with a history of seizures or psychiatric disorders including depression. Efavirenz should be stopped if a severe skin rash, associated with blistering, desquamation, mucosal involvement, or fever, develops. Monitoring of serum lipids and blood-glucose may be considered during efavirenz treatment. Food may increase exposure to efavirenz and lead to an increase in the frequency of undesirable effects.

False-positive results in some urinary cannabinoid tests have been reported in subjects receiving efavirenz.

Pregnancy. Licensed product information states that efavirenz has been associated with teratogenicity in *animals*. No specific malformation pattern was noted in more than 200 pregnancies with first-trimester exposure to efavirenz as part of a combination antiretroviral regimen. However, retrospective analysis of these pregnancies noted a few cases of neural tube defects, including meningomyelocele. The use of adequate contraceptive measures is recommended during, and for 12 weeks after, treatment with regimens containing efavirenz.

Interactions

Efavirenz is metabolised mainly by cytochrome P450 isoenzymes including CYP3A4. Consequently, it may compete with other drugs metabolised by this system, potentially resulting in mutually increased plasma concentrations and toxicity. Enzyme inducers may decrease plasma concentrations of efavirenz; efavirenz itself acts as an enzyme inducer and can reduce plasma concentrations of other drugs. Inhibition of some P450 isoenzymes has also been found *in vitro*.

Efavirenz is contra-indicated with drugs that are highly dependent on CYP3A4 for clearance and for which elevated plasma concentrations are associated with serious or life-threatening events. These drugs include antihistamines (astemizole and terfenadine), calcium-channel blockers (bepridil), ergot derivatives (dihydroergotamine, ergometrine, ergotamine, methylergometrine), gastrointestinal prokinetics (cisapride), antipsychotics (pimozide), and sedatives and hypnotics (midazolam and triazolam). St John's wort decreases the concentration of efavirenz; use with the antiretroviral is not recommended due to the possible loss of its activity and development of resistance. For further information on drug interactions of NNRTIs see Table 2, p.944.

Antibacterials. Plasma concentrations of efavirenz may be reduced by *rifampicin* and may necessitate an increase in the dose of efavirenz. A similar interaction might occur with *rifabutin*.

Use of efavirenz with *clarithromycin* has resulted in a decrease in the plasma concentration of clarithromycin and an increase in its active hydroxy metabolite. The combination has been associated with a high incidence of skin rashes.

Antifungals. Giving efavirenz with voriconazole results in a 2-way interaction; efavirenz decreases the concentration of voriconazole and voriconazole increases the concentration of efavirenz. When efavirenz is given with voriconazole, licensed product information for efavirenz suggests the voriconazole maintenance dose should be increased to 400 mg twice daily and the efavirenz dose reduced to 300 mg once daily.

Antivirals. For the effect of efavirenz on *HIV-protease inhibitors*, see p.883.

Grapefruit. The metabolism of efavirenz may be inhibited by concomitant ingestion of grapefruit juice.

Antiviral Action

Efavirenz acts by non-competitive inhibition of HIV-1 reverse transcriptase; it binds to the enzyme, disrupting the conformation of its catalytic site and impairing its RNA- and DNA-dependent polymerase activity.

Resistance to efavirenz and emergence of cross-resistance to other non-nucleoside reverse transcriptase inhibitors has been seen.

Pharmacokinetics

Efavirenz is absorbed after oral doses with peak plasma concentrations being achieved after about 3 to 5 hours. Steady-state plasma concentrations are reached in 6 to 7 days after multiple dosing. Bioavailability is increased after a high-fat meal. Efavirenz is more than 99% bound to plasma proteins and is distributed into the CSF. It is metabolised mainly by hepatic cytochrome P450 isoenzymes CYP3A4 and CYP2B6 into inactive hydroxylated, metabolites. Efavirenz acts as an enzyme inducer and induces its own metabolism resulting in a terminal half-life of 40 to 55 hours after multiple doses compared with 52 to 76 hours after a single dose. About 14 to 34% of a dose is excreted in the urine (less than 1% unchanged), and 16 to 61% in the faeces (primarily as unchanged drug).

◊ References.
1. Kappelhoff BS, *et al*. Population pharmacokinetics of efavirenz in an unselected cohort of HIV-1-infected individuals. *Clin Pharmacokinet* 2005; **44:** 849–61.
2. Almond LM, *et al*. Intracellular and plasma pharmacokinetics of efavirenz in HIV-infected individuals. *J Antimicrob Chemother* 2005; **56:** 738–44.
3. Burger D, *et al*. Interpatient variability in the pharmacokinetics of the HIV non-nucleoside reverse transcriptase inhibitor efavirenz: the effect of gender, race, and CYP2B6 polymorphism. *Br J Clin Pharmacol* 2006; **61:** 148–54.
4. Back DJ, *et al*. Population pharmacokinetics of efavirenz in an unselected cohort of HIV-1-infected individuals. *Clin Pharmacokinet* 2006; **45:** 213–14.

Uses and Administration

Efavirenz is a non-nucleoside reverse transcriptase inhibitor with activity against HIV. It is used with other antiretrovirals for combination therapy of HIV infection and AIDS (p.856).

Efavirenz is given orally as *capsules* or *tablets* in a dose of 600 mg once daily; alternatively, it may be given as an *oral solution* in a dose of 720 mg once daily. Efavirenz tablets and capsules should be given on an empty stomach. Dosing at bedtime is recommended during the first 2 to 4 weeks of therapy to improve tolerability. Bioavailability of efavirenz from the oral solution is less than that from the capsule and so proportionately higher doses of the solution are used.

For details of doses in children and adolescents, see below.

Fixed-dose combination products have been developed in order to improve patient adherence and avoid monotherapy, thereby decreasing the risk of acquired drug resistance. Products containing efavirenz in combination with emtricitabine and tenofovir are available in some countries.

◊ References.
1. Adkins JC, Noble S. Efavirenz. *Drugs* 1998; **56:** 1055–64.
2. Gazzard BG. Efavirenz in the management of HIV infection. *Int J Clin Pract* 1999; **53:** 60–4.
3. Frampton JE, Croom KF. Efavirenz/emtricitabine/tenofovir disoproxil fumarate: triple combination tablet. *Drugs* 2006; **66:** 1501–12.

Administration in children. For the treatment of HIV infection in children 3 years of age and older and adolescents efavirenz is given daily with other antiretroviral drugs. In the USA oral *capsules* and *tablets* are available and the dose is based on body-weight:

- 10 to 14 kg: 200 mg once daily
- 15 to 19 kg: 250 mg once daily
- 20 to 24 kg: 300 mg once daily
- 25 to 32.4 kg: 350 mg once daily
- 32.5 to 39 kg: 400 mg once daily
- 40 kg or more: as for adults (above)

Capsules are also available in the UK for use in children and adolescents; doses are similar to those used in the USA.

In the UK an *oral solution* is also available; the dose ranges, which are again calculated in terms of body-weight, also depend on the age range:

- 13 to 14 kg: children less than 5 years, 360 mg daily; children 5 years and older, 270 mg once daily
- 15 to 19 kg: children less than 5 years, 390 mg daily; children 5 years and older, 300 mg once daily
- 20 to 24 kg: children less than 5 years, 450 mg daily; children 5 years and older, 360 mg once daily
- 25 to 32.4 kg: children less than 5 years, 510 mg daily; children 5 years and older, 450 mg once daily
- 32.5 to 39 kg: children 5 years and older, 510 mg once daily
- 40 kg or more: children 5 years and older, as for adults, above

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Efavilea; Filginase; Stocrin; Sulfinav; Virorrever; ***Austral.:*** Stocrin; ***Austria:*** Stocrin; ***Belg.:*** Stocrin; ***Braz.:*** Stocrin; ***Canad.:*** Sustiva; ***Chile:*** Stocrin; ***Cz.:*** Stocrin; Sustiva; ***Denm.:*** Stocrin; ***Fin.:*** Stocrin; ***Fr.:*** Sustiva; ***Ger.:*** Sustiva; ***Gr.:*** Stocrin; ***Hong Kong:*** Stocrin; ***Hung.:*** Stocrin; ***India:*** Efavir; ***Irl.:*** Sustiva; ***Israel:*** Stocrin; ***Ital.:*** Sustiva; ***Malaysia:*** Stocrin; ***Mex.:*** Stocrin; ***Neth.:*** Stocrin; Sustiva; ***Norw.:*** Stocrin; ***NZ:*** Stocrin; ***Pol.:*** Stocrin; ***Port.:*** Stocrin; Sustiva; ***Rus.:*** Stocrin (Стокрин); ***S.Afr.:*** Stocrin; ***Singapore:*** Stocrin; ***Spain:*** Sustiva; ***Swed.:*** Stocrin; ***Switz.:*** Stocrin; ***Thai.:*** Stocrin; ***UK:*** Sustiva; ***USA:*** Sustiva; ***Venez.:*** Efavir; Stocrin.

Multi-ingredient: ***India:*** Odivir Kit; ***UK:*** Atripla; ***USA:*** Atripla.

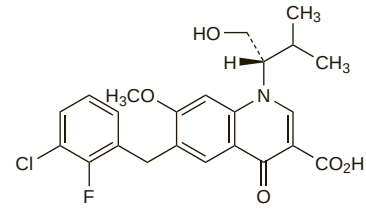
Elvitegravir *(USAN, rINN)*

Elvitégravir; Elvitegravirum; GS-9137; JTK-303. 6-(3-Chloro-2-fluorobenzyl)-1-[(2*S*)-1-hydroxy-3-methylbutan-2-yl]-7-methoxy-4-oxo-1,4-dihydroquinoline-3-carboxylic acid.

Эльвитегравир

$C_{23}H_{23}ClFNO_5$ = 447.9.

CAS — 697761-98-1.



Profile

Elvitegravir is an HIV-integrase inhibitor with antiretroviral activity against HIV-1. It is under investigation for the treatment of HIV infection and AIDS.

◊ References.
1. Ramanathan S, *et al*. Pharmacokinetics of coadministered ritonavir-boosted elvitegravir and zidovudine, didanosine, stavudine, or abacavir. *J Acquir Immune Defic Syndr* 2007; **46:** 160–6.
2. Shimura K, *et al*. Broad antiretroviral activity and resistance profile of the novel human immunodeficiency virus integrase inhibitor elvitegravir (JTK-303/GS-9137). *J Virol* 2008; **82:** 764–74.

Emtricitabine *(USAN, rINN)*

BW-524W91; Emtricitabina; Emtricitabinum; Emtrisitabin; FTC; (−)-FTC; FTC-(−). 5-Fluoro-1-[(2*R*,5*S*)-2-(hydroxymethyl)-1,3-oxathiolan-5-yl]cytosine.

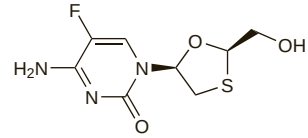
Эмтрицитабин

$C_8H_{10}FN_3O_3S$ = 247.2.

CAS — 143491-57-0.

ATC — J05AF09.

ATC Vet — QJ05AF09.



Adverse Effects

The most common adverse effects associated with antiretroviral regimens containing emtricitabine are headache, diarrhoea, and nausea; hyperpigmented skin discoloration is very common in children and common in adults. Other common adverse effects include abdominal pain, vomiting, dyspepsia, abnormal dreams, asthenia, dizziness, insomnia, pain, allergic skin reactions, pruritus, rashes, and urticaria. Abnormal laboratory test results associated with emtricitabine-containing regimens include hyperbilirubinaemia, increases in serum lipase and pancreatic amylase, and raised liver enzymes. There have also been reports of neutropenia and anaemia. Lactic acidosis, usually associated with severe hepatomegaly and steatosis, has been associated with treatment with NRTIs.

Immune reconstitution syndrome (an inflammatory immune response resulting in clinical deterioration) has been reported during the initial phase of treatment with combination antiretroviral therapy, including emtricitabine, in HIV-infected patients with severe immune deficiency. Accumulation or redistribution of body fat (lipodystrophy) including central obesity, dorsocervical fat enlargement (buffalo hump), peripheral wasting, facial wasting, breast enlargement, and cushingoid appearance have been observed in patients receiving antiretroviral therapy, including emtricitab-