adolescents.

Treatment regimens should follow most recent WHO treatment guidelines, supplemented by other authoritative guidelines.

4.2 Posology and method of administration

Therapy should be initiated by a health care provider experienced in the management of HIV-1 infection.

Posology

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

Adults and adolescents over 35 kg

The recommended dosage of [HA681 trade name] is 600 mg orally (1 tablet), once daily.

Children

[HA681 trade name] is not indicated in children weighing less than 35 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.

Co-administration of voriconazole

If [HA681 trade name] is co-administered with voriconazole, the efavirenz dose must be reduced by 50% whereas 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 [HA681 trade name] is co-administered 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).

† Trade names are not prequalified by WHO. This is the national medicines regulatory agency's responsibility.

Special populations

Hepatic impairment

Efavirenz is contraindicated in patients with severe hepatic impairment and not recommended in patients with moderate hepatic impairment (see sections 4.3, 4.4 and 5.2).

Caution must be exercised in administering efavirenz to patients with mild hepatic impairment. Patients should be monitored carefully for dose-related adverse reactions, particularly nervous system symptoms (see sections 4.3 and 4.4).

Renal impairment

No dose modification is necessary.

Method of administration

Oral use.

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.

4.3 Contraindications

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

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

Patients with:

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

Co-administration with *terfenadine*, *astemizole*, *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).

Co-administration with *elbasvir* (EBR) and *grazoprevir* (GZR) due to the potential for significant decreases in plasma concentrations of EBR and GZR (see section 4.5).

Herbal preparations containing St. John's wort (*Hypericum perforatum*) 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).

Co-administration with medicines that are known to prolong the QTc interval (proarrhythmic).

These include:

- antiarrhythmics of classes IA and III,
- neuroleptics, antidepressive agents,
- certain antibiotics including some agents of the following classes: macrolides, fluoroquinolones, imidazole and triazole antifungal agents,

- certain non-sedating antihistamines (terfenadine, astemizole),
- certain antimalarials.

4.4 Special warnings and precautions for use

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

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

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

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.

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 a health care provider experienced in the treatment of HIV infection.

Discontinuation of efavirenz-containing antiretroviral therapy

Due to the long half-life of efavirenz, discontinuation of the antiretroviral regimen containing [HA681 trade name] 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.

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, has been reported in less than 1% of patients treated with efavirenz. If this occurs, treatment should be discontinued immediately (see section 4.8). Efavirenz is not recommended for patients who have had a life-threatening cutaneous reaction (*e.g.*, Stevens-Johnson syndrome) while taking another NNRTI.

Psychiatric side effects

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 been post-marketing reports of severe depression, death by suicide, delusions, psychosis-like behaviour and catatonia.

Patients should be advised that if they experience symptoms such as severe depression, psychosis or suicidal ideation, they should contact their doctor immediately to assess the possibility that the symptoms may be related to the use of efavirenz, and if so, to determine whether the risks of continued therapy outweigh the benefits (see section 4.8).

Nervous system side effects

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.

Convulsions have been observed in adult and paediatric patients receiving efavirenz, generally in the presence of a 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.

Late-onset neurotoxicity, including ataxia and encephalopathy (impaired consciousness, confusion, psychomotor slowing, psychosis, delirium), may occur months to years after beginning therapy with efavirenz. Effects may be severe or life-threatening but are generally reversible on discontinuation. Events of late-onset neurotoxicity have occurred in patients with CYP2B6 genetic polymorphisms at daily dosages of 600 mg of efavirenz and were associated with increased efavirenz plasma levels. Patients presenting with signs and symptoms of serious neurological adverse events should be evaluated promptly to assess the possibility that these events may be related to efavirenz use, and whether discontinuation of [HA681 trade name] is warranted.

Hepatotoxicity

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.

QTc Prolongation

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

Alternatives to efavirenz for co-administration with a medicine with a known or potential risk of Torsade de should be considered.

Immune Reactivation Syndrome

In HIV-infected patients with severe immune deficiency at the time of initiation of combination ART, an inflammatory reaction to asymptomatic or residual opportunistic pathogens may arise and cause serious clinical conditions or aggravation of symptoms. Typically, such reactions have been observed within the first few weeks or months of initiation of combination ART. Relevant examples are cytomegalovirus retinitis, generalised and/or focal mycobacterial infections, and pneumonia caused by *Pneumocystis jirovecii* (formerly known as *Pneumocystis carinii*). Any inflammatory symptoms should be evaluated, and treatment instituted when necessary.

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

Weight and metabolic parameters

An increase in weight and in levels of blood lipids and glucose may occur during antiretroviral therapy. Such changes may in part be linked to disease control and 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.

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.

Special populations

Hepatic impairment

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.

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

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

Renal 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. There is no experience in patients with severe renal failure and close safety monitoring is recommended in this population.

Elderly patients

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

Paediatric population

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.

Excipients

Patients with congenital lactase deficiency, galactosaemia or glucose-galactose intolerance must not be given this medicine unless strictly necessary.

The small amount of lactose in each dose is unlikely to cause symptoms of lactose intolerance in other patients.

It is important to consider the contribution of excipients from all the medicines that the patient is taking.

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, midazolam, triazolam, pimozide, bepridil or ergot derivatives, since this may result in altered plasma concentration of these medicines (see section 4.3).

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).

QT Prolonging Drugs

Efavirenz is contraindicated with concomitant use of medicines that may cause prolonged QTc interval and torsade de pointes, such as: antiarrhythmics of classes IA and III, neuroleptics and antidepressant agents, certain antibiotics including some agents of the following classes: macrolides, fluoroquinolones, imidazole, and triazole antifungal agents, certain non-sedating antihistamines (terfenadine, astemizole), cisapride and certain antimalarials (see section 4.3).

Table of drug interactions

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

Medicinal products by therapeutic areas (dose) Interaction is with efavirenz 600 mg daily unless otherwise indicated	**Effects on drug levels** **Mean percent change in AUC C_{max}, C_{min}**	**Recommendations on co-administration with efavirenz**
ANTI-INFECTIVES		
Antiretrovirals		
NRTIs		
Zidovudine **Stavudine** **Didanosine** **Lamivudine** **Emtricitabine** **Tenofovir** **Abacavir**	Specific interaction studies have not been performed with efavirenz and NRTIs other than lamivudine, zidovudine and tenofovir disoproxil. Clinically significant interactions are not expected.	No dose adjustment is necessary for either medicinal product.

Medicinal products by therapeutic areas (dose) Interaction is with efavirenz 600 mg daily unless otherwise indicated	**Effects on drug levels** **Mean percent change in AUC C_{max}, C_{min}**	**Recommendations on co-administration with efavirenz**
NNRTIs		
Nevirapine **Etravirine** **Rilpivirine**	Interaction not studied	Concomitant use not recommended because of additive toxicity and no benefit in terms of efficacy.
Protease inhibitors		
Atazanavir/ritonavir (400/100 mg once daily, all drugs administered with food) (400/200 mg once daily)	Atazanavir AUC unchanged C_{min} ↓ 42% AUC unchanged, C_{min} ↑ 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.
Darunavir/ritonavir (300*/100 mg twice daily) * lower than recommended doses; similar findings are expected with recommended doses	Darunavir AUC at steady state ↓ 13%, C_{min} ↓ 31%. Efavirenz AUC ↑ 21%, C_{min} ↑ 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.
Fosamprenavir/ritonavir (700/100 mg twice daily) (1400/200 mg once daily)	Fosamprenavir C_{min} ↓ 17% No significant interaction with twice daily regimen at steady state.	No dose adjustment for any of these products necessary. Avoid concomitant use with once-daily fosamprenavir regimen.
Indinavir (800 mg q8h with efavirenz 200 mg once daily)	Indinavir AUC ↓ 31%, C_{min} ↓ 40% A similar reduction in indinavir exposures was observed when indinavir 1000 mg q8h was given with efavirenz 600 mg daily. Efavirenz No clinically significant 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. Concomitant use with boosted indinavir is only recommended when the plasma concentration of indinavir can be monitored.
Indinavir/ritonavir (800/100 mg twice daily)	Indinavir AUC_{ss} ↓ 25%, C_{min} ↓ 50% Efavirenz No clinically significant interaction	

Medicinal products by therapeutic areas (dose) Interaction is with efavirenz 600 mg daily unless otherwise indicated	**Effects on drug levels** **Mean percent change in AUC C_{max}, C_{min}**	**Recommendations on co-administration with efavirenz**
Lopinavir/ritonavir soft capsules or **oral solution** **Lopinavir/ritonavir tablets** (400/100 mg twice daily) (500/125 mg twice daily)	Substantial decrease in lopinavir exposure. Lopinavir C_{min} ↓ ≈ 40% Lopinavir concentrations: similar to lopinavir/ritonavir 400/100 mg twice daily without efavirenz	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.
Nelfinavir (various doses)	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}.	Although the combination is generally well tolerated, concomitant use is recommended only if the plasma concentration of nelfinavir can be monitored.
Saquinavir (hard gelatin capsules)/**ritonavir** (1000/100 mg twice daily)	No clinically relevant interaction was noted.	Use of efavirenz in combination with saquinavir as the sole protease inhibitor is not recommended.
Tipranavir	Appropriate data on the interaction between the approved tipranavir regimen and efavirenz are lacking.	The combination should be used with caution.
CCR-5 antagonist		
Maraviroc (100 mg twice daily)	Maraviroc AUC: ↓ 45% C_{max}: ↓ 51% Efavirenz concentrations not measured; no effect is expected.	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 (400 mg single dose) (1200 mg single dose)	Raltegravir AUC ↓ 36% C_{max} ↓ 36% AUC ↓ 14%	No dose adjustment necessary.
Elvitegravir/cobicistat/emtricitabine/TDF or TAF		Efavirenz and elvitegravir/cobicistat/emtricitabine/TDF or TAF should not be used together, due to potential interactions.

Medicinal products by therapeutic areas (dose) Interaction is with efavirenz 600 mg daily unless otherwise indicated	**Effects on drug levels** **Mean percent change in AUC C_{max}, C_{min}**	**Recommendations on co-administration with efavirenz**
Dolutegravir	Dolutegravir: ↓ AUC 57% ↓ C_{max} 39% ↓ Ct_{rough}75%	A dose increase of dolutegravir to 50 mg twice daily is recommended.
Hepatitis B antivirals		
Adefovir, entecavir, lamivudine, tenofovir, telbivudine		No interaction expected.
Hepatitis C antivirals		
Boceprevir (800 mg 3 times daily)	Boceprevir: AUC: ↔ 19%* C_{max}: ↔ 8% C_{min}: ↓ 44% Efavirenz: AUC: ↔ 20% C_{max}: ↔ 11% *0-8 hours	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.
Daclatasvir	Daclatasvir: ↓ AUC 32% ↓ Cmax 17% ↓ Cmin 59%	The dose of daclatasvir should be increased to 90 mg once daily when co-administered with efavirenz.
Elbasvir/Grazoprevir	Decreased elbasvir and grazoprevir AUCs by 54% and 83%, respectively. No effect on efavirenz	Co-administration is contraindicated because it may lead to loss of virologic response to elbasvir/grazoprevir.
Glecaprevir/pibrentasvir	↓glecaprevir ↓ pibrentasvir	Co-administration of glecaprevir/pibrentasvir with efavirenz is not recommended because it may lead to loss of virologic response to glecaprevir/pibrentasvir.
Simeprevir (150 mg once daily)	Simeprevir: AUC: ↓71% C_{max}: ↓51% C_{min}: ↓91% Efavirenz: AUC: ↔ C_{max}: ↔ C_{min}: ↔	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.

Medicinal products by therapeutic areas (dose) Interaction is with efavirenz 600 mg daily unless otherwise indicated	**Effects on drug levels** **Mean percent change in AUC C_{max}, C_{min}**	**Recommendations on co-administration with efavirenz**
Sofosbuvir		No interaction expected.
Sofosbuvir/velpatasvir	Velpatasvir: ↓ AUC 53% ↓ C_{max} 47% ↓ C_{min} 57%	Concomitant administration of sofosbuvir/velpatasvir with efavirenz resulted in a reduction (approximately 50%) in the systemic exposure of velpatasvir. Coadministration of sofosbuvir/velpatasvir with efavirenz is not recommended.
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.
Antifungals		
Fluconazole (200 mg once daily)	No significant interaction	No dose adjustment is necessary.
Itraconazole (200 mg twice daily)	Itraconazole: AUC: ↓ 39% C_{max}: ↓ 37% C_{min}: ↓ 44%	Consider alternative antifungal agent, or use therapeutic drug monitoring if available.
Ketoconazole (400 mg single dose; efavirenz 600 mg to steady state)	Ketoconazole AUC ↓ 72%	Consider alternative antifungal agent, or use therapeutic drug monitoring if available.
Posaconazole (400 mg twice daily)	Posaconazole AUC ↓50% C_{max} ↓ 45%	Concomitant use of posaconazole and efavirenz should be avoided.
Voriconazole (200 mg twice daily with efavirenz 600 mg) **Voriconazole** **(**200 mg twice daily with efavirenz 400 mg once daily) **Voriconazole** (400 mg twice daily with efavirenz 300 mg once daily)	No data available Voriconazole: AUC: ↓ 77% C_{max}: ↓ 61% Efavirenz: AUC: ↑ 44% C_{max}: ↑ 38% Voriconazole: AUC: ↓ 7%* C_{max}: ↑ 23%* Efavirenz: AUC: ↑ 17%** C_{max}: ↔** * compared to 200 mg twice daily alone ** compared to 600 mg once daily alone	Efavirenz and voriconazole at standard doses must not be co-administered. The dose reduction for efavirenz with voriconazole at standard dose significantly alters the pharmacokinetics of both drugs and must thus not be used. If co-administration is considered necessary, voriconazole should be dosed at 400 mg twice daily and efavirenz dose reduced by 50%.
Antibacterials/Antimycobacterials		

Medicinal products by therapeutic areas (dose) Interaction is with efavirenz 600 mg daily unless otherwise indicated	**Effects on drug levels** **Mean percent change in AUC C_{max}, C_{min}**	**Recommendations on co-administration with efavirenz**
Azithromycin (600 mg single dose; 400 mg efavirenz once daily)	No clinically significant pharmacokinetic interaction	No dosage adjustment is necessary for either medicinal product
Clarithromycin (500 mg twice daily)	Clarithromycin: AUC: ↓ 39% C_{max}: ↓ 26% Efavirenz: AUC: ↔ C_{max}: ↑ 11%	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.
Rifabutin (300 mg once daily)	Rifabutin: AUC: ↓ 38% C_{max}: ↓ 32% C_{min}: ↓ 45% Efavirenz: AUC: ↔ C_{max}: ↔ C_{min}: ↓ 12%	Increase rifabutin dose by 50%. Consider doubling the rifabutin dose in regimens where rifabutin is given 2 or 3 times a week in combination with efavirenz.
Rifampicin (600 mg once daily)	Efavirenz AUC ↓ 26% C_{max} ↓ 20% C_{min} ↓ 32%	When co-treating, increasing the efavirenz dose by 33% (e.g. from 600 mg to 800 mg once daily) should be considered. No dose adjustment is necessary for rifampicin.
Antimalarials		
Amodiaquine	Amodiaquine AUC ↑, possibly increased hepatic toxicity.	Co-administration is not recommended.
Artemether/lumefantrine (80/480 mg 6 times daily for 3 days)	Artemether AUC ↓ 51% C_{max} ↓ 21% Dihydroartemisinin AUC ↓ 46% C_{max} ↓ 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.
Atovaquone/proguanil (250/100 mg single dose)	Atovaquone AUC ↓ 75% C_{max} ↓ 44% Proguanil AUC ↓ 43%	Co-administration of atovaquone/proguanil with efavirenz should be avoided whenever possible.

Medicinal products by therapeutic areas (dose) Interaction is with efavirenz 600 mg daily unless otherwise indicated	**Effects on drug levels** **Mean percent change in AUC C_{max}, C_{min}**	**Recommendations on co-administration with efavirenz**
Chloroquine **Sulfadoxine** **Pyrimethamine**	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	Co-administration may decrease mefloquine exposure.	Use with caution.
Lumefantrine	No formal interaction studies available. This agent is metabolised by CYP3A; hence, co-treatment with efavirenz may decrease exposure.	Co-administration may decrease comedication exposure. Caution is recommended.
ANTICONVULSANTS		
Carbamazepine (400 mg once daily)	Carbamazepine AUC_{ss}: ↓ 27%, C_{min} ↓ 35%; efavirenz AUC_{ss}: ↓ 36%, C_{min} ↓ 47% 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.	Co-administration should be avoided unless plasma concentrations of carbamazepine and efavirenz can be monitored.
Phenytoin	Co-administration may increase or decrease phenytoin and/or efavirenz concentrations.	No dose adjustment of efavirenz is needed based on DDIs studies with the strong inducer rifampicin. Monitor the therapeutic response of phenytoin and increase dose if needed.
Valproic acid (250 mg twice daily)	No significant interaction is likely.	
Vigabatrin **Gabapentin**	Interaction not studied. Clinically significant interactions are not expected.	
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.

Medicinal products by therapeutic areas (dose) Interaction is with efavirenz 600 mg daily unless otherwise indicated	**Effects on drug levels** **Mean percent change in AUC C_{max}, C_{min}**	**Recommendations on co-administration with efavirenz**
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.
Pravastatin (40 mg once daily)	Pravastatin: AUC: ↓ 40%	Cholesterol levels should be periodically monitored and the dose of pravastatin increased in case of insufficient efficacy.
Simvastatin 40 mg once daily)	Simvastatin AUC ↓ 69% Total active moiety AUC: ↓ 60%	Cholesterol levels should be periodically monitored and the dose of simvastatin increased in case of insufficient efficacy.
Rosuvastatin	Interaction not studied. Rosuvastatin is largely excreted unchanged via the faeces; therefore metabolic drug interaction with efavirenz is not expected.	
HORMONAL CONTRACEPTIVES / HRT		
Desogestrel (COC and POP), drospirenone (COC), norethisterone (POP and COC), norgestimate (COC)		Co-administration is not recommended.
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 and vaginal ring)	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.

Medicinal products by therapeutic areas (dose) Interaction is with efavirenz 600 mg daily unless otherwise indicated	**Effects on drug levels** **Mean percent change in AUC C_{max}, C_{min}**	**Recommendations on co-administration with efavirenz**
Levonorgestrel (POP, COC and implants)	Levonorgestrel levels≈50%	Levonorgestrel implants are not recommended in women on long-term treatment with hepatic enzyme-inducing drugs such as efavirenz.
Ulipristal		Co-administration may decrease ulipristal exposure and thus reduce the efficacy of the emergency contraception pill. Non-hormonal emergency contraception (i.e. a copper intrauterine device (Cu-IUD)) should be considered.
Drospirenone HRT, dydrogesterone HRT, estradiol, levonogestrel HRT		Co-administration may decrease comedication exposure. Monitor for signs of hormone deficiency.
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.
OTHERS		
Methadone	Methadone AUC:↓ 52% Cmax: ↓ 45% (CYP3A4 induction) In a study of HIV infected intravenous drug users, co-administration of efavirenz with methadone resulted in decreased plasma levels of methadone and signs of opiate withdrawal. The methadone dose was increased by a mean of 22% to alleviate withdrawal symptoms.	Patients should be monitored for signs of withdrawal and their methadone dose increased as required.
Buprenorphine	Buprenorphine AUC ↓ 50%; norbuprenorphine AUC ↓ 71% (active metabolite) Despite these decreases in exposure, no patients in the study exhibited withdrawal symptoms.	Monitor for withdrawal symptoms and increase buprenorphine dose if necessary.

Medicinal products by therapeutic areas (dose) Interaction is with efavirenz 600 mg daily unless otherwise indicated	**Effects on drug levels** **Mean percent change in AUC C_{max}, C_{min}**	**Recommendations on co-administration with efavirenz**
Morphine	Co-administration may increase morphine concentrations.	Monitor for signs of opioid toxicity.
Warfarin	No interaction study available Co-administration may decrease (and less likely increase) warfarin exposure.	Monitor INR. Dose adjustments of warfarin may be necessary.
Lorazepam (2 mg single dose)	Lorazepam: AUC: ↑ 7% (↑ 1 to ↑ 14)	No dose adjustment necessary.
Midazolam, Triazolam	No interaction study available These benzodiazepines are metabolised by CYP3A. While efavirenz is an inducer of CYP3A *in vivo*, it acts as an inhibitor *in vitro*. Competition for CYP3A4 by efavirenz could result in inhibition of metabolism of these benzodiazepines with increased exposure.	Concomitant treatment is therefore contraindicated due to the potential for serious and/or life-threatening events.
St. John's wort (*Hypericum perforatum*)	No interaction study available	Concomitant treatment contraindicated. Co-administration likely to decrease efavirenz levels and to precipitate virological failure.

4.6 Fertility, pregnancy and breast-feeding

Pregnancy

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 medicines. Efavirenz can be used in pregnancy if clinically indicated.

Breast-feeding

Efavirenz is excreted into breast milk, and small amounts are found in the serum of some infants. Treatment of HIV-positive mothers with efavirenz does not appear to affect growth and development of their HIV-negative breastfed infants.

Preferred options may vary depending on local circumstances. Current recommendations on HIV and breastfeeding (e.g. those from the WHO) should be consulted before advising patients on this matter.

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.

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).

Nervous system disorders	
Common	Cerebellar coordination and balance disturbances, disturbance in attention, dizziness, headache, somnolence
Uncommon	Agitation, amnesia, ataxia, coordination abnormal, convulsions, thinking abnormal, tremor
Unknown	Encephalopathy
Psychiatric disorders	
Common	Abnormal dreams, anxiety, depression, insomnia
Uncommon	Labile mood, aggression, confusional state, euphoric mood, hallucination, mania, paranoia, psychosis, suicide attempt, suicide ideation, catatonia
Rare	Delusion, neurosis, completed suicide
Immune system disorders	
Uncommon	Hypersensitivity
Hepatobiliary disorders	
Common	Elevation of hepatic transaminases
Uncommon	Acute hepatitis
Rare	Hepatic failure
Skin and subcutaneous tissue disorders	
Very common	Rash
Common	Pruritus
Uncommon	Erythema multiforme, Steven-Johnson syndrome
Rare	Photoallergic dermatitis
Metabolism and nutrition disorders	
Common	Hypertriglyceridaemia
Uncommon	Hypercholesterolaemia
Gastrointestinal disorders	
Common	Abdominal pain, diarrhoea, nausea, vomiting, asymptomatic increase of amylase
Uncommon	Pancreatitis
Reproductive system and breast disorders	
Uncommon	Gynaecomastia

Eye disorders	
Uncommon	Vision blurred
Ear and labyrinth disorders	
Uncommon	Tinnitus, vertigo
Vascular disorders	
Uncommon	Flushing
General disorders and administration site disorders	
Common	Fatigue

Description of selected adverse events

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

Nervous system symptoms: Nervous system symptoms are common with efavirenz. In clinical controlled studies of efavirenz, nervous system symptoms of moderate to severe intensity were experienced by 19% (severe 2%) of patients, and 2% of patients discontinued therapy due to such symptoms. They usually begin during the first 1 or 2 days of efavirenz therapy and generally resolve after the first 2 to 4 weeks. They may occur more frequently when [HA681 trade name] is taken concomitantly with meals possibly due to increased efavirenz plasma levels (see section 5.2). Dosing at bedtime seems to improve the tolerability of these symptoms (see section 4.2 and 4.4).

Delayed neurotoxicity, sometimes severe, has also been reported in patients receiving efavirenz (see section 4.4) and may require treatment with [HA681 trade name] to be stopped.

Hepatic failure: A few of the postmarketing reports of hepatic failure, including cases in patients with no pre-existing hepatic disease or other identifiable risk factors, were characterized by a fulminant course, progressing in some cases to transplantation or death.

Immune Reactivation Syndrome: 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 59 children, who received efavirenz for 48 weeks, rash was reported more frequently and was more often of higher grade than in adults. 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

In a study, 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).

Reporting of suspected adverse reactions

Health care providers are asked to report adverse reactions that may be linked to a medicine, to the marketing authorisation holder, or, if available, to the national reporting system. Reports of suspected adverse reactions to a medicine are important for the monitoring of the medicine's benefits and risks.

4.9 Overdose

Some patients who had accidentally 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.

Cardiac electrophysiology

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

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.

K103N was the most frequently observed RT substitution in viral isolates from patients who experienced a significant rebound in viral load during clinical studies of efavirenz in combination with indinavir or zidovudine + lamivudine. This mutation was observed in 90% of patients receiving efavirenz with

virological failure. Substitutions at RT positions 98, 100, 101, 108, 138, 188, 190 or 225 were also observed, but at lower frequencies, and often only in combination with K103N. The pattern of amino acid substitutions in RT associated with resistance to efavirenz was independent of the other antiviral medicines used in combination with efavirenz.

Cross 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).

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

Clinical efficacy

Efavirenz has 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 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 lamuvidine, 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.

Efavirenz has not been studied in controlled studies in patients with advanced HIV disease, namely with CD4 counts < 50 cells/mm^3, or in PI or NNRTI experienced patients. Clinical experience in controlled studies with combinations including didanosine or zalcitabine is limited.

5.2 Pharmacokinetic properties

The absorption characteristics of [HA681 trade name] have been determined after administration of one tablet of [HA681 trade name] in healthy volunteers as follows:

Pharmacokinetic variable	**Arithmetic mean ± Standard deviation (Geometric mean)**
Maximum concentration (C_{max}) ng/mL	3.09 ± 0.62 (3.02)
Area under the curve (AUC_{0-72h}), a measure of the extent of absorption ng·hour/mL	66.50 ± 19.70 (63.90)
Time to attain maximum concentration (t_{max})* hour	4.0 (1.5-7.0)

*median (range)

Pharmacokinetics of efavirenz

Absolute bioavailability	Not available
Oral bioavailability	40 – 45%
Food effect	<table><tr><td></td><td>$AUC_{(0-\infty)}$</td><td>C_{max}</td></tr><tr><td>High fat</td><td>28%↑</td><td>79%↑</td></tr></table>
Distribution	
Volume of distribution (mean)	NA
Plasma protein binding *in vitro*	> 99.5%, predominantly albumin
Tissue distribution	CSF: mean cerebrospinal fluid concentrations 0.69% of the corresponding plasma concentration for 1 month treatment. This is approximately 3-fold higher than the non-protein-bound fraction of efavirenz in plasma
Metabolism	
	Mainly by CYP3A4 and CYP2B6 to hydroxylated metabolites with subsequent glucuronidation of the hydroxylated metabolites
Active metabolite(s)	None
Elimination	
Elimination half life	At least 52 hours (single dose) and 40-55 hours after multiple doses. Individuals with certain mutant CYP2B6 genotypes have a substantially prolonged terminal half life
% of dose excreted in urine	13–34%, of which less than 1% is unchanged efavirenz.
% of dose excreted in faeces	16–61% (primarily as metabolites)
Pharmacokinetic linearity	In healthy volunteers, less than dose proportional increase (dose range 100 – 1600 mg). In HIV infected patients, linear steady state pharmacokinetics (dose range 200 – 600 mg/day).
Drug interactions *(in vitro*)	
Metabolizing enzymes	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. Efavirenz induces UGT1A1. Inhibits in vitro CYP3A4. Although *in vitro* data suggest that efavirenz inhibits CYP2C9 and CYP2C19, there have been contradictory reports of both increased and decreased exposures to substrates of these enzymes when coadministered with efavirenz *in vivo*. The net effect of co-administration is not clear.

Special populations

Renal impairment

No data are available in patients with impaired renal function.

Hepatic impairment

A multiple-dose study showed no significant effect on efavirenz pharmacokinetics in patients with mild hepatic impairment (Child-Pugh Class A) compared with controls. In a single-dose study, half-life was doubled in a single patient with severe hepatic impairment (Child-Pugh Class C) indicating a potential for accumulation.

There are insufficient data to determine whether moderate or severe hepatic impairment (Child-Hugh Class B or C) affects efavirenz pharmacokinetics.

Gender and race

Although limited data suggest that females as well as Asian and Pacific Island patients may have higher exposure to efavirenz, they do not appear to be less tolerant of efavirenz.

Paediatric population

The pharmacokinetic parameters for efavirenz at steady state in paediatric patients were predicted by a population pharmacokinetic model and are summarized below by weight ranges that correspond to the recommended doses.

Body weight	**Dose**	**Mean $AUC_{(0-24)}$ µM·h**	**Mean C_{max} µg/mL**	**Mean C_{min} µg/mL**
3.5-5 Kg	100 mg	220.52	5.81	2.43
5-7.5 Kg	150 mg	262.62	7.07	2.71
7.5-10 Kg	200 mg	284.28	7.75	2.87
10-15 Kg	200 mg	238.14	6.54	2.32
15-20 Kg	250 mg	233.98	6.47	2.30
20-25 Kg	300 mg	257.56	7.04	2.55
25-32.5 Kg	350 mg	262.37	7.12	2.68
32.5-40 Kg	400 mg	259.79	6.96	2.69
> 40 Kg	600 mg	254.78	6.57	2.82

Elderly population

Pharmacokinetic studies have not been performed in the elderly.

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: Hypromellose
Titanium dioxide
Polyethylene glycol
Iron oxide yellow
Iron oxide red

This medicine is essentially ‘sodium-free’. It contains less than 1 mmol sodium (23 mg) per tablet.

6.2 Incompatibilities

Not applicable

6.3 Shelf life

24 months

6.4 Special precautions for storage

Store below 30°C, in a dry place. Protect from light.

6.5 Nature and contents of container

The tablets are packed in a white high-density polyethylene (HDPE) bottle with narrow screw neck with aluminium foil and fitted with a white HDPE screw closure with Hi-sheet liner.
A desiccant comprised of a plastic bag with perforation for breathing containing silica gel beads is included in each bottle.

Each bottle contains 30 tablets.

6.6 Special precautions for disposal and other handling

No special requirements

7. SUPPLIER

The Government Pharmaceutical Organization
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HA681

9. DATE OF PREQUALIFICATION

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