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.

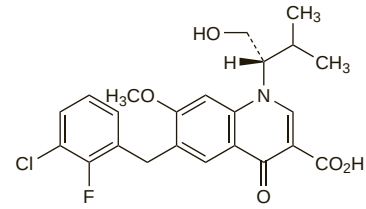
Elvitegravir *(USAN, rINN)*

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.

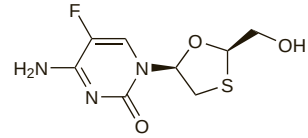
Эмтрицитабин

$C_8H_{10}FN_3O_3S$ = 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-

ine. Metabolic abnormalities such as hypertriglyceridaemia, hypercholesterolaemia, insulin resistance, hyperglycaemia, and hyperlactataemia have also been reported. NRTIs have also been associated with mitochondrial dysfunction manifesting as abnormal behaviour, anaemia, convulsions, hyperlipasaemia, hypertonia, and neutropenia. Elevated creatine phosphokinase, myalgia, myositis, and rarely rhabdomyolysis have been reported, particularly when nucleoside analogues have been given with HIV-protease inhibitors. Osteonecrosis has been reported, particularly in patients with advanced HIV disease or long-term exposure to combination antiretroviral therapy. For further information on adverse effects associated with NRTIs see Zidovudine, p.914.

Precautions

Treatment with emtricitabine should be stopped if there is a rapid increase in aminotransferase concentrations, progressive hepatomegaly or steatosis, or metabolic or lactic acidosis of unknown aetiology. Emtricitabine should be given with caution to patients with hepatomegaly or other risk factors for liver disease. Patients co-infected with chronic hepatitis B or C and treated with combination antiretroviral therapy are at increased risk for severe and potentially fatal hepatic adverse events; treatment should be interrupted or stopped if there is evidence of exacerbation of liver disease. It is recommended that all patients should be tested for the presence of hepatitis B infection before treatment is begun, and that patients co-infected with HIV and hepatitis B should be monitored for several months after stopping treatment with emtricitabine for signs of exacerbations of hepatitis. Emtricitabine should be used with caution and doses adjusted in patients with renal impairment.

Interactions

Caution should be exercised when emtricitabine is given with other drugs eliminated by active tubular secretion as competition for the elimination pathway may increase the serum concentrations of either drug.

Antiviral Action

Emtricitabine is converted intracellularly in stages to the triphosphate. This triphosphate halts the DNA synthesis of HIV through competitive inhibition of reverse transcriptase. Emtricitabine-resistant strains of HIV have been identified and cross-resistance to other nucleoside reverse transcriptase inhibitors may occur.

Pharmacokinetics

Emtricitabine is rapidly and extensively absorbed from the gastrointestinal tract after oral doses, with peak plasma concentrations occurring after 1 to 2 hours. Bioavailability is reported to be 93% for the capsules. Binding to plasma proteins is reported to be less than 4%. The plasma elimination half-life is about 10 hours. Emtricitabine is metabolised to a limited degree, but is excreted largely unchanged in the urine and to a lesser extent in the faeces. It is partially removed by haemodialysis.

Uses and Administration

Emtricitabine is a nucleoside reverse transcriptase inhibitor related to cytosine with antiviral activity against HIV-1 and hepatitis B virus. It is used in the treatment of HIV infection and AIDS (p.856). Viral resistance emerges rapidly when emtricitabine is used alone, and it is therefore used with other antiretrovirals.

Emtricitabine is given orally once daily as capsules in a usual adult dose of 200 mg or 240 mg as oral solution.

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

For details of doses of emtricitabine to be used in patients with renal impairment, 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 emtricitabine in combination with tenofovir, and with efavirenz plus tenofovir are available in some countries.

◊ Reviews.

1. Dando TM, Wagstaff AJ. Emtricitabine/tenofovir disoproxil fumarate. *Drugs* 2004; **64:** 2075–82.
2. Modrzejewski KA, Herman RA. Emtricitabine: a once-daily nucleoside reverse transcriptase inhibitor. *Ann Pharmacother* 2004; **38:** 1006–14.
3. Frampton JE, Perry CM. Emtricitabine: a review of its use in the management of HIV infection. *Drugs* 2005; **65:** 1427–48.
4. Saag MS. Emtricitabine, a new antiretroviral agent with activity against HIV and hepatitis B virus. *Clin Infect Dis* 2006; **42:** 126–31.

Administration in children. For the treatment of HIV infection in infants, children, and adolescents emtricitabine is given with other antiretroviral drugs. Doses, given once daily, are based on body-weight:

- in infants up to 3 months of age the *oral solution* is given in a dose of 3 mg/kg daily
- in infants, children, and adolescents over 3 months of age the oral solution is given in a dose of 6 mg/kg daily to a maximum daily dose of 240 mg
- the *capsules* may be given to children and adolescents weighing more then 33 kg in the usual adult dose of 200 mg daily.

Administration in renal impairment. Doses of emtricitabine should be reduced in patients with renal impairment, according to the patient's creatinine clearance (CC):

- CC at least 50 mL/minute: usual adult doses (as capsules or solution)
- CC 30 to 49 mL/minute: 200 mg every 48 hours (capsules) or 120 mg every 24 hours (oral solution)
- CC 15 to 29 mL/minute: 200 mg every 72 hours (capsules) or 80 mg every 24 hours (oral solution)
- CC less than 15 mL/minute: 200 mg every 96 hours (capsules) or 60 mg every 24 hours (oral solution)

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Emtriva; ***Austral.:*** Emtriva; ***Belg.:*** Emtriva; ***Cz.:*** Emtriva; ***Denm.:*** Emtriva; ***Fin.:*** Emtriva; ***Fr.:*** Emtriva; ***Ger.:*** Emtriva; ***Gr.:*** Emtriva; ***Hung.:*** Emtriva; ***Irl.:*** Emtriva; ***Ital.:*** Emtriva; ***Mex.:*** Emtriva; ***Neth.:*** Emtriva; ***Norw.:*** Emtriva; ***NZ:*** Emtriva; ***Pol.:*** Emtriva; ***Port.:*** Emtriva; ***Spain:*** Emtriva; ***Swed.:*** Emtriva; ***Switz.:*** Emtriva; ***UK:*** Emtriva; ***USA:*** Emtriva.

Multi-ingredient: ***Arg.:*** Truvada; ***Austral.:*** Truvada; ***Cz.:*** Truvada; ***Fin.:*** Truvada; ***Fr.:*** Truvada; ***Ger.:*** Truvada; ***Gr.:*** Truvada; ***Irl.:*** Truvada; ***Ital.:*** Truvada; ***Mex.:*** Truvada; ***Neth.:*** Truvada; ***NZ:*** Truvada; ***Port.:*** Truvada; ***Spain:*** Truvada; ***Swed.:*** Truvada; ***UK:*** Atripla; Truvada; ***USA:*** Atripla; Truvada.

Enfuvirtide *(BAN, USAN, rINN)*

DP-178; Enfuvirtida; Enfuvirtidum; Pentafusida; Pentafuside; T-20.

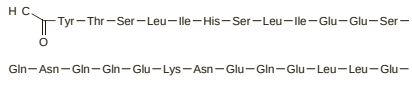
Энфувиртид

$C_{204}H_{301}N_{51}O_{64}$ = 4491.9.

CAS — 159519-65-0.

ATC — J05AX07.

ATC Vet — QJ05AX07.



Adverse Effects

The most common adverse effects associated with antiretroviral regimens containing enfuvirtide are local injection site reactions with resultant pain, erythema, induration, nodules and cysts, pruritus, and ecchymosis. These reactions have been reported to occur in 98% of patients, but only a small minority needed to stop therapy. Other very common adverse effects include nausea, diarrhoea, weight loss, and peripheral neuropathy. Anorexia, abdominal pain, constipation, pancreatitis, myalgia, weakness or loss of strength, lymphadenopathy, insomnia, depression, 'flu-like' illness, sinusitis, and conjunctivitis are also common. An increased incidence of some bacterial infections, in particular of pneumonia, has occurred in patients receiving enfuvirtide. Hypersensitivity reactions have occurred in about 1% of patients. Other adverse effects have included anxiety, hyperglycaemia, hypertriglyceridaemia, and eosinophilia.

Immune reconstitution syndrome (an inflammatory immune response resulting in clinical deterioration) has been reported during the initial phase of treatment with combination antiretroviral therapy in HIV-infected patients with severe immune deficiency. Osteonecrosis has been reported, particularly in patients with advanced HIV disease or long-term exposure to combination antiretroviral therapy.

◊ References.

1. Maggi P, *et al.* Cutaneous injection site reactions to long-term therapy with enfuvirtide. *J Antimicrob Chemother* 2004; **53:** 678–81.

Precautions

Enfuvirtide should be stopped immediately and should not be restarted in patients who develop signs of a systemic hypersensitivity reaction. An increased incidence of some bacterial infections, in particular of pneumonia, has been seen and patients receiving enfuvirtide should be closely monitored for signs of pneumonia. UK licensed product information recommends that enfuvirtide be used with caution in patients with hepatic impairment and in those with moderate to severe renal impairment. Patients co-infected with chronic hepatitis B or C and treated with combination antiretroviral therapy are at increased risk for severe and potentially fatal hepatic adverse events.

Antiviral Action

Enfuvirtide is an HIV fusion inhibitor that interferes with entry of HIV into cells by binding to the gp41 subunit of the viral envelope glycoprotein, thereby inhibiting fusion of viral and cellular membranes. Strains of HIV with reduced susceptibility to enfuvirtide have been isolated in patients receiving the drug but, owing to the different mode of action of enfuvirtide and the fact that it does not require intracellular activation for its activity, cross-resistance with other antiretrovirals may occur less frequently.

Resistance. References to the development of resistance to enfuvirtide.

1. Greenberg ML, Cammack N. Resistance to enfuvirtide, the first HIV fusion inhibitor. *J Antimicrob Chemother* 2004; **54:** 333–40.

Pharmacokinetics

Enfuvirtide is absorbed after subcutaneous injection with a mean absolute bioavailability of 84%. It is 92% bound to plasma proteins. Enfuvirtide is a peptide and is metabolised by hydrolysis; it does not inhibit cytochrome P450 isoenzymes. The elimination half-life is 3.8 hours after subcutaneous use, although elimination pathways have yet to be identified.

◊ References.

1. Patel IH, *et al.* Pharmacokinetics, pharmacodynamics and drug interaction potential of enfuvirtide. *Clin Pharmacokinet* 2005; **44:** 175–86.
2. Zhang X, *et al.* Population pharmacokinetics of enfuvirtide in HIV-1-infected pediatric patients over 48 weeks of treatment. *J Clin Pharmacol* 2007; **47:** 510–17.

Uses and Administration

Enfuvirtide is a synthetic 36-amino acid peptide that blocks HIV cell fusion and viral entry. It is used with other antiretrovirals for combination therapy of HIV infection and AIDS. Enfuvirtide is given by subcutaneous injection into the upper arm, anterior thigh, or abdomen in a usual dose of 90 mg twice daily. Each injection should be given at a different site from the preceding one. For details of doses in children and adolescents, see below.

◊ References.

1. Lalezari JP, *et al.* Enfuvirtide, an HIV-1 fusion inhibitor, for drug-resistant HIV infection in North and South America. *N Engl J Med* 2003; **348:** 2175–85. Correction. *ibid.*; **349:** 1100.
2. Duffalo ML, James CW. Enfuvirtide: a novel agent for the treatment of HIV-1 infection. *Ann Pharmacother* 2003; **37:** 1448–56.
3. Oldfield V, *et al.* Enfuvirtide: a review of its use in the management of HIV infection. *Drugs* 2005; **65:** 1139–60.