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.

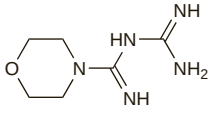
Мороксидин

$C_6H_{13}N_5O$ = 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.

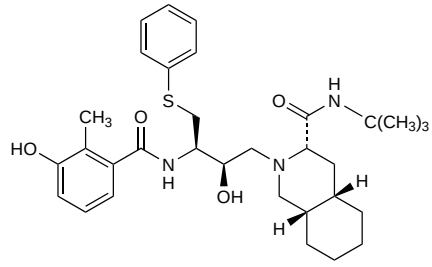
Нелфинавира Мезилат

$C_{32}H_{45}N_3O_4S,CH_4O_3S$ = 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-

tease inhibitors are given alone and therefore they are used with other antiretrovirals. Mechanisms of resistance to nelfinavir may differ sufficiently from those to other HIV-protease inhibitors to reduce the occurrence of cross-resistance between nelfinavir and other HIV-protease inhibitors. Cross-resistance between nelfinavir and NNRTIs is unlikely because they target different enzymes.

Pharmacokinetics

Nelfinavir is absorbed from the gastrointestinal tract and peak plasma concentrations occur in 2 to 4 hours. Absorption is enhanced when given with food. Nelfinavir is extensively bound to plasma proteins (more than 98%). It is metabolised by oxidation by cytochrome P450 isoenzymes including CYP3A4 and CYP2C19. The major oxidative metabolite has *in-vitro* antiviral activity equal to that of nelfinavir. In patients 13 years of age and older the plasma terminal half-life is 3.5 to 5 hours; in children 2 to 13 years of age, clearance is two to three times greater than in adults. Nelfinavir is excreted mainly in the faeces both as unchanged drug (22%) and as metabolites (78%). Only about 1 to 2% is excreted in the urine, mainly as unchanged drug.

Uses and Administration

Nelfinavir is an HIV-protease inhibitor with antiviral activity against HIV-1. It is used in the treatment of HIV infection and AIDS (p.856). Viral resistance emerges rapidly when nelfinavir is used alone, and it is therefore used with other antiretrovirals.

Nelfinavir is given orally as the mesilate, but doses are expressed in terms of the base. Nelfinavir mesilate 292 mg is equivalent to about 250 mg of nelfinavir. Nelfinavir is available as tablets and oral powder. The oral powder should not be taken with acidic foods or drinks as this may result in a bitter taste. Nelfinavir is given in an adult dose of 1.25 g twice daily or 0.75 g three times daily with food.

For details of doses in children, see below.

◊ Reviews.

1. Pai VB, Nahata MC. Nelfinavir mesylate: a protease inhibitor. *Ann Pharmacother* 1999; **33:** 325–39.
2. Perry CM, *et al.* Nelfinavir: a review of its use in the management of HIV infection. *Drugs* 2005; **65:** 2209–44.

Administration in children. For the treatment of HIV infection in children nelfinavir is given orally with other antiretroviral drugs. The US licensed product information permits the use of nelfinavir in children 2 years of age and older, whereas UK licensed product information permits use from 3 years of age.

In the UK, the recommended dose of nelfinavir is 50 to 55 mg/kg twice daily or 25 to 30 mg/kg three times daily with food. In the USA, the recommended dose is 45 to 55 mg/kg twice daily or 25 to 35 mg/kg three times daily with food.

Preparations

Proprietary Preparations (details are given in Part 3)

Arg.: Filosfil; Nalvir; Nelfilea; Retroinhi; Viracept†; ***Austral.:*** Viracept; ***Austria:*** Viracept; ***Belg.:*** Viracept; ***Braz.:*** Viracept; ***Canad.:*** Viracept; ***Chile:*** Viracept; ***Cz.:*** Viracept; ***Denm.:*** Viracept; ***Fin.:*** Viracept; ***Fr.:*** Viracept; ***Ger.:*** Viracept; ***Gr.:*** Viracept; ***Hong Kong:*** Viracept; ***Hung.:*** Viracept; ***India:*** Nelvir; ***Irl.:*** Viracept; ***Israel:*** Viracept; ***Ital.:*** Viracept; ***Jpn:*** Viracept; ***Mex.:*** Viracept; ***Neth.:*** Viracept; ***Norw.:*** Viracept; ***NZ:*** Viracept; ***Philipp.:*** Viracept; ***Pol.:*** Viracept; ***Port.:*** Viracept; ***S.Afr.:*** Viracept; ***Singapore:*** Viracept†; ***Spain:*** Viracept; ***Swed.:*** Viracept; ***Switz.:*** Viracept; ***Thai.:*** Viracept; ***UK:*** Viracept; ***USA:*** Viracept; ***Venez.:*** Nelvir; Viracept.

Nevirapine *(BAN, USAN, rINN)*

BI-RG-587; BIRG-0587; Nevirapiini; Nevirapiini, vedetön; Nevirapin; Nevirapin bezvodý; Nevirapin, vattenfritt; Nevirapina; Névirapine; Névirapine anhydre; Nevirapinum; Nevirapinum anhydricum; Newirapina bezwodna. 11-Cyclopropyl-5,11-dihydro-4-methyl-6*H*-dipyrido[3,2-*b*:2′,3′-*e*]-[1,4]diazepin-6-one.

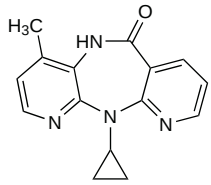
Невирапин

$C_{15}H_{14}N_4O$ = 266.3.

CAS — 129618-40-2.

ATC — J05AG01.

ATC Vet — QJ05AG01.



NOTE. Nevirapine should not be confused with nelfinavir (above).

Pharmacopoeias. In *Eur.* (see p.vii) and *US.*

Int. permits anhydrous or the hemihydrate.

Ph. Eur. 6.2 (Nevirapine, Anhydrous). A white or almost white powder. Practically insoluble in water; sparingly soluble or slightly soluble in dichloromethane; slightly soluble in methyl alcohol.

USP 31 (Nevirapine). It is anhydrous or contains one-half molecule of water of hydration. A white to off-white, odourless to nearly odourless, crystalline powder. Practically insoluble in water; slightly soluble in alcohol and in methyl alcohol. The hydrous form is also slightly insoluble in propylene glycol. Store in airtight containers at a temperature of 25°, excursions permitted between 15° and 30°.

Adverse Effects

The most common adverse effect associated with antiretroviral regimens containing nevirapine is skin rash (usually mild to moderate, maculopapular, erythematous, and sometimes pruritic), generally occurring within 6 weeks of starting therapy. Severe and life-threatening skin reactions (with some fatalities) have occurred, including Stevens-Johnson syndrome and, more rarely, toxic epidermal necrolysis. Hypersensitivity reactions including angioedema, urticaria, and anaphylaxis have been reported. Rashes may occur alone or in the context of hypersensitivity reactions when they may be accompanied by other symptoms such as fever, arthralgia, myalgia, lymphadenopathy, eosinophilia, granulocytopenia, or renal dysfunction. Granulocytopenia occurs more commonly in children than in adults. Severe hepatotoxicity, including hepatitis and hepatic necrosis, occasionally fatal, has occurred and may be more prevalent in women and patients with high CD4+ cell counts at the start of treatment. Serious hepatotoxicity has also been reported in HIV-uninfected persons taking multiple doses of nevirapine for HIV postexposure-prophylaxis. Rhabdomyolysis has occurred in patients with skin and/or liver reactions. Other common adverse effects include nausea, vomiting, diarrhoea, abdominal pain, fatigue, drowsiness, fever, myalgia, and headache.

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 nevirapine, 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 nevirapine. Metabolic abnormalities such as hypertriglyceridaemia, hypercholesterolaemia, insulin resistance, hyperglycaemia, and hyperlactataemia have also been reported. Osteonecrosis has been reported, particularly in patients with advanced HIV disease or long-term exposure to combination antiretroviral therapy.

Effects on the liver. References.

1. Martinez E, *et al.* Hepatotoxicity in HIV-1-infected patients receiving nevirapine-containing antiretroviral therapy. *AIDS* 2001; **15:** 1261–8.
2. Committee on Safety of Medicines/Medicines Control Agency. Nevirapine (Viramune): serious adverse reactions when used in HIV post exposure prophylaxis. *Current Problems* 2001; **27:** 13. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON007456&RevisionSelectionMethod=LatestReleased (accessed 13/06/08)
3. Gonzalez de Requena D, *et al.* Liver toxicity caused by nevirapine. *AIDS* 2002; **16:** 290–1.
4. De Maat MM, *et al.* Hepatotoxicity following nevirapine-containing regimens in HIV-1-infected individuals. *Pharmacol Res* 2002; **46:** 295–300.
5. Patel SM, *et al.* Serious adverse cutaneous and hepatic toxicities associated with nevirapine use by non-HIV-infected individuals. *J Acquir Immune Defic Syndr* 2004; **35:** 120–5.
6. Torti C, *et al.* BHCC Study Group. Analysis of severe hepatic events associated with nevirapine-containing regimens: CD4+ T-cell count and gender in hepatitis C seropositive and seronegative patients. *Drug Safety* 2007; **30:** 1161–9.

Effects on the skin. References.

1. Warren KJ, *et al.* Nevirapine-associated Stevens-Johnson syndrome. *Lancet* 1998; **351:** 567.
2. Wetterwald E, *et al.* Nevirapine-induced overlap Stevens-Johnson syndrome/toxic epidermal necrolysis. *Br J Dermatol* 1999; **140:** 980–2.
3. Committee on Safety of Medicines/Medicines Control Agency. Nevirapine (Viramune): serious adverse reactions when used in HIV post exposure prophylaxis. *Current Problems* 2001; **27:** 13. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON007456&RevisionSelectionMethod=LatestReleased (accessed 13/06/08)
4. Antinori A, *et al.* Female sex and the use of anti-allergic agents increase the risk of developing cutaneous rash associated with nevirapine therapy. *AIDS* 2001; **15:** 1579–81.
5. de Maat MM, *et al.* Incidence and risk factors for nevirapine-associated rash. *Eur J Clin Pharmacol* 2003; **59:** 457–62.
6. Manosuthi W, *et al.* Incidence and risk factors of nevirapine-associated skin rashes among HIV-infected patients with CD4 cell counts <250 cells/microL. *Int J STD AIDS* 2007; **18:** 782–6.
7. Wit FW, *et al.* Discontinuation of nevirapine because of hypersensitivity reactions in patients with prior treatment experience, compared with treatment-naive patients: the ATHENA cohort study. *Clin Infect Dis* 2008; **46:** 933–40.
8. Kiertiburanakul S, *et al.* Risk factors for nevirapine-associated rash among HIV-infected patients with low CD4 cell counts in resource-limited settings. *Curr HIV Res* 2008; **6:** 65–9.

Precautions

Patients taking nevirapine should be closely monitored for adverse skin reactions and hepatotoxicity during the first 18 weeks of treatment; extra vigilance is advised during the first 6 weeks of treatment. Nevirapine should be used with extreme caution in patients with moderate hepatic impairment (Child-Pugh class B); it is contra-indicated in those with severe hepatic impairment (Child-Pugh class C). Patients with high CD4+ cell counts (greater than 250 cells/microlitre in women or 400 cells/microlitre in men), as well as patients co-infected with chronic hepatitis B or C are at increased risk of hepatotoxicity. The UK licensed product information suggests that liver function should be monitored every 2 weeks during the first 2 months of treatment, again at 3 months, and then regularly thereafter.

Treatment should be permanently stopped in patients who suffer a severe rash, rash accompanied by constitutional symptoms (such as fever, blistering, oral lesions, conjunctivitis, facial oedema, muscle or joint aches, or general malaise), hypersensitivity reactions, or clinical hepatitis. Transaminase levels should be checked for all patients who develop a rash in the first 18 weeks of treatment and nevirapine should be temporarily stopped if liver enzyme levels increase to greater than 5 times the upper limit of normal or the patient has symptoms suggestive of hepatitis. In some patients treatment may be restarted at the initial dose if liver function returns to baseline values and the patient has no clinical symptoms of hepatitis or signs of a rash (although permanent stoppage is necessary if abnormalities recur). In some cases hepatic injury progresses despite stopping the drug. Dose escalation should not be attempted in patients developing any rash during the first 14 days of treatment until the rash has resolved. Patients or their carers should be counselled on how to recognise hypersensitivity reactions and instructed to seek immediate medical attention if they occur. Doses may need to be modified in patients on renal dialysis.

Pregnancy. Nevirapine has not been associated with teratogenicity in *animals*. Licensed product information states that the Antiretroviral Pregnancy Registry has not found an increased risk of birth defects after first trimester exposures to nevirapine and the prevalence of birth defects after exposure in any trimester was comparable to the prevalence in the general population.

Interactions

Nevirapine is metabolised mainly by the cytochrome P450 isoenzymes CYP3A4 and CYP2B6. Consequently it may compete with other drugs metabolised by this system, possibly resulting in mutually increased plasma concentrations and toxicity. Alternatively, en-