SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Efavirenz Milpharm 600 mg film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 600 mg of efavirenz.

Excipient with known effect: Each film-coated tablet contains 152 mg of lactose monohydrate.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet.

Yellow coloured, oval shaped, beveled edge, biconvex, film-coated tablets, debossed with 'L' on one side and '11' on the other side. The size is 20.1 mm X 9.6 mm.

4.1 Therapeutic indications

Efavirenz is indicated in antiviral combination treatment of human immunodeficiency virus-1 (HIV-1) infected adults, adolescents and children 3 months of age and older and weighing at least 3.5 kg.

Efavirenz has not been adequately studied in patients with advanced HIV disease, namely in patients with CD4 counts < 50 cells/mm3, or after failure of protease inhibitor (PI) containing regimens. Although cross-resistance of efavirenz with PIs has not been documented, there are at present insufficient data on the efficacy of subsequent use of PI based combination therapy after failure of regimens containing efavirenz.

For a summary of clinical and pharmacodynamic information, see section 5.1.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

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For a summary of clinical and pharmacodynamic information, see section 5.1.

4.3 Contraindications

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

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).

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

Herbal preparations containing St. John's wort (Hypericum perforatum) due to the risk of decreased plasma concentrations and reduced clinical effects of efavirenz (see section 4.5).

Patients with:

- a family history of sudden death or of congenital prolongation of the QTc interval on electrocardiograms, or with any other clinical condition known to prolong the QTc interval.
- a history of symptomatic cardiac 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. hypokalemia or hypomagnesemia.

Patients taking drugs that are known to prolong the QTc interval (proarrythmic).
These drugs 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),
- cisapride,
- flecainide,
- certain antimalarials,
- methadone.

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).

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

Coadministration of sofosbuvir/velpatasvir with efavirenz is not recommended (see section 4.5).

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

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

Concomitant use of Ginkgo biloba extracts is not recommended (see section 4.5).

When prescribing medicinal products concomitantly with efavirenz, physicians 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.

Rash

Mild-to-moderate rash has been reported in clinical studies with efavirenz and usually resolves with continued therapy. Appropriate antihistamines and/or corticosteroids may improve the tolerability and hasten the resolution of rash. Severe rash associated with blistering, moist desquamation or ulceration has been reported in less than 1% of patients treated with efavirenz. The incidence of erythema multiforme or Stevens-Johnson syndrome was approximately 0.1%. Efavirenz must be discontinued in patients developing severe rash associated with blistering, desquamation, mucosal involvement or fever. If therapy with efavirenz is discontinued, consideration should also be given to interrupting therapy with other antiretroviral agents to avoid development of resistant virus (see section 4.8). Experience with efavirenz in patients who discontinued other antiretroviral agents of the NNRTI class is limited (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 symptoms

Psychiatric adverse reactions have been reported in patients treated with efavirenz. Patients with a prior history of psychiatric disorders appear to be at greater risk of these serious psychiatric adverse reactions. In particular, severe depression was more common in those with a history of depression. There have also been post-marketing reports of severe depression, death by suicide, delusions, 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 symptoms

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

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.

Hepatic events

A few of the postmarketing reports of hepatic failure occurred in patients with no pre-existing hepatic disease or other identifiable risk factors (see section 4.8). Liver enzyme monitoring should be considered for patients without pre-existing hepatic dysfunction or other risk factors.

QTc Prolongation

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

Consider alternatives to efavirenz for coadministration with a drug with a known risk of Torsade de Pointes or when to be administered to patients at higher risk of Torsade de Pointes.

Effect of food

The administration of 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.

Immune Reactivation Syndrome

In HIV infected patients with severe immune deficiency at the time of institution of combination antiretroviral therapy (CART), 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 CART. Relevant examples are cytomegalovirus retinitis, generalised and/or focal mycobacterial infections, and pneumonia caused by Pneumocystis jiroveci (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

Weight and levels of blood lipids and glucose may increase during antiretroviral therapy. Such changes may in part be linked to disease control and life style. 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 patients with advanced HIV-disease and/or long-term exposure to combination antiretroviral therapy (CART).

Patients should be advised to seek medical advice if they experience joint aches and pain, joint stiffness or difficulty in movement.

Special populations:

Liver disease

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.

Renal insufficiency

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

Elderly patients

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

Paediatric population

Efavirenz has not been evaluated in children below 3 months of age or who weigh less than 13 kg. Therefore, efavirenz should not be given to children less than 3 months of age. Efavirenz film-coated tablets are not suitable for children weighing less than 40 kg.

Rash was reported in 59 of 182 children (32%) treated with efavirenz and was severe in six patients. Prophylaxis with appropriate antihistamines prior to initiating therapy with efavirenz in children may be considered.

This medicinal product contains Lactose Monohydrate. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

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Efavirenz contains lactose

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Efavirenz contains sodium

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

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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.

Late-onset neurotoxicity, including ataxia and encephalopathy (impaired consciousness, confusion, psychomotor slowing, psychosis, delirium), may occur months to years after beginning efavirenz therapy. Some events of late-onset neurotoxicity have occurred in patients with CYP2B6 genetic polymorphisms, which are associated with increased efavirenz levels despite standard dosing of efavirenz. Patients presenting with signs and symptoms of serious neurologic adverse experiences should be evaluated promptly to assess the possibility that these events may be related to efavirenz use, and whether discontinuation of efavirenz is warranted.

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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 insufficiency

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

Elderly patients

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

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Efavirenz contains sodium

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

4.6 Fertility, pregnancy and lactation

Women of childbearing potential

See below and section 5.3. Efavirenz should not be used during pregnancy, unless the patient's clinical condition requires such treatment. Women of childbearing potential should undergo pregnancy testing before initiation of efavirenz.

Contraception in males and females

Barrier contraception should always be used in combination with other methods of contraception (for example, oral or other hormonal contraceptives, see section 4.5). Because of the long half-life of efavirenz, use of adequate contraceptive measures for 12 weeks after discontinuation of efavirenz is recommended.

Pregnancy

There have been seven retrospective reports of findings consistent with neural tube defects, including meningomyelocele, all in mothers exposed to efavirenz-containing regimens (excluding any efavirenz-containing fixed-dose combination tablets) in the first trimester. Two additional cases (1 prospective and 1 retrospective) including events consistent with neural tube defects have been reported with the fixed-dose combination tablet containing efavirenz, emtricitabine, and tenofovir disoproxil fumarate. A causal relationship of these events to the use of efavirenz has not been established, and the denominator is unknown. As neural tube defects occur within the first 4 weeks of foetal development (at which time neural tubes are sealed), this potential risk would concern women exposed to Efavirenz during the first trimester of pregnancy.

As of July 2013, the Antiretroviral Pregnancy Registry (APR) has received prospective reports of 904 pregnancies with first trimester exposure to efavirenz-containing regimens, resulting in 766 live births. One child was reported to have a neural tube defect, and the frequency and pattern of other birth defects were similar to those seen in children exposed to non-efavirenz-containing regimens, as well as those in HIV negative controls. The incidence of neural tube defects in the general population ranges from 0.5-1 case per 1,000 live births.

Malformations have been observed in foetuses from efavirenz-treated monkeys (see section 5.3).

Breast-feeding

Efavirenz has been shown to be excreted in human milk. There is insufficient information on the effects of efavirenz in newborns/infants. Risk to the infant cannot be excluded. Breastfeeding should be discontinued during treatment with efavirenz. It is recommended that women living with HIV do not breast feed their infants in order to avoid transmission of HIV.

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/bid), and did not affect sperm or offspring of treated male rats (doses up to 200 mg/bid). 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 dizziness, impaired concentration, and/or 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

Summary of the safety profile

Efavirenz has been studied in over 9,000 patients. In a subset of 1,008 adult patients who received 600 mg efavirenz daily in combination with PIs and/or NRTIs in controlled clinical studies, the most frequently reported adverse reactions of at least moderate severity reported in at least 5% of patients were rash (11.6%), dizziness (8.5%), nausea (8.0%), headache (5.7%) and fatigue (5.5%). The most notable adverse reactions associated with efavirenz are rash and nervous system symptoms. Nervous system symptoms usually begin soon after therapy onset and generally resolve after the first 2 - 4 weeks. Severe skin reactions such as Stevens-Johnson syndrome and erythema multiforme; psychiatric adverse reactions including severe depression, death by suicide, and psychosis like behaviour; and seizures have been reported in patients treated with efavirenz. The administration of efavirenz with food may increase efavirenz exposure and may lead to an increase in the frequency of adverse reactions (see section 4.4).

The long-term safety profile of efavirenz-containing regimens was evaluated in a controlled trial (006) in which patients received efavirenz + zidovudine + lamivudine (n = 412, median duration 180 weeks), efavirenz + indinavir (n = 415, median duration 102 weeks), or indinavir + zidovudine + lamivudine (n = 401, median duration 76 weeks). Long-term use of efavirenz in this study was not associated with any new safety concerns.

Tabulated list of adverse reactions

Adverse reactions of moderate or greater severity with at least possible relationship to treatment regimen (based on investigator attribution) reported in clinical trials of efavirenz at the recommended dose in combination therapy (n = 1,008) 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 (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); or very rare (< 1/10,000).

Immune system disorders	
uncommon	hypersensitivity
Metabolism and nutrition disorders	
common	hypertriglyceridaemia*
uncommon	hypercholesterolaemia*
Psychiatric disorders	
common	abnormal dreams, anxiety, depression, insomnia*
uncommon	affect lability, aggression, confusional state, euphoric mood, hallucination, mania, paranoia, *psychosis†*, suicide attempt, suicide ideation, catatonia*
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†*
Eye disorders	
uncommon	vision blurred
Ear and labyrinth disorders	
uncommon	*tinnitus†*, vertigo
Vascular disorders	
uncommon	*flushing*[†]
Gastrointestinal disorders	
common	abdominal pain, diarrhoea, nausea, vomiting
uncommon	pancreatitis
Hepatobiliary disorders	
common	aspartate aminotransferase (AST) increased*, alanine aminotransferase (ALT) increased*, gamma-glutamyltransferase (GGT) increased*
uncommon	hepatitis acute
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 conditions	
common	fatigue

*,†,‡ See section Description of selected adverse reactions for more details.

Description of selected adverse reactions

Information regarding post-marketing surveillance

†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 per A Guideline on Summary of Product Characteristics (SmPC) (rev. 2, Sept 2009) 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).

Rash

In clinical studies, 26% of patients treated with 600 mg of efavirenz experienced skin rash compared with 17% of patients treated in control groups. Skin rash was considered treatment related in 18% of patients treated with efavirenz. Severe rash occurred in less than 1% of patients treated with efavirenz, and 1.7% discontinued therapy because of rash. The incidence of erythema multiforme or Stevens-Johnson syndrome was approximately 0.1%.

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 appropriate 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. (See section 4.4.)

Psychiatric symptoms: serious psychiatric adverse reactions have been reported in patients treated with efavirenz. In controlled trials, the frequency of specific serious psychiatric events were:

	Efavirenz regimen (n=1,008)	Control regimen (n=635)
severe depression	1.6%	0.6%
suicidal ideation	0.6%	0.3%
non-fatal suicide attempts	0.4%	0%
aggressive behaviour	0.4%	0.3%
paranoid reactions	0.4%	0.3%
manic reactions	0.1%	0%

Patients with a history of psychiatric disorders appear to be at greater risk of these serious psychiatric adverse reactions with frequencies ranging from 0.3% for manic reactions to 2.0% for both severe depression and suicidal ideation. There have also been post-marketing reports of death by suicide, delusions and psychosis-like behaviour catatonia.

Nervous system symptoms

In clinical controlled trials, frequently reported adverse reactions included, but were not limited to dizziness, insomnia, somnolence, impaired concentration and abnormal dreaming. Nervous system symptoms 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. In a study of uninfected volunteers, a representative nervous system symptom had a median time to onset of 1 hour post-dose and a median duration of 3 hours. Nervous system symptoms may occur more frequently when efavirenz is taken concomitantly with meals possibly due to increased efavirenz plasma levels (see section 5.2). Dosing at bedtime seems to improve the tolerability of these symptoms and can be recommended during the first weeks of therapy and in patients who continue to experience these symptoms (see section 4.2). Dose reduction or splitting the daily dose has not been shown to provide benefit.

Analysis of long-term data showed that, beyond 24 weeks of therapy, the incidences of new-onset nervous system symptoms among efavirenz-treated patients were generally similar to those in the control arm.

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

In HIV infected patients with severe immune deficiency at the time of initiation of combination antiretroviral therapy (CART), an inflammatory reaction to asymptomatic or residual opportunistic infections may arise. Autoimmune disorders (such as Grave's disease and autoimmune hepatitis) 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

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

Laboratory test abnormalities:

Liver enzymes: Elevations of AST and ALT to greater than five times the upper limit of the normal range (ULN) were seen in 3% of 1,008 patients treated with 600 mg of efavirenz (5-8% after long-term treatment in study 006). Similar elevations were seen in patients treated with control regimens (5% after long-term treatment). Elevations of GGT to greater than five times ULN were observed in 4% of all patients treated with 600 mg of efavirenz and 1.5-2% of patients treated with control regimens (7% of efavirenz-treated patients and 3% of control-treated patients after long-term treatment). Isolated elevations of GGT in patients receiving efavirenz may reflect enzyme induction. In the long-term study (006), 1% of patients in each treatment arm discontinued because of liver or biliary system disorders.

Amylase: in the clinical trial subset of 1,008 patients, asymptomatic increases in serum amylase levels greater than 1.5 times the upper limit of normal were seen in 10% of patients treated with efavirenz and 6% of patients treated with control regimens. The clinical significance of asymptomatic increases in serum amylase is unknown.

Metabolic parameters

Weight and levels of blood lipids and glucose may increase during antiretroviral therapy (see section 4.4).

Paediatric population

Undesirable effects in children were generally similar to those of adult patients. Rash was reported more frequently in children (59 of 182 (32%) treated with efavirenz) and was more often of higher grade than in adults (severe rash was reported in 6 of 182 (3.3%) of children). Prophylaxis with appropriate antihistamines prior to initiating therapy with efavirenz in children may be considered.

Other special populations

Liver enzymes in hepatitis B or C co-infected patients: in the long-term data set from study 006, 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 co-infected patients in study 006, elevations in AST to greater than five times ULN developed in 13% of efavirenz-treated patients and in 7% of control, and elevations in ALT to greater than five times ULN developed 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

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme at: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store

4.8 Undesirable effects

Summary of the safety profile

Efavirenz has been studied in over 9,000 patients. In a subset of 1,008 adult patients who received 600 mg efavirenz daily in combination with PIs and/or NRTIs in controlled clinical studies, the most frequently reported adverse reactions of at least moderate severity reported in at least 5% of patients were rash (11.6%), dizziness (8.5%), nausea (8.0%), headache (5.7%) and fatigue (5.5%). The most notable adverse reactions associated with efavirenz are rash and nervous system symptoms. Nervous system symptoms usually begin soon after therapy onset and generally resolve after the first 2 - 4 weeks. Severe skin reactions such as Stevens-Johnson syndrome and erythema multiforme; psychiatric adverse reactions including severe depression, death by suicide, and psychosis like behaviour; and seizures have been reported in patients treated with efavirenz. The administration of efavirenz with food may increase efavirenz exposure and may lead to an increase in the frequency of adverse reactions (see section 4.4).

The long-term safety profile of efavirenz-containing regimens was evaluated in a controlled trial (006) in which patients received efavirenz + zidovudine + lamivudine

(n = 412, median duration 180 weeks), efavirenz + indinavir (n = 415, median duration 102 weeks), or indinavir + zidovudine + lamivudine (n = 401, median duration 76 weeks). Long-term use of efavirenz in this study was not associated with any new safety concerns.

Tabulated list of adverse reactions

Adverse reactions of moderate or greater severity with at least possible relationship to treatment regimen (based on investigator attribution) reported in clinical trials of efavirenz at the recommended dose in combination therapy (n = 1,008) 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 (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); or very rare (< 1/10,000).

Immune system disorders	
uncommon	hypersensitivity
Metabolism and nutrition disorders	
common	hypertriglyceridaemia*
uncommon	hypercholesterolaemia*
Psychiatric disorders	
common	abnormal dreams, anxiety, depression, insomnia*
uncommon	affect lability, aggression, confusional state, euphoric mood, hallucination, mania, paranoia, *psychosis†*, suicide attempt, suicide ideation, catatonia*
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†*
not known	encephalopathy
Eye disorders	
uncommon	vision blurred
Ear and labyrinth disorders	
uncommon	*tinnitus†*, vertigo

Vascular disorders	
uncommon	*flushing*[†]
Gastrointestinal disorders	
common	abdominal pain, diarrhoea, nausea, vomiting
uncommon	pancreatitis
Hepatobiliary disorders	
common	aspartate aminotransferase (AST) increased*, alanine aminotransferase (ALT) increased*, gamma-glutamyltransferase (GGT) increased*
uncommon	hepatitis acute
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 conditions	
common	fatigue

*,†,‡ See section Description of selected adverse reactions for more details.

Description of selected adverse reactions

Information regarding post-marketing surveillance

†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 per A Guideline on Summary of Product Characteristics (SmPC) (rev. 2, Sept 2009) 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).

Rash

In clinical studies, 26% of patients treated with 600 mg of efavirenz experienced skin rash compared with 17% of patients treated in control groups. Skin rash was considered treatment related in 18% of patients treated with efavirenz. Severe rash occurred in less than 1% of patients treated with efavirenz, and 1.7% discontinued therapy because of rash. The incidence of erythema multiforme or Stevens-Johnson syndrome was approximately 0.1%.

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 appropriate 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. (See section 4.4.)

Psychiatric symptoms: serious psychiatric adverse reactions have been reported in patients treated with efavirenz. In controlled trials, the frequency of specific serious psychiatric events were:

	Efavirenz regimen (n=1,008)	Control regimen (n=635)
severe depression	1.6%	0.6%
suicidal ideation	0.6%	0.3%
non-fatal suicide attempts	0.4%	0%
aggressive behaviour	0.4%	0.3%
paranoid reactions	0.4%	0.3%
manic reactions	0.1%	0%

Patients with a history of psychiatric disorders appear to be at greater risk of these serious psychiatric adverse reactions with frequencies ranging from 0.3% for manic reactions to 2.0% for both severe depression and suicidal ideation. There have also been post-marketing reports of death by suicide, delusions and psychosis-like behaviour catatonia.

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receiving control regimens. In clinical studies 2% of patients treated with efavirenz discontinued therapy due to such symptoms.

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Ataxia and encephalopathy associated with high levels of efavirenz, occurring months to years after beginning efavirenz therapy have been reported post-marketing (see section 4.4).

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

In HIV infected patients with severe immune deficiency at the time of initiation of combination antiretroviral therapy (CART), an inflammatory reaction to asymptomatic or residual opportunistic infections may arise. Autoimmune disorders (such as Grave's disease and autoimmune hepatitis) 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).

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GGT to greater than five times ULN were observed in 4% of all patients treated with 600 mg of efavirenz and 1.5-2% of patients treated with control regimens (7% of efavirenz-treated patients and 3% of control-treated patients after long-term treatment). Isolated elevations of GGT in patients receiving efavirenz may reflect enzyme induction. In the long-term study (006), 1% of patients in each treatment arm discontinued because of liver or biliary system disorders.

Amylase: in the clinical trial subset of 1,008 patients, asymptomatic increases in serum amylase levels greater than 1.5 times the upper limit of normal were seen in 10% of patients treated with efavirenz and 6% of patients treated with control regimens. The clinical significance of asymptomatic increases in serum amylase is unknown.

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5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

ATC code: J05AG03

Mechanism of action*:* efavirenz is a NNRTI of HIV-1. Efavirenz is a non-competitive inhibitor of HIV-1 reverse transcriptase (RT) and does not significantly inhibit HIV-2 RT or cellular DNA polymerases (α, β, γ or δ).

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 Cmax 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 Cmax 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).

Antiviral activity: the free concentration of efavirenz required for 90 to 95% inhibition of wild type or zidovudine-resistant laboratory and clinical isolates *in vitro* ranged from 0.46 to 6.8 nM in lymphoblastoid cell lines, peripheral blood mononuclear cells (PBMCs) and macrophage/monocyte cultures.

Resistance: the potency of efavirenz in cell culture against viral variants with amino acid substitutions at positions 48, 108, 179, 181 or 236 in RT or variants with amino acid substitutions in the protease was similar to that observed against wild type viral strains. The single substitutions which led to the highest resistance to efavirenz in cell culture correspond to a leucine-to-isoleucine change at position 100 (L100I, 17 to 22-fold resistance) and a lysine-to-asparagine at position 103 (K103N, 18 to 33-fold resistance). Greater than 100-fold loss of susceptibility was observed against HIV variants expressing K103N in addition to other amino acid substitutions in RT.

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: cross resistance profiles for efavirenz, nevirapine and delavirdine in cell culture demonstrated that the K103N substitution confers loss of susceptibility to all three NNRTIs. Two of three delavirdine-resistant clinical isolates examined were cross-resistant to efavirenz and contained the K103N substitution. A third isolate which carried a substitution at position 236 of RT was not cross-resistant to efavirenz.

Viral isolates recovered from PBMCs of patients enrolled in efavirenz clinical studies who showed evidence of treatment failure (viral load rebound) were assessed for

susceptibility to NNRTIs. Thirteen isolates previously characterised as efavirenz-resistant were also resistant to nevirapine and delavirdine. Five of these NNRTI-resistant isolates were found to have K103N or a valine-to-isoleucine substitution at position 108 (V108I) in RT. Three of the efavirenz treatment failure isolates tested remained sensitive to efavirenz in cell culture and were also sensitive to nevirapine and delavirdine.

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 not been studied in controlled studies in patients with advanced HIV disease, namely with CD4 counts < 50 cells/mm3, or in PI or NNRTI experienced patients. Clinical experience in controlled studies with combinations including didanosine or zalcitabine is limited.

Two controlled studies (006 and ACTG 364) of approximately one year duration with efavirenz in combination with NRTIs and/or PIs, have demonstrated reduction of viral load below the limit of quantification of the assay and increased CD4 lymphocytes in antiretroviral therapy-naïve and NRTI-experienced HIV-infected patients. Study 020 showed similar activity in NRTI-experienced patients over 24 weeks. In these studies the dose of efavirenz was 600 mg once daily; the dose of indinavir was 1,000 mg every 8 hours when used with efavirenz and 800 mg every 8 hours when used without efavirenz. The dose of nelfinavir was 750 mg given three times a day. The standard doses of NRTIs given every 12 hours were used in each of these studies.

Study 006, a randomized, open-label trial, compared efavirenz + zidovudine + lamivudine or efavirenz + indinavir with indinavir + zidovudine + lamivudine in 1,266 patients who were required to be efavirenz-, lamivudine-, NNRTI-, and PI-naive at study entry. The mean baseline CD4 cell count was 341 cells/mm3 and the mean baseline HIV-RNA level was 60,250 copies/ml. Efficacy results for study 006 on a subset of 614 patients who had been enrolled for at least 48 weeks are found in Table 2. In the analysis of responder rates (the non-completer equals failure analysis [NC = F]), patients who terminated the study early for any reason, or who had a missing HIV-RNA measurement that was either preceded or followed by a measurement above the limit of assay quantification were considered to have HIV-RNA above 50 or above 400 copies/ml at the missing time points.

Table 2: Efficacy results for study 006

		Responder rates (NC = F[a]) Plasma HIV-RNA		Mean change from baseline-CD4 cell count cells/mm3 (S.E.M.[c])
		< 400 copies/ml (95% C.I.[b])	< 50 copies/ml (95% C.I.[b])	
Treatment Regimen[d]	n	48 weeks	48 weeks	48 weeks

EFV + ZDV + 3TC	202	67% (60%, 73%)	62% (55%, 69%)	187 (11.8)
EFV + IDV	206	54% (47%, 61%)	48% (41%, 55%)	177 (11.3)
IDV + ZDV + 3TC	206	45% (38%, 52%)	40% (34%, 47%)	153 (12.3)

[a] NC = F, noncompleter = failure.

[b] C.I., confidence interval.

[c] S.E.M., standard error of the mean.

[d] EFV, efavirenz; ZDV, zidovudine; 3TC, lamivudine; IDV, indinavir.

Long-term results at 168 weeks of study 006 (160 patients completed study on treatment with EFV+IDV, 196 patients with EFV+ZDV+3TC and 127 patients with IDV+ZDV+3TC, respectively), suggest durability of response in terms of proportions of patients with HIV RNA < 400 copies/ml, HIV RNA < 50 copies/ml and in terms of mean change from baseline CD4 cell count.

Efficacy results for studies ACTG 364 and 020 are found in Table 3. Study ACTG 364 enrolled 196 patients who had been treated with NRTIs but not with PIs or NNRTIs. Study 020 enrolled 327 patients who had been treated with NRTIs but not with PIs or NNRTIs. Physicians were allowed to change their patient's NRTI regimen upon entry into the study. Responder rates were highest in patients who switched NRTIs.

Table 3: Efficacy results for studies ACTG 364 and 020

		Responder rates (NC = F[a]) Plasma HIV-RNA				Mean change from baseline-CD4 cell count	
Study Number/Treatment Regimens[b]	n	%	(95% C.I.[c])	%	(95% C.I.)	cells/mm^3	(S.E.M.[d])
Study ACTG 364 48 weeks		< 500 copies/ml		< 50 copies/ml			
EFV + NFV + NRTIs	65	70	(59, 82)	---	---	107	(17.9)
EFV + NRTIs	65	58	(46, 70)	---	---	114	(21.0)
NFV + NRTIs	66	30	(19, 42)	---	---	94	(13.6)

Study 020 24 weeks		< 400 copies/ml		< 50 copies/ml			
EFV + IDV + NRTIs	157	60	(52, 68)	49	(41, 58)	104	(9.1)
IDV + NRTIs	170	51	(43, 59)	38	(30, 45)	77	(9.9)

- [a] NC = F, noncompleter = failure.

  [b] EFV, efavirenz; ZDV, zidovudine; 3TC, lamivudine; IDV, indinavir; NRTI, nucleoside reverse transcriptase inhibitor; NFV, nelfinavir.

  [c] C.I., confidence interval for proportion of patients in response.

  [d] S.E.M., standard error of the mean.

  ---, not performed.

  Paediatric population:
  Study AI266922 was an open-label study to evaluate the pharmacokinetics, safety, tolerability, and antiviral activity of EFAVIRENZ in combination with didanosine and emtricitabine in antiretroviral-naïve and -experienced paediatric patients. Thirty-seven patients 3 months to 6 years of age (median 0.7 years) were treated with EFAVIRENZ. At baseline, median plasma HIV-1 RNA was 5.88 log10copies/mL, median CD4+ cell count was 1144 cells/mm3, and median CD4+ percentage was 25%. The median time on study therapy was 132 weeks; 27% of patients discontinued before Week 48. Using an ITT analysis, the overall proportions of patients with HIV RNA <400 copies/mL and <50 copies/mL at Week 48 were 57% (21/37) and 46% (17/37), respectively. The median increase from baseline in CD4+ count at 48 weeks was 215 cells/mm3 and the median increase in CD4+ percentage was 6%.

  Study PACTG 1021 was an open-label study to evaluate the pharmacokinetics, safety, tolerability, and antiviral activity of EFAVIRENZ in combination with didanosine and emtricitabine in paediatric patients who were antiretroviral therapy naive. Forty-three patients 3 months to 21 years of age (median 9.6 years) were dosed with EFAVIRENZ. At baseline, median plasma HIV-1 RNA was 4.8 log10 copies/mL, median CD4+ cell count was 367 cells/mm3, and median CD4+ percentage was 18%. The median time on study therapy was 181 weeks; 16% of patients discontinued before Week 48. Using an ITT analysis, the overall proportions of patients with HIV RNA <400 copies/mL and <50 copies/mL at Week 48 were 77% (33/43) and 70% (30/43), respectively. The median increase from baseline in CD4+ count at 48 weeks of therapy was 238 cells/mm3 and the median increase in CD4+ percentage was 13%.

  Study PACTG 382 was an open-label study to evaluate the pharmacokinetics, safety, tolerability, and antiviral activity of EFAVIRENZ in combination with nelfinavir and an NRTI in antiretroviral-naive and NRTI-experienced paediatric patients. One hundred two patients 3 months to 16 years of age (median 5.7 years) were treated with EFAVIRENZ. Eighty-seven percent of patients had received prior antiretroviral therapy. At baseline, median plasma HIV-1 RNA was 4.57 log10 copies/mL, median CD4+ cell count was 755 cells/mm3, and median CD4+ percentage was 30%. The median time on study therapy was 118 weeks; 25% of patients discontinued before

Week 48. Using an ITT analysis, the overall proportion of patients with HIV RNA <400 copies/mL and <50 copies/mL at Week 48 were 57% (58/102) and 43% (44/102), respectively. The median increase from baseline in CD4+ count at 48 weeks of therapy was 128 cells/mm3 and the median increase in CD4+ percentage was 5%.

5.2 Pharmacokinetic properties

Absorption: peak efavirenz plasma concentrations of 1.6 - 9.1 μM were attained by 5 hours following single oral doses of 100 mg to 1,600 mg administered to uninfected volunteers. Dose related increases in Cmax and AUC were seen for doses up to 1,600 mg; the increases were less than proportional suggesting diminished absorption at higher doses. Time to peak plasma concentrations (3 - 5 hours) did not change following multiple dosing and steady-state plasma concentrations were reached in 6 - 7 days.

In HIV infected patients at steady state, mean $C_{max,}$ mean C_{min}, and mean AUC were linear with 200 mg, 400 mg, and 600 mg daily doses. In 35 patients receiving efavirenz 600 mg once daily, steady state C_{max} was 12.9 ± 3.7 μM (29%) [mean ± S.D. (% C.V.)], steady state Cmin was 5.6 ± 3.2 μM (57%), and AUC was 184 ± 73 μM·h (40%).

Effect of food: The AUC and C_{max} of a single 600 mg dose of efavirenz film-coated tablets in uninfected volunteers was increased by 28% (90% CI: 22-33%) and 79% (90% CI: 58-102%), respectively, when given with a high fat meal, relative to when given under fasted conditions (see section 4.4).

Distribution: Efavirenz is highly bound (approximately 99.5 - 99.75%) to human plasma proteins, predominantly albumin. In HIV-1 infected patients (n = 9) who received efavirenz 200 to 600 mg once daily for at least one month, cerebrospinal fluid concentrations ranged from 0.26 to 1.19% (mean 0.69%) of the corresponding plasma concentration. This proportion is approximately 3-fold higher than the non-protein-bound (free) fraction of efavirenz in plasma.

Biotransformation: Studies in humans and in vitro studies using human liver microsomes have demonstrated that efavirenz is principally metabolised by the cytochrome P450 system to hydroxylated metabolites with subsequent glucuronidation of these hydroxylated metabolites. These metabolites are essentially inactive against HIV-1. The in vitrostudies suggest that CYP3A4 and CYP2B6 are the major isozymes responsible for efavirenz metabolism and that it inhibited P450 isozymes 2C9, 2C19, and 3A4. In in vitro studies efavirenz did not inhibit CYP2E1 and inhibited CYP2D6 and CYP1A2 only at concentrations well above those achieved clinically.

Efavirenz plasma exposure may be increased in patients with the homozygous G516T genetic variant of the CYP2B6 isoenzyme. The clinical implications of such an association are unknown; however, the potential for an increased frequency and severity of efavirenz-associated adverse events cannot be excluded.

Efavirenz has been shown to induce CYP3A4 and CYP2B6, resulting in the induction of its own metabolism, which may be clinically relevant in some patients. In uninfected volunteers, multiple doses of 200 - 400 mg per day for 10 days resulted in a lower than predicted extent of accumulation (22 - 42% lower) and a shorter terminal half-life compared with single dose administration (see below).). Efavirenz has also been shown to induce UGT1A1. Exposures of raltegravir (a UGT1A1 substrate) are reduced in the presence of efavirenz (see section 4.5, table 3). 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 coadministration is not clear.

Elimination*:* efavirenz has a relatively long terminal half-life of at least 52 hours after single doses and 40 - 55 hours after multiple doses. Approximately 14 - 34% of a radiolabelled dose of efavirenz was recovered in the urine and less than 1% of the dose was excreted in urine as unchanged efavirenz.

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

Gender, race, elderly: 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. Pharmacokinetic studies have not been performed in the elderly.

Paediatric population

The pharmacokinetic parameters for efavirenz at steady state in paediatric patients were predicted by a population pharmacokinetic model and are summarized in Table 4 by weight ranges that correspond to the recommended doses.

Table 4: Predicted steady-state pharmacokinetics of efavirenz (capsules/capsule sprinkles) in HIV-infected paediatric patients

Body Weight	Dose	Mean AUC(0-24) µM·h	Mean Cmax µg/mL	Mean Cmin 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	2.3
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

5.3 Preclinical safety data

Efavirenz was not mutagenic or clastogenic in conventional genotoxicity assays.

Efavirenz induced foetal resorptions in rats. Malformations were observed in 3 of 20 foetuses/ newborns from efavirenz-treated cynomolgus monkeys given doses resulting in plasma efavirenz concentrations similar to those seen in humans. Anencephaly and unilateral anophthalmia with secondary enlargement of the tongue were observed in one foetus, microophthalmia was observed in another foetus, and cleft palate was observed in a third foetus. No malformations were observed in foetuses from efavirenz-treated rats and rabbits.

Biliary hyperplasia was observed in cynomolgus monkeys given efavirenz for ≥ 1 year at a dose resulting in mean AUC values approximately 2-fold greater than those in humans given the recommended dose. The biliary hyperplasia regressed upon cessation of dosing. Biliary fibrosis has been observed in rats. Non-sustained convulsions were observed in some monkeys receiving efavirenz for ≥ 1 year, at doses yielding plasma AUC values 4- to 13-fold greater than those in humans given the recommended dose (see sections 4.4 and 4.8).

Carcinogenicity studies showed an increased incidence of hepatic and pulmonary tumours in female mice, but not in male mice. The mechanism of tumour formation and the potential relevance for humans are not known.

Carcinogenicity studies in male mice, male and female rats were negative. While the carcinogenic potential in humans is unknown, these data suggest that the clinical benefit of efavirenz outweighs the potential carcinogenic risk to humans.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:
Cellulose, microcrystalline (Grade -101) (E460)
Low-substituted hydroxypropyl cellulose (LH-21)
Lactose monohydrate
Hydroxypropyl cellulose (low viscosity grade)
Silica, colloidal anhydrous

Crospovidone (type – B)
Sodium lauryl sulphate
Cellulose, microcrystalline (Grade 200) (E460)
Crospovidone (type – A)
Magnesium stearate

Tablet coat:
Hypromellose type 2910 (E464)
Macrogol
Titanium dioxide (E171)
Iron oxide yellow (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

4 years.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions

6.5 Nature and contents of container

Efavirenz 600 mg film-coated tablets are available in clear PVC/ PVdC- Aluminium foil blister pack and white opaque HDPE bottle pack with white opaque polypropylene closure.

Blister pack: 30 and 90 tablets
HDPE bottle pack: 30, 90 and 500 tablets

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

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

7 MARKETING AUTHORISATION HOLDER

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Ruislip HA4 6QD

United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

PL 16363/0397

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

13/06/2014

10 DATE OF REVISION OF THE TEXT

Variation Approval Date

10 DATE OF REVISION OF THE TEXT

12/05/2026