- CC 5 to 14 mL/minute: 4 mg/kg for the first dose then 1.3 mg/kg once daily
- CC less than 5 mL/minute: 1.3 mg/kg for the first dose then 0.7 mg/kg once daily

For the treatment of chronic hepatitis B infection in children and adolescents aged between 2 and 17 years, US licensed product information recommends an oral dose of lamivudine of 3 mg/kg once daily to a maximum daily dose of 100 mg. Dosage reduction would need to be considered in those with renal impairment. UK licensed product information does not recommend the use of lamivudine for the treatment of chronic hepatitis B in those under 17 years of age.

Administration in renal impairment. Dosage of lamivudine should be reduced in patients with moderate to severe renal impairment (creatinine clearance (CC) below 50 mL/minute).

adults: HIV infection:

- CC 30 to 49 mL/minute: 150 mg for the first dose then 150 mg once daily
- CC 15 to 29 mL/minute: 150 mg for the first dose then 100 mg once daily
- CC 5 to 14 mL/minute: 150 mg for the first dose then 50 mg once daily
- CC less than 5 mL/minute: 50 mg for the first dose then 25 mg once daily
- dialysis patients: no additional doses required after routine haemodialysis or peritoneal dialysis

adults: chronic hepatitis B infection:

- CC 30 to 49 mL/minute: 100 mg for the first dose then 50 mg once daily
- CC 15 to 29 mL/minute: 100 mg for the first dose then 25 mg once daily
- CC 5 to 14 mL/minute: 35 mg for the first dose then 15 mg once daily
- CC less than 5 mL/minute: 35 mg for the first dose then 10 mg once daily
- dialysis patients: no additional doses required after routine haemodialysis or peritoneal dialysis

children:

- see Administration in Children, above

Hepatitis. Lamivudine is one of the antivirals being used as an alternative to interferon alfa in the treatment of chronic hepatitis B (p.851).[1-3] In a preliminary study, lamivudine 100 or 300 mg daily reduced hepatitis B virus DNA to low or undetectable levels.[4] In a 1-year double-blind study involving about 350 patients with chronic hepatitis B, lamivudine 100 mg daily was associated with substantial histological improvement in many patients; a dose of 25 mg daily was less effective.[5] Relapses have been reported once treatment with lamivudine is stopped, and a case of reactivation of hepatitis B infection has been observed.[6] Lamivudine may also be effective in preventing re-infection with hepatitis B in patients during chemotherapy[7-9] and in those who have had liver transplants,[10,11] and beneficial responses have been seen in transplant patients with acute hepatitis B infection treated with lamivudine 100 mg daily for prolonged periods.[12]

1. Dienstag JL, *et al.* Lamivudine as initial treatment for chronic hepatitis B in the United States. *N Engl J Med* 1999; **341:** 1256–63.
2. Hagmeyer KO, Pan Y-Y. Role of lamivudine in the treatment of chronic hepatitis B virus infection. *Ann Pharmacother* 1999; **33:** 1104–12.
3. Jonas MM, *et al.* Clinical trial of lamivudine in children with chronic hepatitis B. *N Engl J Med* 2002; **346:** 1706–13. Correction. *ibid.*; **347:** 955.
4. Dienstag JL, *et al.* A preliminary trial of lamivudine for chronic hepatitis B infection. *N Engl J Med* 1995; **333:** 1657–61.
5. Lai C-L, *et al.* A one-year trial of lamivudine for chronic hepatitis B. *N Engl J Med* 1998; **339:** 61–8.
6. Honkoop P, *et al.* Hepatitis B reactivation after lamivudine. *Lancet* 1995; **346:** 1156–7.
7. Yeo W, *et al.* Lamivudine for the prevention of hepatitis B virus reactivation in hepatitis B s-antigen seropositive cancer patients undergoing cytotoxic chemotherapy. *J Clin Oncol* 2004; **22:** 927–34.
8. Idilman R. Lamivudine prophylaxis in HBV carriers with haemato-oncological malignancies who receive chemotherapy. *J Antimicrob Chemother* 2005; **55:** 828–31.
9. Loomba R, *et al.* Systematic review: the effect of preventive lamivudine on hepatitis B reactivation during chemotherapy. *Ann Intern Med* 2008; **148:** 519–28.
10. Grellier L, *et al.* Lamivudine prophylaxis against reinfection in liver transplantation for hepatitis B cirrhosis. *Lancet* 1996; **348:** 1212–15. Correction. *ibid.* 1997; **349:** 364.
11. Perrillo RP, *et al.* A multicenter United States-Canadian trial to assess lamivudine monotherapy before and after liver transplantation for chronic hepatitis B. *Hepatology* 2001; **33:** 424–32.
12. Andreone P, *et al.* Lamivudine treatment for acute hepatitis B after liver transplantation. *J Hepatol* 1998; **29:** 985–9.

HIV infection and AIDS. Lamivudine is a potent inhibitor of HIV-1 and HIV-2 *in vitro*, including variants resistant to zidovudine.[1] Resistance emerges rapidly when lamivudine is given alone to patients with HIV infections,[2] although sustained responses have been reported despite the emergence of resistance.[3] Combination therapy with lamivudine delays, and may even reverse, the emergence of zidovudine resistance and produces a sustained synergistic antiretroviral effect,[4] but HIV strains resistant to both lamivudine and zidovudine may arise.[5] As discussed on p.856, combination therapy, typically with two nucleoside reverse transcriptase inhibitors and either a non-nucleoside reverse transcriptase inhibitor or an HIV-protease inhibitor, is standard therapy for HIV infection. Treatment with lamivudine plus zidovudine has produced better responses than either drug alone in antiretroviral-naive patients,[6,7] and has produced additional responses in antiretroviral-experienced patients,[8,9] with little additional toxicity. The addition of lamivudine to existing antiretroviral therapy was reported to slow the progression of the disease and improve survival,[10] and treatment with lamivudine, indinavir, and nevirapine produced beneficial responses in patients who had previously failed on combined nucleoside analogue therapy.[11] Clinically useful CNS concentrations of lamivudine were achieved in patients with HIV infection given combination therapy with lamivudine and zidovudine or stavudine.[12]

Lamivudine is also used in prophylactic regimens after occupational exposure to HIV infection (see p.858) and has been tried for reducing vertical transmission from mother to neonate.[13,14]

1. Anonymous. Lamivudine: impressive benefits in combination with zidovudine. *WHO Drug Inf* 1996; **10:** 5–7.
2. Wainberg MA, *et al.* Development of HIV-1 resistance to (–)2′-deoxy-3′-thiacytidine in patients with AIDS or advanced AIDS-related complex. *AIDS* 1995; **9:** 351–7.
3. Ingrand D, *et al.* Phase I/II study of 3TC (lamivudine) in HIV-positive, asymptomatic or mild AIDS-related complex patients: sustained reduction in viral markers. *AIDS* 1995; **9:** 1323–9.
4. Larder BA, *et al.* Potential mechanism for sustained antiretroviral efficacy of AZT-3TC combination therapy. *Science* 1995; **269:** 696–9.
5. Miller V, *et al.* Dual resistance to zidovudine and lamivudine in patients treated with zidovudine-lamivudine combination therapy: association with therapeutic failure. *J Infect Dis* 1998; **177:** 1521–32.
6. Eron JJ, *et al.* Treatment with lamivudine, zidovudine, or both in HIV-positive patients with 200 to 500 CD4+ cells per cubic millimeter. *N Engl J Med* 1995; **333:** 1662–9.
7. Katlama C, *et al.* Safety and efficacy of lamivudine-zidovudine combination therapy in antiretroviral-naive patients: a randomized controlled comparison with zidovudine monotherapy. *JAMA* 1996; **276:** 118–25.
8. Staszewski S, *et al.* Safety and efficacy of lamivudine-zidovudine combination therapy in zidovudine-experienced patients: a randomized controlled comparison with zidovudine monotherapy. *JAMA* 1996; **276:** 111–17.
9. Bartlett JA, *et al.* Lamivudine plus zidovudine compared with zalcitabine plus zidovudine in patients with HIV infection: a randomized, double-blind, placebo-controlled trial. *Ann Intern Med* 1996; **125:** 161–72.
10. CAESAR Coordinating Committee. Randomised trial of addition of lamivudine or lamivudine plus loviride to zidovudine-containing regimens for patients with HIV-1 infection: the CAESAR trial. *Lancet* 1997; **349:** 1413–21.
11. Harris M, *et al.* A pilot study of nevirapine, indinavir, and lamivudine among patients with advanced human immunodeficiency virus disease who have had failure of combination nucleoside therapy. *J Infect Dis* 1998; **177:** 1514–20.
12. Foudraine NA, *et al.* Cerebrospinal-fluid HIV-1 RNA and drug concentrations after treatment with lamivudine plus zidovudine or stavudine. *Lancet* 1998; **351:** 1547–51.
13. Mandelbrot L, *et al.* Lamivudine-zidovudine combination for prevention of maternal-infant transmission of HIV-1. *JAMA* 2001; **285:** 2083–93.
14. The Petra Study Team. Efficacy of three short-course regimens of zidovudine and lamivudine in preventing early and late transmission of HIV-1 from mother to child in Tanzania, South Africa, and Uganda (Petra study): a randomised, double-blind, placebo-controlled trial. *Lancet* 2002; **359:** 1178–86.

Preparations

Proprietary Preparations (details are given in Part 3)

Arg.: 3TC; Amilitrap; Birvac†; Ganvirel; Heptodine; Hivirux†; Imunoxa; Kess; Lamibergen; Lamilea; Oralmuv; Ultraviral; Vuclodir; Zeffix†; ***Austral.:*** 3TC; Zeffix; ***Austria:*** Epivir; Zeffix; ***Belg.:*** Epivir; Zeffix; ***Braz.:*** Epivir; Lami; Vudirax; Zeffix†; ***Canad.:*** 3TC; Heptovir; ***Chile:*** 3TC/Epivir; ***Cz.:*** Epivir; Zeffix; ***Denm.:*** Epivir; Zeffix; ***Fin.:*** Epivir; Zeffix; ***Fr.:*** Epivir; Zeffix; ***Ger.:*** Epivir; Kivexa; Zeffix; ***Gr.:*** Epivir; Zeffix; ***Hong Kong:*** 3TC; Zeffix; ***Hung.:*** Epivir; Zeffix; ***India:*** Ladiwin; Lamda; Lamidac; Lamirex†; Lamivir; ***Indon.:*** 3TC; 3TC-HBV; ***Irl.:*** Epivir; Zeffix; ***Israel:*** Epivir; Zeffix; ***Ital.:*** Epivir; Zeffix; ***Jpn:*** Epivir†; ***Malaysia:*** 3TC; Zeffix; ***Mex.:*** 3TC; ***Neth.:*** Epivir; Zeffix; ***Norw.:*** Epivir; Zeffix; ***NZ:*** 3TC; Zeffix; ***Philipp.:*** Zeffix; ***Pol.:*** Epivir; Zeffix; ***Port.:*** Epivir; Zeffix; ***Rus.:*** Epivir (Эпивир); Zeffix (Зеффикс); ***S.Afr.:*** 3TC; ***Singapore:*** Epivir; Zeffix; ***Spain:*** Epivir; Zeffix; ***Swed.:*** Epivir; Zeffix; ***Switz.:*** 3TC; Zeffix; ***Thai.:*** Epivir; Zeffix; ***Turk.:*** Epivir; Zeffix; ***UK:*** Epivir; Zeffix; ***USA:*** Epivir; ***Venez.:*** Epivir; Heptodine†; Lamivir.

Multi-ingredient: Arg.: 3TC Complex; 3TC/AZT; Ganvirel Duo; Hivirux Complex†; Imunoxa Complex; Kess Complex; Kivexa; Muvidina; Tricivir; Trivudin; Ultraviral Duo; Zetavudin; ***Austral.:*** Combivir; Kivexa; Trizivir; ***Austria:*** Combivir; Trizivir; ***Belg.:*** Combivir; Kivexa; Trizivir; ***Braz.:*** Biovir; Duovir†; Vir-Complex†; Zidolam; ***Canad.:*** Combivir; Kivexa; Trizivir; ***Chile:*** Combivir; Kivexa; Tricivir; ***Cz.:*** Combivir; Kivexa; Trizivir; ***Denm.:*** Combivir; Kivexa; Trizivir; ***Fin.:*** Combivir; Kivexa; Trizivir; ***Fr.:*** Combivir; Kivexa; Trizivir; ***Ger.:*** Combivir; Trizivir; ***Gr.:*** Combivir; Kivexa; Trizivir; ***Hong Kong:*** Combivir; Trizivir; ***Hung.:*** Combivir; Kivexa; Trizivir; ***India:*** Combirex†; Duovir; Duovir N; Lamda-Z; Lamivir S; Lamuzid; Odivir Kit; Triomune; ***Irl.:*** Combivir; Kivexa; Trizivir; ***Israel:*** Combivir; Trizivir; ***Ital.:*** Combivir; Kivexa; Trizivir; ***Malaysia:*** Combivir; ***Mex.:*** Combivir; Kivexa; Trizivir; ***Neth.:*** Combivir; Kivexa; Trizivir; ***Norw.:*** Combivir; Kivexa; Trizivir; ***NZ:*** Combivir; Kivexa; Trizivir; ***Philipp.:*** Combivir; ***Pol.:*** Combivir; Kivexa; Trizivir; ***Port.:*** Combivir; Kivexa; Trizivir; ***Rus.:*** Combivir (Комбивир); Trizivir (Тризивир); ***S.Afr.:*** Combivir; Duovir; Lamzid; Retrovir/3TC Post-HIV Exposure†; Triomune; Trizivar; ***Singapore:*** Combivir; Trizivir†; ***Spain:*** Combivir; Kivexa; Trizivir; ***Swed.:*** Combivir; Kivexa; Trizivir; ***Switz.:*** Combivir; Trizivir; ***Thai.:*** Combid; ***Turk.:*** Combivir; ***UK:*** Combivir; Kivexa; Trizivir; ***USA:*** Combivir; Epzicom; Trizivir; ***Venez.:*** Combivir; Duovir; Triomune; Trizivir.

Lopinavir *(BAN, USAN, rINN)*

A-157378.0; ABT-378; Lopinaviiri; Lopinavirum. (αS)-Tetrahydro-*N*-((αS)-α-{(2*S*,3*S*)-2-hydroxy-4-phenyl-3-[2-(2,6-xylyloxy)acetamido]butyl}phenethyl)-α-isopropyl-2-oxo-1(2*H*)-pyrimidineacetamide.

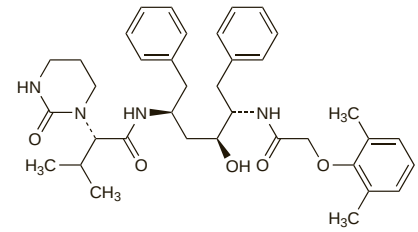
Лопинавир

$C_{37}H_{48}N_4O_5$ = 628.8.

CAS — 192725-17-0.

ATC — J05AE06.

ATC Vet — QJ05AE06.



Adverse Effects

The most common adverse effect associated with antiretroviral regimens containing lopinavir (formulated with ritonavir) is diarrhoea of mild to moderate severity. Pancreatitis has been seen in patients receiving lopinavir, including those who developed marked triglyceride elevations; in some cases fatalities have occurred. Other commonly reported adverse effects include asthenia, headache, insomnia, pain, paraesthesia, gastrointestinal disturbances, acne, and rash. Abnormal laboratory test results associated with lopinavir-containing regimens include increases in serum cholesterol and triglycerides and raised liver enzymes.

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 lopinavir, 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 seen in patients receiving antiretroviral therapy, including lopinavir. Metabolic abnormalities such as hypertriglyceridaemia, hypercholesterolaemia, insulin resistance, hyperglycaemia, and hyperlactataemia have also been reported. Elevated creatine phosphokinase, myalgia, myositis, and rarely rhabdomyolysis have been reported with HIV-protease inhibitors, particularly when given with nucleoside analogues. 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 HIV-protease inhibitors see under Indinavir Sulfate, p.882.

Precautions

Patients with advanced HIV disease may be at increased risk of elevated triglycerides and pancreatitis, and patients with a history of pancreatitis may be at increased risk for recurrence during treatment with ritonavir-boosted lopinavir. Such therapy should be stopped if symptoms of pancreatitis occur.

The oral solution (*Kaletra, Abbott*) has a high content of alcohol and propylene glycol, present as excipients, and appropriate precautions should be taken; it is contra-indicated in infants and young children, in pregnancy, and in hepatic or renal impairment. For further information on propylene glycol toxicity, see Adverse Effects and Precautions, p.2374.

Pregnancy. Licensed product information notes that in *rats* given toxic doses of ritonavir-boosted lopinavir, there was early resorption, decreased fetal viability and body weight, and an increased incidence of skeletal variation and delayed skeletal ossification in the offspring.

Interactions

Lopinavir is extensively metabolised by the cytochrome P450 isoenzyme CYP3A4. It is formulated with low-dose ritonavir, which inhibits this enzyme and thus increases exposure. The combination is an inhibitor of CYP3A4 and increases plasma concentration of drugs mainly metabolised by this isoenzyme. It has also been shown *in vivo* to induce its own metabolism and to increase the biotransformation of some drugs metabolised by cytochrome P450 isoenzymes and by glucuronidation. Drugs that strongly induce CYP3A4 may result in decreased plasma concentrations of the combination.

Ritonavir-boosted lopinavir 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), ergot derivatives (dihydroergotamine, ergometrine, ergotamine, and methylergometrine), gastrointestinal prokinetics (cisapride), antipsychotics (pimozide), sedatives and hypnotics (midazolam and triazolam), and statins (simvastatin and lovastatin). Rifampicin and St John's wort decrease the concentration of lopinavir; use with the antiretroviral is not recommended due to the possible loss of its activity and development of resistance. UK licensed product information contra-indicates the use of vardenafil and amiodarone with ritonavir-boosted lopinavir.

For further information on drug interactions of HIV-protease inhibitors see under Indinavir Sulfate, p.883 and Table 1, p.917.

Antiviral Action

Lopinavir is a selective, competitive, reversible inhibitor of HIV-1 protease. It interferes with the formation of essential viral proteins making them incapable of infecting other cells. Viral resistance develops rapidly when HIV-protease inhibitors are given alone and therefore they are used with other antiretrovirals. Various degrees of cross-resistance between HIV-protease inhibitors may occur.

Pharmacokinetics

Lopinavir is rapidly absorbed from the gastrointestinal tract after oral doses, with peak plasma concentrations occurring after 4 hours. Bioavailability is enhanced when given with a high fat meal. Lopinavir is reported to be 98 to 99% bound to serum proteins. Lopinavir is extensively metabolised, mainly by oxidation by cytochrome P450 isoenzyme CYP3A4; 13 metabolites have been identified with some, such as 4-oxylopinavir and 4-hydroxylopinavir, having antiviral activity. Lopinavir is predominantly excreted in faeces and to a smaller extent in the urine; unchanged lopinavir accounts for about 2.2% of a dose excreted in the urine and 19.8% in the faeces. After multiple dosing, less than 3% of the absorbed lopinavir dose is excreted unchanged in the urine. The terminal elimination half-life of lopinavir is reported to be about 5 to 6 hours.

◊ References.

1. Jullien V, *et al.* Population analysis of weight-, age-, and sex-related differences in the pharmacokinetics of lopinavir in children from birth to 18 years. *Antimicrob Agents Chemother* 2006; **50:** 3548–55.

Uses and Administration

Lopinavir is an HIV-protease inhibitor with antiviral activity against HIV. It is formulated with low-dose ritonavir, which acts as a pharmacokinetic enhancer. The combination is used in the treatment of HIV infection and AIDS (p.856). Ritonavir-boosted lopinavir is also recommended for HIV postexposure prophylaxis (p.858). Viral resistance emerges rapidly when ritonavir-boosted lopinavir is used alone, and it is therefore used with other antiretrovirals.

The dose in treatment-naive and -experienced adults is lopinavir 400 mg (with ritonavir 100 mg) twice daily. Alternatively, treatment-naive patients may take a once-daily dose of lopinavir 800 mg (with ritonavir 200 mg).

US licensed product information recommends that if the tablets are given in a treatment regimen with either *amprenavir, fosamprenavir, nelfinavir, efavirenz,* or *nevirapine* in treatment-experienced patients consideration be given to increasing the dose of lopinavir to 600 mg (with ritonavir 150 mg) twice daily. For patients taking the oral solution in such regimens the dose should be increased to lopinavir 533 mg (with ritonavir 133 mg) twice daily.

Lopinavir film-coated tablets may be taken with or without food; the soft capsules and solution should be taken with food.

For details of doses in children, see below.

◊ Reviews.

1. Oldfield V, Plosker GL. Lopinavir/ritonavir: a review of its use in the management of HIV infection. *Drugs* 2006; **66:** 1275–99.

Administration in children. For the treatment of HIV infection in children, ritonavir-boosted lopinavir is given daily with other antiretroviral drugs. The US licensed product information permits use in infants as young as 14 days old, whereas in the UK the age is 2 years. The dose given should not exceed the maximum adult dose (see above).

In the UK the use of the oral solution is preferred to the soft capsules as a more accurate dose may be given. Doses are based on body-surface.

- In children 2 years of age or more the recommended dose of the *oral solution* is lopinavir 230 mg/m^2 (with ritonavir 57.5 mg/m^2) twice daily with food. The dose should be increased to 300 mg/m^2 (with ritonavir 75 mg/m^2) twice daily with food when given with *efavirenz* or *nevirapine*
- The recommended dose of the *oral soft capsules* in children is according to body-surface as follows:
  - 0.40 to 0.75 m^2: lopinavir 133.3 mg (with ritonavir 33.3 mg) twice daily
  - 0.80 to 1.3 m^2: lopinavir 266.6 mg (with ritonavir 66.6 mg) twice daily
  - 1.4 to 1.75 m^2: lopinavir 400 mg (with ritonavir 100 mg) twice daily

In the USA the dose is based on body-weight or body-surface as follows:

- given without interacting antiretrovirals
  - 14 days to 6 months of age: lopinavir 16 mg/kg (with ritonavir 4 mg/kg) twice daily or lopinavir 300 mg/m^2 (with ritonavir 75 mg/m^2) twice daily
  - 6 months or older and less than 15 kg: lopinavir 12 mg/kg (with ritonavir 3 mg/kg) twice daily or lopinavir 230 mg/m^2 (with ritonavir 57.5 mg/m^2) twice daily
  - 15 to 40 kg: lopinavir 10 mg/kg (with ritonavir 2.5 mg/kg) twice daily or lopinavir 230 mg/m^2 (with ritonavir 57.5 mg/m^2) twice daily
  - over 40 kg: normal adult dose
- given in a treatment regimen with either *amprenavir, fosamprenavir, efavirenz, nelfinavir,* or *nevirapine* (requiring the dose of lopinavir/ritonavir to be increased):
  - 6 months or older and less than 15 kg: lopinavir 13 mg/kg (with ritonavir 3.25 mg/kg) twice daily or lopinavir 300 mg/m^2 (with ritonavir 75 mg/m^2) twice daily
  - 15 to 45 kg: lopinavir 11 mg/kg (with ritonavir 2.75 mg/kg) twice daily or lopinavir 300 mg/m^2 (with ritonavir 75 mg/m^2) twice daily
  - over 45 kg: as for adults, above

SARS. In a preliminary open study[1] 41 patients with probable SARS were given ritonavir-boosted lopinavir as well as the local standard treatment of ribavirin and corticosteroids. At 21 days there was improved outcome with reductions in viral load, corticosteroid dose, and the incidence of nosocomial infections.

1. Chu CM, *et al.* Role of lopinavir/ritonavir in the treatment of SARS: initial virological and clinical findings. *Thorax* 2004; **59:** 252–6.

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Arg.:*** Kaletra; ***Austral.:*** Kaletra; ***Austria:*** Kaletra; ***Belg.:*** Kaletra; ***Braz.:*** Kaletra; ***Canad.:*** Kaletra; ***Chile:*** Kaletra; ***Cz.:*** Kaletra; ***Denm.:*** Kaletra; ***Fin.:*** Kaletra; ***Fr.:*** Kaletra; ***Ger.:*** Kaletra; ***Gr.:*** Kaletra; ***Hong Kong:*** Kaletra; ***Hung.:*** Kaletra; ***India:*** Ritomax-L; ***Israel:*** Kaletra; ***Ital.:*** Kaletra; ***Malaysia:*** Kaletra; ***Mex.:*** Kaletra; ***Neth.:*** Kaletra; ***Norw.:*** Kaletra; ***NZ:*** Kaletra; ***Pol.:*** Kaletra; ***Port.:*** Kaletra; ***Rus.:*** Kaletra (Калетра); ***S.Afr.:*** Kaletra; ***Singapore:*** Kaletra; ***Spain:*** Kaletra; ***Swed.:*** Kaletra; ***Switz.:*** Kaletra; ***Thai.:*** Kaletra; ***Turk.:*** Kaletra; ***UK:*** Kaletra; ***USA:*** Kaletra; ***Venez.:*** Kaletra.

Maraviroc *(USAN, rINN)*

Maravirocum; UK-427857. 4,4-Difluoro-*N*-((1*S*)-3-{(1*R*,3*s*,5*S*)-3-[3-methyl-5-(propan-2-yl)-4*H*-1,2,4-triazol-4-yl]-8-azabicyclo[3.2.1]octan-8-yl}-1-phenylpropyl)cyclohexanecarboxamide.

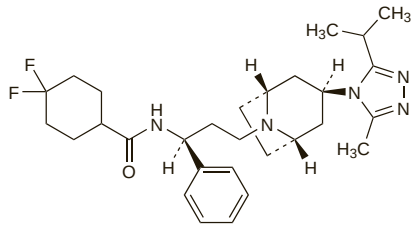
Маравирок

$C_{29}H_{41}F_2N_5O$ = 513.7.

CAS — 376348-65-1.

ATC — J05AX09.

ATC Vet — QJ05AX09.



Adverse Effects and Precautions

On the basis of limited data, maraviroc appears to be well tolerated; non-specific adverse effects associated with maraviroc-based regimens include asthenia, cough and upper respiratory-tract infections, dizziness, abdominal pain and distension, constipation, diarrhoea, dyspepsia, nausea, vomiting, fever, headache, insomnia, somnolence, muscle spasms and back pain, pruritus, and rash. Less frequently reported adverse effects include osteonecrosis and cardiovascular effects such as myocardial ischaemia and myocardial infarction; cardiac adverse effects were reported mainly for patients with pre-existing cardiac disease or risk factors.

Hepatotoxicity has occurred; raised liver enzyme values and bilirubin have also been reported and caution is advised in patients with pre-existing liver dysfunction or co-infection with hepatitis B or C. Although renal clearance normally accounts for only a small proportion of the dose, maraviroc should be used with caution in patients with renal impairment (creatinine clearance less than 80 mL/minute) who are also taking potent inhibitors of the cytochrome P450 isoenzyme CYP3A4 as concentrations of maraviroc may be significantly increased.

Interactions

Maraviroc is a substrate for the cytochrome P450 isoenzyme CYP3A4 and for P-glycoprotein, and may therefore have a number of clinically significant interactions. Inhibitors of CYP3A4, such as HIV-protease inhibitors (other than tipranavir), increase the serum concentration of maraviroc. Inducers of CYP3A4 such as efavirenz may decrease serum maraviroc concentrations. No clinically significant interaction is expected between maraviroc and NRTIs, nevirapine, or boosted fosamprenavir or tipranavir.

Non-antiretroviral medications that significantly alter maraviroc metabolism include the CYP3A4 inhibitors ketoconazole, itraconazole, clarithromycin, and nefazodone and the CYP3A4 inducers rifampicin and St John's wort. Maraviroc does not appear to cause clinically significant changes in concentrations of other medications.

Antiviral Action

Maraviroc is an antagonist of the CCR5 chemokine receptor. During infection, HIV binds to the CD4 receptor on the surface of host cells, and then interacts with one of two co-receptors, CCR5 or CXCR4, to allow cell membrane fusion and entry to the cell. By binding to CCR5, maraviroc inhibits this process and prevents strains of HIV-1 that use CCR5 (CCR5-tropic viruses), which appear to be more common in early infection, from entering the cell. It is not active against CXCR4-tropic strains or those with dual or mixed tropism.