should not be given etravirine in a regimen containing only NRTIs.

Interactions
Etravirine is metabolised mainly by the cytochrome P450 isoenzymes CYP3A4, CYP2C9, and CYP2C19. It is an inducer of CYP3A4 and an inhibitor of CYP2C9 and CYP2C19. Consequently it may compete with other drugs metabolised by these systems, potentially resulting in mutually altered plasma concentrations and possibly toxicity. Enzyme inducers may decrease plasma concentrations of etravirine.

Etravirine should not be given with other NNRTIs. It should also not be used in regimens with HIV-protease inhibitors given without ritonavir-boosting but use with ritonavir-boosted tipranavir, fosamprenavir, or atazanavir should be avoided. For further information on drug interactions of NNRTIs see Table 2, p.944.

Antiviral Action
Etravirine acts by inhibition of HIV-1 reverse transcriptase and blocks viral RNA- and DNA-dependent DNA polymerase activities. It is a flexible molecule designed to fit in the active pocket of viral reverse transcriptase in different ways, even when the shape of that pocket changes because of viral mutations. This is considered to reduce the risk of the development of resistance; phase II studies in treatment-experienced patients have shown activity against HIV resistant to other NNRTIs (delavirdine, efavirenz, and nevirapine).

Pharmacokinetics
Etravirine is readily absorbed after oral doses and peak plasma concentrations occur after about 2.5 to 4 hours; absorption is increased by food. It is about 99.9% bound to plasma proteins. Etravirine is extensively metabolised by hepatic microsomal enzymes, principally by the cytochrome P450 isoenzymes CYP3A4, CYP2C9, and CYP2C19 families, to substantially less active metabolites. The mean plasma half-life after usual dosage is about 41 hours and ranges from 21 to 61 hours. About 93.7% of a dose appears in the faeces (81.2 to 86.4% as unchanged drug), and 1.2% in the urine (unchanged drug was not detected in the urine).

Uses and Administration
Etravirine is a non-nucleoside reverse transcriptase inhibitor with activity against HIV-1. It is given with other antiretrovirals for the treatment of HIV infection and AIDS (p.856) in treatment-experienced patients, who have evidence of viral replication and HIV-1 strains resistant to a NNRTI and other antiretrovirals. Etravirine is given orally in a usual dose of 200 mg twice daily after food.

◊ References.

1. Madruga JV, *et al.* Efficacy and safety of TMC125 (etravirine) in treatment-experienced HIV-1-infected patients in DUET-1: 24-week results from a randomised, double-blind, placebo-controlled trial. *Lancet* 2007; **370:** 29–38.
2. Lazzarin A, *et al.* Efficacy and safety of TMC125 (etravirine) in treatment-experienced HIV-1-infected patients in DUET-2: 24-week results from a randomised, double-blind, placebo-controlled trial. *Lancet* 2007; **370:** 39–48.

Preparations
Proprietary Preparations (details are given in Part 3)
USA: Intelence.

Famciclovir *(BAN, USAN, rINN)*

AV-42810; BRL-42810; Famciclovirum; Famciklovir; Famsikloviiri; Famsiklovir. 2[2-(2-Amino-9*H*-purin-9-yl)ethyl]trimethylene diacetate.

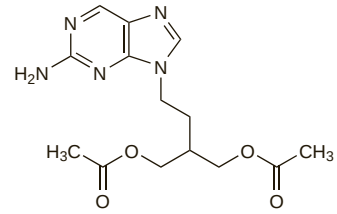
Фамцикловир

$C_{14}H_{19}N_5O_4$ = 321.3.

CAS — 104227-87-4.

ATC — J05AB09; S01AD07.

ATC Vet — QJ05AB09; QS01AD07.



Pharmacopoeias. In *Chin.*

Adverse Effects and Precautions
The most common adverse effects of famciclovir are headache and nausea. Other adverse effects rarely reported include jaundice, vomiting, dizziness, skin rash, pruritus, urticaria, somnolence, confusion, and hallucinations. In addition, abdominal pain and fever have been reported in immunocompromised patients given famciclovir.

Dosage should be reduced in patients with renal impairment. Acute renal failure has occurred in patients with renal impairment taking inappropriately high doses of famciclovir.

◊ References.

1. Saltzman R, *et al.* Safety of famciclovir in patients with herpes zoster and genital herpes. *Antimicrob Agents Chemother* 1994; **38:** 2454–7.

Interactions
As for Penciclovir, p.901.

Antiviral Action
As for Penciclovir, p.901.

Pharmacokinetics
Famciclovir is rapidly absorbed after oral doses. Absorption is delayed but not reduced by food. Famciclovir is rapidly converted to penciclovir (see p.901), peak plasma concentrations occurring within about 1 hour of a dose, and virtually no famciclovir is detectable in the plasma or urine. Bioavailability of penciclovir is reported to be 77%. Famciclovir is mainly excreted in the urine (partly by renal tubular secretion) as penciclovir and its 6-deoxy precursor; elimination is reduced in patients with renal impairment.

◊ References.

1. Pue MA, Benet LZ. Pharmacokinetics of famciclovir in man. *Antiviral Chem Chemother* 1993; **4** (suppl 1): 47–55.
2. Boike SC, *et al.* Pharmacokinetics of famciclovir in subjects with varying degrees of renal impairment. *Clin Pharmacol Ther* 1994; **55:** 418–26.
3. Boike SC, *et al.* Pharmacokinetics of famciclovir in subjects with chronic hepatic disease. *J Clin Pharmacol* 1994; **34:** 1199–1207.
4. Gill KS, Wood MJ. The clinical pharmacokinetics of famciclovir. *Clin Pharmacokinet* 1996; **31:** 1–8.

Uses and Administration
Famciclovir is a prodrug of the antiviral penciclovir (p.901). It is given orally in the treatment of herpes zoster (see Varicella-zoster Infections, p.855) and genital and mucocutaneous herpes (see Herpes Simplex Infections, p.854).

For **herpes zoster**, famciclovir is given in a dose of 250 mg three times daily, or 750 mg once daily, for 7 days (in the USA the recommended dose is 500 mg three times daily for 7 days); immunocompromised patients are given 500 mg three times daily for 10 days.

For **herpes simplex infections**, famciclovir is given in a dose of 250 mg three times daily for 5 days for first episodes of genital herpes; immunocompromised patients are given 500 mg twice daily for 7 days. For acute treatment of recurrent episodes of genital herpes, 125 mg is given twice daily for 5 days (in the USA, the recommended dose is 1 g twice daily for 1 day). Treatment should start in the prodromal period as soon as the first signs or symptoms appear. Immunocompromised patients are given 500 mg twice daily for 7 days.

For suppression of recurrent episodes of genital herpes, 250 mg is given twice daily; HIV patients may be given 500 mg twice daily. Such suppressive treatment is interrupted every 6 to 12 months to observe possible changes in the natural history of the disease.

For acute treatment of recurrent mucocutaneous herpes in HIV-infected patients, 500 mg is given twice daily for 7 days.

In the USA, famciclovir may also be given for the treatment of recurrent herpes labialis as a single 1.5 g dose, preferably begun in the prodromal period.

Doses of famciclovir should be reduced in patients with renal impairment (see below).

◊ Reviews.

1. Perry CM, Wagstaff AJ. Famciclovir: a review of its pharmacological properties and therapeutic efficacy in herpesvirus infections. *Drugs* 1995; **50:** 396–415.
2. Faro S. A review of famciclovir in the management of genital herpes. *Infect Dis Obstet Gynecol* 1998; **6:** 38–43.
3. Vinh DC, Aoki FY. Famciclovir for the treatment of recurrent genital herpes: a clinical and pharmacological perspective. *Expert Opin Pharmacother* 2006; **7:** 2271–86.
4. Simpson D, Lyseng-Williamson KA. Famciclovir: a review of its use in herpes zoster and genital and orolabial herpes. *Drugs* 2006; **66:** 2397–2416.

Administration in renal impairment. Doses of famciclovir need to be reduced in patients with renal impairment. UK licensed product information recommends the following oral doses based on creatinine clearance (CC):

Immunocompetent patients:

Herpes zoster or an initial episode of genital herpes
- CC 30 to 59 mL/minute per 1.73 m^2: 250 mg twice daily
- CC 10 to 29 mL/minute per 1.73 m^2: 250 mg once daily

Acute recurrent genital herpes, treatment
- CC 30 to 59 mL/minute per 1.73 m^2: no dosage adjustment necessary
- CC 10 to 29 mL/minute per 1.73 m^2: 125 mg once daily

Recurrent genital herpes, suppression
- CC 30 mL/minute per 1.73 m^2 and over: 250 mg twice daily
- CC 10 to 29 mL/minute per 1.73 m^2: 125 mg twice daily

Immunocompromised patients:

Herpes zoster
- CC 40 mL/minute per 1.73 m^2 and over: 500 mg three times daily
- CC 30 to 39 mL/minute per 1.73 m^2: 250 mg three times daily
- CC 10 to 29 mL/minute per 1.73 m^2: 125 mg three times daily

Herpes simplex infections
- CC 40 mL/minute per 1.73 m^2 and over: 500 mg twice daily
- CC 30 to 39 mL/minute per 1.73 m^2: 250 mg twice daily
- CC 10 to 29 mL/minute per 1.73 m^2: 125 mg twice daily

Patients on haemodialysis should be given doses of famciclovir immediately after dialysis.

Preparations
Proprietary Preparations (details are given in Part 3)
Arg.: Pentavir; Zosvir†; ***Austral.:*** Famvir; ***Austria:*** Famvir; ***Belg.:*** Famvir; ***Braz.:*** Famvir; Fanclomax; Penvir; ***Canad.:*** Famvir; ***Cz.:*** Famvir; ***Denm.:*** Famvir; ***Fin.:*** Famvir; ***Fr.:*** Oravir; ***Ger.:*** Famvir; ***Gr.:*** Famvir; ***Hong Kong:*** Famvir; ***Hung.:*** Famvir; ***India:*** Famtrex; ***Irl.:*** Famvir; ***Israel:*** Famvir†; ***Ital.:*** Famvir; Ziravir; ***Neth.:*** Famvir; ***NZ:*** Famvir†; ***Port.:*** Famvir; Zyvir; ***Rus.:*** Famvir (Фамвир); ***S.Afr.:*** Famvir; ***Singapore:*** Famvir; ***Spain:*** Ancivin; Famvir; ***Swed.:*** Famvir; ***Switz.:*** Famvir; ***Thai.:*** Famvir; ***Turk.:*** Famvir; ***UK:*** Famvir; ***USA:*** Famvir.

Fomivirsen Sodium *(BANM, USAN, rINNM)*

Fomivirseeninatrium; Fomivirsén sódico; Fomivirsen Sodique; Fomivirsennatrium; Fomivirsenum Natricum; Isis-2922; Natrii Fomivirsenum.

Натрий Фомивирсен

$C_{204}H_{243}N_{63}Na_{20}O_{114}P_{20}S_{20}$ = 7122.0.

CAS — 144245-52-3 (fomivirsen); 160369-77-7 (fomivirsen sodium).

ATC — S01AD08.

ATC Vet — QS01AD08.

Adverse Effects and Precautions
Adverse effects after intra-ocular injection of fomivirsen are confined to the treated eye. They include intra-ocular inflammation, transient increases in intra-ocular pressure, retinal detachment and oedema, and visual abnormalities. Other adverse effects associated with the intravitreal injection procedure include vitreal haemorrhage, endophthalmitis, uveitis, and cataract formation.

Patients should be monitored during treatment for changes in intra-ocular pressure and visual field and for extra-ocular CMV disease or disease in the contralateral eye.

Interactions
In order to reduce the risk of inflammation, intra-ocular use of fomivirsen is not recommended within 2 to 4 weeks of cidofovir treatment.

Antiviral Action
Fomivirsen is an antisense oligonucleotide that inhibits human CMV replication. It is active against strains of CMV resistant to ganciclovir, foscarnet, and cidofovir. Resistance to fomivirsen has been induced *in vitro*, but cross-resistance to antivirals with other modes of action is unlikely.

Uses and Administration
Fomivirsen is an antisense oligonucleotide that has been used as the sodium salt for the local treatment of CMV retinitis (p.853) in patients with AIDS. For newly diagnosed disease, a dose of 165 micrograms has been given by intravitreal injection into the affected eye once each week for 3 weeks, then on alternate weeks thereafter. For previously treated disease, 330 micrograms has been injected into the affected eye; this dose may be repeated once after 2 weeks and then once every 4 weeks thereafter.

◊ Reviews.

1. Perry CM, Barman Balfour JA. Fomivirsen. *Drugs* 1999; **57:** 375–80.
2. Geary RS, *et al.* Fomivirsen: clinical pharmacology and potential drug interactions. *Clin Pharmacokinet* 2002; **41:** 255–60.

Preparations
Proprietary Preparations (details are given in Part 3)
Ger.: Vitravene†; ***Switz.:*** Vitravene†; ***USA:*** Vitravene†.

Fosamprenavir Calcium *(USAN, rINNM)*

Calcii Fosamprenavirum; Fosamprenavir cálcico; Fosamprénavir Calcique; GW-433908G. (3*S*)-Tetrahydro-3-furyl{(α*S*)-α-[(1*R*)-1-hydroxy-2-(*N*^{1}-isobutylsulfanilamido)ethyl]phenethyl}carbamate calcium phosphate (1:1).

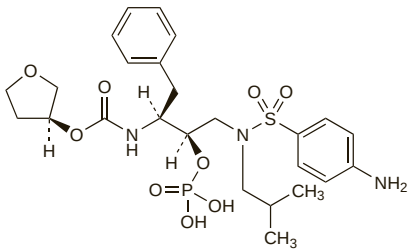
Кальций Фосампренавир

$C_{25}H_{36}CaN_3O_9PS$ = 625.7.

CAS — 226700-79-4 (fosamprenavir); 226700-81-8 (fosamprenavir calcium).

ATC — J05AE07.

ATC Vet — QJ05AE07.



(fosamprenavir)

Adverse Effects and Precautions
As for Amprenavir, p.865.

Interactions
Drugs interacting with amprenavir (p.866) might reasonably also be expected to interact with fosamprenavir.

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

Antiviral Action
As for Amprenavir (see p.866). Fosamprenavir is a prodrug that is rapidly hydrolysed to amprenavir (p.865) by cellular phosphatases in the gut epithelium as it is absorbed. Fosamprenavir itself has little or no antiviral activity *in vitro*

Pharmacokinetics
After oral doses, fosamprenavir is rapidly hydrolysed to amprenavir in the gastrointestinal epithelium as it is absorbed. Peak plasma concentrations of amprenavir are attained after 1.5 to 4 hours. Fosamprenavir may be given with or without food. For details of the pharmacokinetics of amprenavir, see p.866.

◊ Reviews.

1. Wire MB, *et al.* Fosamprenavir: clinical pharmacokinetics and drug interactions of the amprenavir prodrug. *Clin Pharmacokinet* 2006; **45:** 137–68.

Uses and Administration
Fosamprenavir is a prodrug of amprenavir, which is an HIV-protease inhibitor with antiviral activity against HIV. Fosamprenavir is used in the treatment of HIV infection and AIDS (p.856). Viral resistance emerges rapidly when fosamprenavir is used alone, and it is therefore used with other antiretrovirals.

Fosamprenavir may be given with or without food. It is given orally as the calcium salt, but doses are expressed in terms of the base. Fosamprenavir calcium 748 mg is equivalent to about 700 mg of fosamprenavir or to 600 mg of amprenavir and 50 mg of fosamprenavir solution is equivalent to about 43 mg of amprenavir.

In the UK, the recommended dose of ritonavir-boosted fosamprenavir in both treatment-experienced and treatment-naive adult patients is fosamprenavir 700 mg twice daily *plus* ritonavir 100 mg twice daily.

In the USA, recommended doses in treatment-naive adult patients are:

- fosamprenavir 1.4 g twice daily *without ritonavir*, or
- fosamprenavir 1.4 g once daily *plus* ritonavir 200 mg once daily, or
- fosamprenavir 1.4 g once daily *plus* ritonavir 100 mg once daily, or
- fosamprenavir 700 mg twice daily *plus* ritonavir 100 mg twice daily

The recommended dose in treatment-experienced patients is fosamprenavir 700 mg twice daily *plus* ritonavir 100 mg twice daily.

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

Doses should be reduced in patients with mild or moderate hepatic impairment (see below).

◊ Reviews.

1. Chapman TM, *et al.* Fosamprenavir: a review of its use in the management of antiretroviral therapy-naive patients with HIV infection. *Drugs* 2004; **64:** 2101–24.
2. Hester EK, *et al.* Fosamprenavir: drug development for adherence. *Ann Pharmacother* 2006; **40:** 1301–10.

Administration in children. For the treatment of HIV infection in children and adolescents, fosamprenavir is given daily with other antiretroviral drugs. Doses are based on body-weight and should not exceed the adult dose.

In the UK, the recommended dose of fosamprenavir oral solution in children and adolescents weighing 25 to 38 kg is 18 mg/kg twice daily *plus* ritonavir oral solution 3 mg/kg twice daily. Children and adolescents weighing at least 39 kg may be given the adult fosamprenavir tablet dose, see above. It is not licensed for use in children below 25 kg in weight or 6 years of age.

In the USA, the recommended dose of fosamprenavir oral suspension in treatment-naive children 2 to 5 years of age is fosamprenavir 30 mg/kg twice daily. Treatment-naive children 6 years of age or older may be given fosamprenavir 30 mg/kg twice daily or 18 mg/kg twice daily *plus* ritonavir 3 mg/kg twice daily. Treatment-experienced patients 6 years of age or older may be given fosamprenavir 18 mg/kg twice daily *plus* ritonavir 3 mg/kg twice daily.

Ritonavir 100-mg capsules may be given to children and adolescents taking fosamprenavir oral suspension if they weigh at least 33 kg.

Administration in hepatic impairment. Fosamprenavir should be used with caution in all patients with hepatic impairment.

UK licensed product information recommends:

- in patients with mild hepatic impairment (Child-Pugh score 5 to 6): fosamprenavir 700 mg twice daily *plus* ritonavir 100 mg once daily
- in patients with moderate hepatic impairment (Child-Pugh score 7 to 9): fosamprenavir 450 mg twice daily *plus* ritonavir 100 mg once daily

US licensed product information recommends:

- in treatment-naive patients with mild hepatic impairment (Child-Pugh score 5 to 6): fosamprenavir 700 mg twice daily *without ritonavir*, or *plus* ritonavir 100 mg once daily
- in treatment-experienced patients with mild hepatic impairment (Child-Pugh score 5 to 6): fosamprenavir 700 mg twice daily *plus* ritonavir 100 mg once daily
- in treatment-naive patients with moderate hepatic impairment (Child-Pugh score 7 to 9): fosamprenavir 700 mg twice daily *without ritonavir*, or fosamprenavir 450 mg twice daily *plus* ritonavir 100 mg once daily
- in treatment-experienced patients with moderate hepatic impairment (Child-Pugh score 7 to 9): fosamprenavir 450 mg twice daily *plus* ritonavir 100 mg once daily
- in treatment-naive patients with severe hepatic impairment (Child-Pugh score 10 to 12): fosamprenavir 350 mg twice daily *without ritonavir*

Fosamprenavir *plus* ritonavir should not be used in patients with severe hepatic impairment.

Preparations
Proprietary Preparations (details are given in Part 3)
Arg.: Telzir; ***Austral.:*** Telzir; ***Belg.:*** Telzir; ***Canad.:*** Telzir; ***Cz.:*** Telzir; ***Denm.:*** Telzir; ***Fin.:*** Telzir; ***Fr.:*** Telzir; ***Ger.:*** Telzir; ***Gr.:*** Telzir; ***Hung.:*** Telzir; ***Irl.:*** Telzir; ***Israel:*** Lexiva; ***Ital.:*** Telzir; ***Mex.:*** Telzer; ***Neth.:*** Telzir; ***Norw.:*** Telzir; ***Pol.:*** Telzir; ***Port.:*** Telzir; ***Spain:*** Telzir; ***Swed.:*** Telzir; ***Switz.:*** Telzir; ***UK:*** Telzir; ***USA:*** Lexiva.

Foscarnet Sodium *(BAN, USAN, rINN)*

A-29622; EHB-776 (anhydrous and hexahydrate); Foscarnet sódico; Foscarnet Sodique; Foscarnet sodique hexahydraté; Foscarnetum Natricum; Foscarnetum natricum hexahydricum; Foskarneettinatriumheksahydraatti; Foskarnet sodná sůl hexahydrát; Foskarnet Sodyum; Foskarnetnatriumhexahydrat; Foskarneto natrio druska heksahidratas; Foszkarnet-nátrium; Phosphonatoformate Trisodium; Phosphonoformate Trisodium. Trisodium phosphonatoformate hexahydrate.

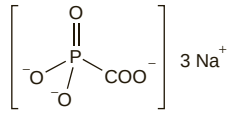
Фоскарнет Натрий

$CNa_3O_5P,6H_2O$ = 300.0.

CAS — 63585-09-1 (foscarnet sodium); 34156-56-4 (foscarnet sodium hexahydrate).

ATC — J05AD01.

ATC Vet — QJ05AD01.



Pharmacopoeias. In *Eur.* (see p.vii).
Ph. Eur. 6.2 (Foscarnet Sodium Hexahydrate; Foscarnet Sodium BP 2008). A white or almost white crystalline powder. Soluble in water; practically insoluble in alcohol. A 2% solution in water has a pH of 9.0 to 11.0. Protect from light.

Incompatibility. Foscarnet sodium has been found to be visually incompatible with some commonly used injectable drugs including amphotericin B, aciclovir sodium, co-trimoxazole, ganciclovir, and pentamidine isetionate;[1,2] licensed product information also lists incompatibilities with vancomycin, glucose 30% solution, and solutions containing calcium. It is therefore recommended that foscarnet should not be infused via an intravenous line with any other drug.

1. Lor E, Takagi J. Visual compatibility of foscarnet with other injectable drugs. *Am J Hosp Pharm* 1990; **47:** 157–9.
2. Baltz JK, *et al.* Visual compatibility of foscarnet with other injectable drugs during simulated Y-site administration. *Am J Hosp Pharm* 1990; **47:** 2075–7.

Adverse Effects and Treatment
The most serious common adverse effect of foscarnet sodium is renal impairment, which may be severe. Anaemia may be common and granulocytopenia and thrombocytopenia have been reported. Foscarnet can chelate bivalent metal ions, and may be associated with an acute decrease in ionised calcium in the plasma that is not necessarily reflected by measurements of total calcium; the decrease is proportional to the rate of infusion. Other electrolyte disturbances may occur. Some patients may have convulsions. Excretion of high concentrations in the urine can cause local irritation and genital ulceration. Other adverse effects reported include nausea, vomiting, diarrhoea, malaise, fatigue, fever, headache, dizziness, paraesthesia, tremor, mood disturbances, rash, abnormal liver function tests, blood pressure and ECG changes, and isolated reports of pancreatitis. Intravenous injection may cause phlebitis at the site of injection.

In cases of overdosage it is important to maintain hydration. Foscarnet elimination may be increased by haemodialysis.

Effects on the CNS. Convulsions may occur in up to 10% of AIDS patients receiving foscarnet and have been reported after overdoses. Contributing factors include underlying CNS pathol-