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.

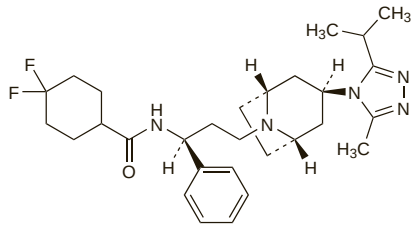
Маравирок

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

Pharmacokinetics

Maraviroc is absorbed after oral doses, and peak concentrations occur in 0.5 to 4 hours. There is considerable interindividual variation in the pharmacokinetics. It is 76% bound to plasma proteins. Maraviroc is metabolised by the cytochrome P450 system (specifically the isoenzyme CYP3A4) to inactive metabolites. It is excreted in both urine (20%) and faeces (76%) as unchanged drug and metabolites.

Uses and Administration

Maraviroc is an antagonist of the CCR5 chemokine receptor (see Antiviral Action, above). It is used, with other antiretrovirals, for the treatment of HIV infection and AIDS (p.856) in treatment-experienced adult patients with exclusively CCR5-tropic HIV-1 infection. Co-receptor tropism should be determined by specific testing before maraviroc is used.

Maraviroc is given orally in a dose of 300 mg twice daily, although dose adjustments may be needed depending on interactions with other medicines.

- For patients also taking CYP3A4 inhibitors such as HIV-protease inhibitors (other than fosamprenavir or tipranavir), delavirdine, ketoconazole, itraconazole, clarithromycin, nefazodone, and telithromycin, the recommended dose is 150 mg twice daily.
- In those whose therapy includes CYP3A4 inducers (without a CYP3A4 inhibitor) such as efavirenz, rifampicin, carbamazepine, phenobarbital, and phenytoin, the recommended dose is 600 mg twice daily.

Patients taking other antiretrovirals (including fosamprenavir or tipranavir), or other drugs, may be given the standard dose of 300 mg twice daily.

◊ References.

1. Carter NJ, Keating GM. Maraviroc. *Drugs* 2007; **67:** 2277–88.
2. Vandekerckhove L, *et al*. Maraviroc: integration of a new antiretroviral drug class into clinical practice. *J Antimicrob Chemother* 2008; **61:** 1187–90.

Administration in renal impairment. UK licensed product information recommends that the oral dose of maraviroc be adjusted in patients with renal impairment who are also taking potent inhibitors of cytochrome P450 isoenzyme CYP3A4. The dosing interval should be modified according to the creatinine clearance (CC) of the patient:

- For patients also taking CYP3A4 inhibitors such as ritonavir-boosted HIV-protease inhibitors (other than fosamprenavir, tipranavir, or saquinavir), ketoconazole, itraconazole, clarithromycin, and telithromycin and who have a CC less than 80 mL/minute: 150 mg every 24 hours
- For patients also taking ritonavir-boosted saquinavir:
  - CC 50 to 80 mL/minute: 150 mg every 24 hours
  - CC 30 to 49 mL/minute: 150 mg every 48 hours
  - CC 29 mL/minute or less: 150 mg every 72 hours

No adjustment is necessary when maraviroc is given without potent CYP3A4 inhibitors or with fosamprenavir or tipranavir

Preparations

Proprietary Preparations (details are given in Part 3)

Canad.: Celsentri; ***Cz.:*** Celsentri; ***Fr.:*** Celsentri; ***UK:*** Celsentri; ***USA:*** Selzentry.

Moroxydine *(BAN, rINN)*

Moroksidiini; Moroxidin; Moroxidina; Moroxydinum.

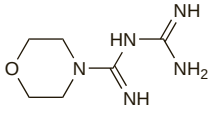
Мороксидин

$C_6H_{13}N_5O$ = 171.2.

CAS — 3731-59-7.

ATC — J05AX01.

ATC Vet — QJ05AX01.



Moroxydine Hydrochloride *(BANM, rINNM)*

Abitilguanide Hydrochloride; ABOB; Hidrocloruro de moroxidina; Moroxydine, Chlorhydrate de; Moroxydini Hydrochloridum. 1-(Morpholinoformimidoyl)guanidine hydrochloride.

Мороксидина Гидрохлорид

$C_6H_{13}N_5O,HCl$ = 207.7.

CAS — 3160-91-6.

ATC — J05AX01.

ATC Vet — QJ05AX01.

Profile

Moroxydine hydrochloride has been given orally in the treatment of herpes simplex and varicella-zoster infections. It has also been used topically. It is included as an ingredient in preparations for the treatment of cold and influenza symptoms.

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Hong Kong:*** Virulex Forte; ***Mex.:*** Amgrip; Clorfriol†; Flepin X-3†; Friral†; Singnil; Singnilen; ***S.Afr.:*** Corenza C; Virobis†.

Nelfinavir Mesilate *(BANM, rINNM)*

AG-1343 (nelfinavir or nelfinavir mesilate); Mesilato de nelfinavir; Nelfinavir, Mésilate de; Nelfinavir Mesylate *(USAN)*; Nelfinaviri Mesilas. 3*S*[2(2*S**,3*S**),3α,4aβ,8aβ]-*N*-(1,1-Dimethylethyl)decahydro-2-2-hydroxy-3-[(3-hydroxy-2-methylbenzoyl)amino]-4-(phenylthio)butyl-3-isoquinolinecarboxamide monomethanesulphonate; (3*S*,4a*S*,8a*S*)-*N*-*tert*-Butyldecahydro-2-[(2*R*,3*R*)-3-(3-hydroxy-*o*-toluamido)-2-hydroxy-4-(phenylthio)butyl]isoquinoline-3-carboxamide monomethanesulphonate.

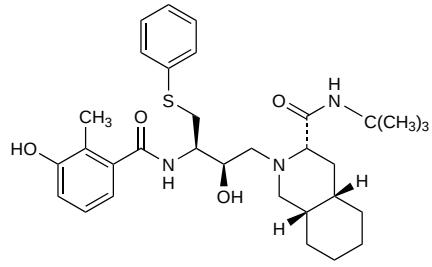
Нелфинавира Мезилат

$C_{32}H_{45}N_3O_4S,CH_4O_3S$ = 663.9.

CAS — 159989-64-7 (nelfinavir); 159989-65-8 (nelfinavir mesilate).

ATC — J05AE04.

ATC Vet — QJ05AE04.



(nelfinavir)

NOTE. Nelfinavir should not be confused with nevirapine (below).

Pharmacopoeias. In *Int.*

Adverse Effects

The most common adverse effects associated with antiretroviral regimens containing nelfinavir are diarrhoea, flatulence, nausea, and rash. Raised liver enzymes and decreases in white blood cell counts have also been reported.

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 nelfinavir, 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 nelfinavir. 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.

Contamination. In June 2007, high levels of ethyl mesilate (ethyl methanesulfonate; EMS) were detected in European-made nelfinavir (*Viracept; Roche*). EMS may cause cancer in humans and has caused birth defects and cancer in *animals*. Nelfinavir was subsequently recalled from the European market in August 2007.[1] The manufacturer later identified and rectified the source of contamination and in September 2007 the EMEA recommended the lifting of the drug's suspension.[2] The US manufacturer (*Pfizer, USA*) notified doctors in September 2007 that EMS had been detected in nelfinavir manufactured in the USA but in much lower amounts than in European-made nelfinavir.[3] The FDA considered the risk of stopping nelfinavir therapy resulting from a drug recall to be greater than the risk of taking US-made nelfinavir but advised that children and pregnant women starting treatment with antiretrovirals for the first time not be given nelfinavir-containing regimens. Pregnant women taking nelfinavir as part of an HIV treatment regimen should be given alternative therapy. All other HIV-infected patients taking nelfinavir-containing regimens could continue to do so.

1. EMEA. European Medicines Agency agrees on action plan following the recall of Viracept and recommends suspension of the marketing authorisation (issued 21 June, 2007). Available at: http://www.emea.europa.eu/pdfs/general/direct/pr/27536707en.pdf (accessed 13/06/08).
2. EMEA. European medicines agency recommends lifing of suspension for Viracept (issued 20 September, 2007). Available at: http://www.emea.europa.eu/pdfs/general/direct/pr/41816807en.pdf (accessed 13/06/08).
3. Pfizer, USA. Viracept (nelfinavir mesylate) 250 mg, 625 mg tablets, and powder for oral suspension: important information for prescribers (issued 10 September 2007). Available at: http://www.fda.gov/medwatch/safety/2007/VIRACEPT_HCPLetter_9_10_07.pdf (accessed 13/06/08).

Precautions

Nelfinavir should be used with caution, and liver enzyme values monitored, in patients with moderate 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. Caution is advised in treating patients with haemophilia A and B as reports of spontaneous bleeding have been associated with the use of HIV-protease inhibitors.

For cautions concerning use in children and in pregnancy see under Contamination, above

Interactions

Nelfinavir is reported to be metabolised in part by cytochrome P450 isoenzymes CYP3A4 and CYP2C19. Drugs that induce these isoenzymes may reduce the plasma concentration of nelfinavir. Conversely, when nelfinavir is given with drugs that inhibit CYP3A4 plasma concentrations, nelfinavir concentrations may be increased. It may also alter the pharmacokinetics of drugs metabolised by this isoenzyme system and possibly cause serious adverse effects.

Nelfinavir 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 antiarrhythmics (amiodarone and quinidine), antihistamines (astemizole and terfenadine), ergot derivatives (dihydroergotamine, ergometrine, ergotamine, and methylergometrine), gastrointestinal motility agents (cisapride), antipsychotics (pimozide), sedatives and hypnotics (midazolam and triazolam), and statins (simvastatin and lovastatin). Omeprazole, rifampicin, and St John's wort decrease the concentration of nelfinavir; 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 HIV-protease inhibitors see under Indinavir Sulfate, p.883 and Table 1, p.917.

Antiviral Action

Nelfinavir is a selective, 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-pro-