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.

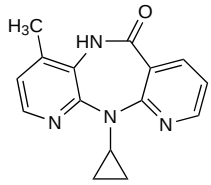
Невирапин

$C_{15}H_{14}N_4O$ = 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-

zyme inducers may decrease plasma concentrations of nevirapine; nevirapine itself acts as a mild to moderate enzyme inducer and may thus reduce plasma concentrations of other drugs.

Rifampicin and St John's wort decrease the concentration of nevirapine; 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.

Antivirals. For the effect of nevirapine on *HIV-protease inhibitors*, see p.883.

Methadone. Nevirapine may induce the metabolism of methadone (p.84) resulting in reduced plasma-methadone concentrations.

Antiviral Action

Nevirapine 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 nevirapine and emergence of cross-resistance to other non-nucleoside reverse transcriptase inhibitors has been seen.

Pharmacokinetics

Nevirapine is readily absorbed after oral doses and absorption is not affected by food or antacids. Bioavailability is greater than 90%. Nevirapine tablets and oral suspension are comparably bioavailable and interchangeable at doses up to 200 mg. Peak plasma concentrations occur 4 hours after a single dose. Nevirapine is about 60% bound to plasma proteins. Concentrations in the CSF are about 45% of those in plasma. Nevirapine crosses the placenta and is distributed into breast milk. It is extensively metabolised by hepatic microsomal enzymes, principally by the cytochrome P450 isoenzymes CYP3A4 and CYP2B6, to several hydroxylated metabolites. Autoinduction of these enzymes results in a 1.5- to 2-fold increase in apparent oral clearance after 2 to 4 weeks at usual dosage, and a decrease in terminal half-life from 45 hours to 25 to 30 hours over the same period. Nevirapine is mainly excreted in the urine as glucuronide conjugates of the hydroxylated metabolites.

In children, nevirapine elimination accelerates during the first years of life, reaching a maximum at around 2 years of age, followed by a gradual decline during the rest of childhood; values in children under 8 years are about twice those in adults.

◊ References.

1. Mirochnick M, *et al.* Nevirapine: pharmacokinetic considerations in children and pregnant women. *Clin Pharmacokinet* 2000; **39:** 281–93.
2. Almond LM, *et al.* Intracellular and plasma pharmacokinetics of nevirapine in human immunodeficiency virus-infected individuals. *Clin Pharmacol Ther* 2005; **78:** 132–42.
3. von Hentig N, *et al.* A comparison of the steady-state pharmacokinetics of nevirapine in men, nonpregnant women and women in late pregnancy. *Br J Clin Pharmacol* 2006; **62:** 552–9.

Uses and Administration

Nevirapine is a non-nucleoside reverse transcriptase inhibitor with activity against HIV-1. It is used in the treatment of HIV infection and AIDS (p.856). Viral resistance emerges rapidly when nevirapine is used alone, and it is therefore used with other antiretrovirals.

Nevirapine is given orally in an adult dose of 200 mg once daily for the first 14 days, then increased to 200 mg twice daily provided that no rash is present (see Precautions, above).

If treatment is interrupted for more than 7 days, it should be reintroduced using the lower dose for the first 14 days as for new treatment.

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

Nevirapine is often used in regimens for the prophylaxis of vertical transmission (mother-to-child) of HIV infection. In women in whom HAART is not indicated, or where it is not available, a single oral dose of nevirapine 200 mg may be given at the onset of labour, together with a course of zidovudine and lamivudine, for perinatal cover (see HIV Infection Prophylaxis, p.858).

◊ References.

1. Floridia M, *et al.* A randomized, double-blind trial on the use of a triple combination including nevirapine, a nonnucleoside reverse transcriptase HIV inhibitor, in antiretroviral-naive patients with advanced disease. *J Acquir Immune Defic Syndr Hum Retrovirol* 1999; **20:** 11–19.
2. Guay LA, *et al.* Intrapartum and neonatal single-dose nevirapine compared with zidovudine for prevention of mother-to-child transmission of HIV-1 in Kampala, Uganda: HIVNET 012 randomised trial. *Lancet* 1999; **354:** 795–802.
3. Bardsley-Elliot A, Perry CM. Nevirapine: a review of its use in the prevention and treatment of paediatric HIV infection. *Paediatr Drugs* 2000; **2:** 373–407.
4. Dorenbaum A, *et al.* Two-dose intrapartum/newborn nevirapine and standard antiretroviral therapy to reduce perinatal HIV transmission: a randomized trial. *JAMA* 2002; **288:** 189–98.
5. Moodley D, *et al.* A multicenter randomized controlled trial of nevirapine versus a combination of zidovudine and lamivudine to reduce intrapartum and early postpartum mother-to-child transmission of human immunodeficiency virus type 1. *J Infect Dis* 2003; **187:** 725–35.
6. Taha TE, *et al.* Short postexposure prophylaxis in newborn babies to reduce mother-to-child transmission of HIV-1: NVAZ randomised clinical trial. *Lancet* 2003; **362:** 1171–7.
7. Lallemant M, *et al.* Single-dose perinatal nevirapine plus standard zidovudine to prevent mother-to-child transmission of HIV-1 in Thailand. *N Engl J Med* 2004; **351:** 217–28.
8. Shapiro RL, *et al.* Maternal single-dose nevirapine versus placebo as part of an antiretroviral strategy to prevent mother-to-child HIV transmission in Botswana. *AIDS* 2006; **20:** 1281–8.
9. Lockman S, *et al.* Response to antiretroviral therapy after a single, peripartum dose of nevirapine. *N Engl J Med* 2007; **356:** 135–47.
10. Parienti JJ, *et al.* SIROCCO study team. Efavirenz to nevirapine switch in HIV-1-infected patients with dyslipidemia: a randomized, controlled study. *Clin Infect Dis* 2007; **45:** 263–6.
11. Dart Trial Team. Twenty-four-week safety and tolerability of nevirapine vs. abacavir in combination with zidovudine/lamivudine as first-line antiretroviral therapy: a randomized double-blind trial (NORA). *Trop Med Int Health* 2008; **13:** 6–16.

Administration in children. For the treatment of HIV infection in infants, children, and adolescents nevirapine is given orally with other antiretroviral drugs. The following doses by bodyweight have been suggested according to age:

- from 15 days to 8 years: 4 mg/kg once daily for 14 days and then, if no rash is present, 7 mg/kg twice daily
- 8 to 16 years: 4 mg/kg once daily for 14 days then 4 mg/kg twice daily thereafter

Alternatively, the dose may be calculated according to body-surface; an oral dose of 150 mg/m^2 once daily for two weeks is given followed by 150 mg/m^2 twice daily thereafter. A total dose of 400 mg daily should not be exceeded.

For information on the use of nevirapine in regimens for the prophylaxis of vertical transmission (mother-to-child) of HIV infection see HIV Infection Prophylaxis, p.858.

Administration in renal impairment. Dose adjustments are not required for patients with a creatinine clearance more than 20 mL/min. Patients on dialysis should receive an additional 200 mg of nevirapine after each dialysis session.

Preparations

USP 31: Nevirapine Oral Suspension; Nevirapine Tablets.

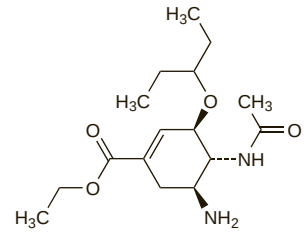
Proprietary Preparations (details are given in Part 3)

Arg.: Filide; Nerapin; Neviralea†; Protease; Ritvir; Virainhi; Viramune; ***Austral.:*** Viramune; ***Austria:*** Viramune; ***Belg.:*** Viramune; ***Braz.:*** Viramune; ***Canad.:*** Viramune; ***Chile:*** Viramune; ***Cz.:*** Viramune; ***Denm.:*** Viramune; ***Fin.:*** Viramune; ***Fr.:*** Viramune; ***Ger.:*** Viramune; ***Gr.:*** Viramune; ***Hong Kong:*** Viramune; ***Hung.:*** Viramune; ***India:*** Neve; Nevimune; ***Indon.:*** Viramune; ***Irl.:*** Viramune; ***Israel:*** Viramune; ***Ital.:*** Viramune; ***Jpn:*** Viramune; ***Malaysia:*** Nevipan; Viramune; ***Mex.:*** Viramune; ***Neth.:*** Viramune; ***Norw.:*** Viramune; ***NZ:*** Viramune; ***Pol.:*** Viramune; ***Port.:*** Viramune; ***Rus.:*** Viramune (Вирамун); ***S.Afr.:*** Viramune; ***Singapore:*** Viramune; ***Spain:*** Viramune; ***Swed.:*** Viramune; ***Switz.:*** Viramune; ***Thai.:*** Viramune; ***Turk.:*** Viramune; ***UK:*** Viramune; ***USA:*** Viramune; ***Venez.:*** Nevimune; Viramune.

Multi-ingredient: ***India:*** Duovir N; Triomune; ***S.Afr.:*** Triomune; ***Venez.:*** Triomune.

Oseltamivir Phosphate

(BANM, USAN, rINNM)



(oseltamivir)

Fosfato de oseltamivir; GS-4104/002; Oséltamivir, Phosphate d'; Oseltamiviri Phosphas; Ro-64-0796/002. Ethyl (3*R*,4*R*,5*S*)-4-acetamido-5-amino-3-(1-ethylpropoxy)-1-cyclohexene-1-carboxylate phosphate (1:1).

Осельтамивира Фосфат

$C_{16}H_{28}N_2O_4,H_3PO_4$ = 410.4.

CAS — 196618-13-0 (oseltamivir); 204255-11-8 (oseltamivir phosphate).

ATC — J05AH02.

ATC Vet — QJ05AH02.

Adverse Effects

The most commonly reported adverse effects associated with oseltamivir treatment or prophylaxis in adults are nausea and vomiting, abdominal pain, bronchitis, insomnia, and vertigo. Diarrhoea, dizziness, headache, cough, and fatigue may occur, but many adverse effects may be difficult to distinguish from the symptoms of influenza. Other adverse effects occurring less commonly have included unstable angina, anaemia, pseudomembranous colitis, pneumonia, pyrexia, and peritonsillar abscess. There have been occasional reports of anaphylaxis and skin rashes, including toxic epidermal necrolysis, Stevens-Johnson syndrome, and erythema multiforme. Elevated liver enzymes and hepatitis have been reported rarely. Prophylaxis in adults has also been associated with aches and pains, dyspepsia, rhinorrhoea, and upper respiratory-tract infections.

The most commonly reported adverse effects in children receiving treatment or prophylaxis with oseltamivir are vomiting and other gastrointestinal problems. Other commonly occurring adverse events include asthma, bronchitis, conjunctivitis, dermatitis, epistaxis, ear disorders and otitis media, lymphadenopathy, pneumonia, and sinusitis.

There have been postmarketing reports (mainly in Japanese children and adolescents) of neuropsychiatric adverse effects (see below).

Neuropsychiatric effects. A FDA review of the Adverse Event Reporting System (AERS) database from March 2004 to April 2005 reported 75 cases of serious adverse effects linked to the use of oseltamivir in children; 69 from Japan, 5 from USA, and 1 from Canada. Thirty-two cases of neuropsychiatric adverse effects including cases of delirium, abnormal behaviour, hallucinations, convulsions, and encephalitis, were reported, with 31 of these cases being reported from Japan. Twelve deaths were reported; 4 from sudden death, 4 due to cardiopulmonary arrest, and others due to disturbance of consciousness (without falling), pneumonia, asphyxiation, and acute pancreatitis with cardiopulmonary arrest. All deaths were reported from Japan.[1] The Japanese Ministry of Health Labour and Welfare reported that from 2001 to May 2007 they received 1377 adverse effects reports associated with the use of oseltamivir, including 567 reports of serious neuropsychiatric adverse effects and 211 cases of abnormal behaviour. Death was reported in 71 cases.[2] After the suicides of 2 adolescents, the Japanese authorities advised against the use of oseltamivir in adolescents aged 10 to 19 years.[3] However, given that influenza itself may have neuropsychiatric sequelae, any causal relationship with the drug remains unproven.[1,3]

1. FDA, Center for Drug Evaluation and Research. Pediatric safety update for Tamiflu: Pediatric Advisory Committee meeting (issued 18 November 2005). Available at: http://www.fda.gov/ohrms/dockets/ac/05/briefing/2005-4180b_06_06_summary.pdf (accessed 13/06/08).
2. Hama R. Oseltamivir's adverse reactions: Fifty sudden deaths may be related to central suppression. *BMJ* 2007; **335:** 59.
3. Maxwell SRJ. Tamiflu and neuropsychiatric disturbance in adolescents. *BMJ* 2007; **334:** 1232–3.

Precautions

Oseltamivir is not recommended in patients with severe renal impairment and it should be given with caution and dosage should be reduced in patients with moderate renal impairment.

Patients should be monitored for abnormal behaviour throughout the treatment period.

Breast feeding. Oseltamivir and its active metabolite are distributed into breast milk in *rodents*. Licensed product informa-