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.

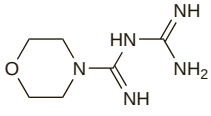
Мороксидин

$C_6H_{13}N_5O$ = 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.

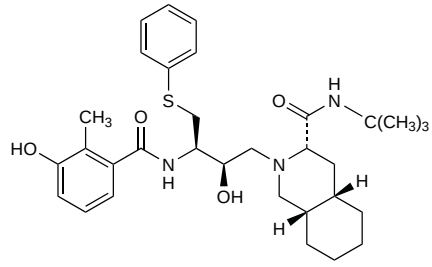
Нелфинавира Мезилат

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