4. Reynes J, *et al.* TORO: ninety-six-week virologic and immunologic response and safety evaluation of enfuvirtide with an optimized background of antiretrovirals. *AIDS Patient Care STDS* 2007; **21:** 533–43.
5. Wiznia A, *et al.* T20-310 Study Group. Safety and efficacy of enfuvirtide for 48 weeks as part of an optimized antiretroviral regimen in pediatric human immunodeficiency virus 1-infected patients. *Pediatr Infect Dis J* 2007; **26:** 799–805.
6. Rockstroh J, *et al.* Adherence to enfuvirtide and its impact on treatment efficacy. *AIDS Res Hum Retroviruses* 2008; **24:** 141–8.
7. Saberi P, *et al.* Immunologic benefits of enfuvirtide in patients enrolled in a drug assistance program. *Ann Pharmacother* 2008; **42:** 621–6.

Administration in children. For the treatment of HIV infection, enfuvirtide may be given to children 6 to 16 years of age by subcutaneous injection into the upper arm, anterior thigh, or abdomen in a dose of 2 mg/kg twice daily (to a maximum of 90 mg twice daily). Each injection should be given at a different site from the preceding one.

Preparations

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

Entecavir *(USAN, rINN)*

BMS-200475-01; Entécavir; Entecavirum; SQ-34676. 9-[(1*S*,3*R*,4*S*)-4-Hydroxy-3-(hydroxymethyl)-2-methylenecyclopentyl]guanine monohydrate.

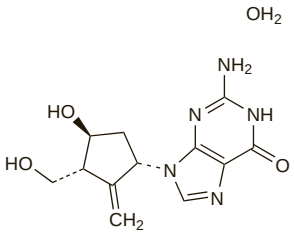
Энтекавир

$C_{12}H_{15}N_5O_3,H_2O$ = 295.3.

CAS — 142217-69-4 (anhydrous entecavir); 209216-23-9 (entecavir monohydrate).

ATC — J05AF10.

ATC Vet — QJ05AF10.



Adverse Effects

The most common adverse effects of entecavir have been headache, fatigue, dizziness, and nausea. Other adverse effects include diarrhoea, dyspepsia, insomnia, somnolence, and vomiting.

Raised liver enzyme concentrations may occur and exacerbation of hepatitis has been reported after stopping treatment with entecavir. Lactic acidosis, usually associated with severe hepatomegaly and steatosis, has been associated with treatment with nucleoside analogues alone or with antiretrovirals (see Zidovudine, p.914).

Entecavir is carcinogenic in *rodents*, but a relationship with human cancer has not been established.

Precautions

Entecavir should be withdrawn if there is a rapid increase in aminotransferase concentrations, progressive hepatomegaly or steatosis, or metabolic or lactic acidosis of unknown aetiology. Entecavir should be given with caution to patients with hepatomegaly or other risk factors for liver disease. Careful differentiation should be made between patients whose liver enzyme concentrations become elevated due to response to treatment and those in whom it is indicative of toxicity. Exacerbation of hepatitis B has been reported both during and after stopping treatment with entecavir. Hepatic function should be monitored closely while on treatment and for several months after treatment is stopped. Dosage reduction may be necessary in patients with renal impairment.

Limited clinical experience suggests there is a potential for HIV to develop resistance to NRTIs if entecavir is used to treat chronic hepatitis B virus infection in patients with undiagnosed or untreated HIV infection. Treatment with entecavir is not recommended for co-infected patients who are not also receiving HAART. US licensed product information recommends that all patients be tested for HIV antibodies before starting treatment with entecavir.

HIV-infected patients. It was initially thought that entecavir did not inhibit replication of HIV-1 at clinically relevant doses. However, a small consistent decrease in HIV-1 RNA was noted in 3 patients with HIV-1 and hepatitis B virus co-infection being treated with entecavir monotherapy.[1] In 1 of these patients, an HIV variant containing the M184V resistance substitution was found. Subsequent *in vitro* analyses showed that HIV-1 strains containing M184V were resistant to entecavir.

1. McMahon MA, *et al.* The HBV drug entecavir—effects on HIV-1 replication and resistance. *N Engl J Med* 2007; **356:** 2614–21.

Interactions

Caution should be exercised when entecavir is given with other drugs eliminated by active tubular secretion as competition for the elimination pathway may increase the serum concentrations of either drug.

Antiviral Action

Entecavir is phosphorylated intracellularly to the active triphosphate form which competes with deoxyguanosine triphosphate, the natural substrate of hepatitis B virus reverse transcriptase, thereby inhibiting every stage of the enzyme's activity.

Although initially thought to be inactive against HIV at clinically relevant doses, entecavir may have sufficient action to result in the selection of resistant HIV variants (see HIV-infected Patients, under Precautions, above).

Pharmacokinetics

Entecavir is rapidly absorbed from the gastrointestinal tract after oral doses. Peak plasma concentrations occur 30 to 90 minutes after an oral dose and steady state concentrations after 6 to 10 days of treatment. Absorption is both delayed and reduced by food; this is not considered to be clinically relevant in nucleoside treatment-naive patients but may affect efficacy in lamivudine-refractory patients in whom entecavir should be taken on an empty stomach. Bioavailability of the tablet formulation is equal to that of the oral solution and they may be given interchangeably. Binding of entecavir to plasma proteins is about 13% *in vitro*. Entecavir is not metabolised by the cytochrome P450 system. It is mainly eliminated by the kidneys by glomerular filtration and active tubular secretion, with a terminal elimination half-life of 128 to 149 hours. Small amounts of glucuronide and sulfate conjugates are formed. Entecavir is partially removed by haemodialysis.

Uses and Administration

Entecavir is a nucleoside reverse transcriptase inhibitor, structurally related to guanosine with selective antiviral activity against hepatitis B virus. It is used for the treatment of chronic hepatitis B (p.851) in adults with compensated liver disease with evidence of active viral replication, persistently elevated liver enzyme values, and histologically active disease, including those resistant to lamivudine. The usual oral dose of entecavir in nucleoside treatment-naive patients is 500 micrograms once daily, either with or without food. An oral dose of 1 mg once daily on an empty stomach should be used in patients with a history of hepatitis B viraemia during lamivudine therapy or with known resistance to lamivudine. For details of reduced doses to be used in patients with renal impairment, see below.

◊ Reviews.

1. Sims KA, Woodland AM. Entecavir: a new nucleoside analog for the treatment of chronic hepatitis B infection. *Pharmacotherapy* 2006; **26:** 1745–57.
2. Robinson DM, *et al.* Entecavir: a review of its use in chronic hepatitis B. *Drugs* 2006; **66:** 1605–22.
3. Matthews SJ. Entecavir for the treatment of chronic hepatitis B virus infection. *Clin Ther* 2006; **28:** 184–203.

Administration in renal impairment. Doses of entecavir should be reduced in patients with renal impairment according to creatinine clearance (CC) as follows:

- CC 30 to 49 mL/minute: 250 micrograms once daily or 500 micrograms every 48 hours in nucleoside treatment-naive patients; 500 micrograms once daily in lamivudine-refractory patients
- CC 10 to 29 mL/minute: 150 micrograms once daily or 500 micrograms every 72 hours in nucleoside treatment-naive patients; 300 micrograms once daily or 500 micrograms every 48 hours in lamivudine-refractory patients
- CC less than 10 mL/minute (and patients on haemodialysis or continuous ambulatory peritoneal dialysis): 50 micrograms once daily or 500 micrograms every 5 to 7 days in nucleoside treatment-naive patients; 100 micrograms once daily or 500 micrograms every 72 hours in lamivudine-refractory patients

Patients receiving haemodialysis should receive the appropriate dose after each dialysis session.

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Baraclude; ***Austral.:*** Baraclude; ***Cz.:*** Baraclude; ***Fr.:*** Baraclude; ***Gr.:*** Baraclude; ***Hung.:*** Baraclude; ***Indon.:*** Baraclude; ***Malaysia:*** Baraclude; ***NZ:*** Baraclude; ***Philipp.:*** Baraclude; ***Port.:*** Baraclude; ***Singapore:*** Baraclude; ***UK:*** Baraclude; ***USA:*** Baraclude.

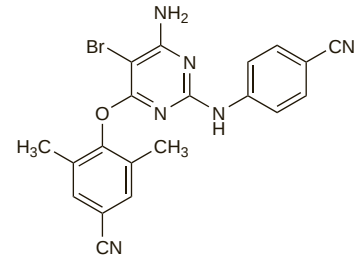
Etravirine *(USAN, rINN)*

Etravirina; Étravirine; Etravirinum; R-165335; TMC-125. 4-[6-Amino-5-bromo-2-(4-cyanoanilino)pyrimidin-4-yloxy]-3,5-dimethylbenzonitrile.

Этравирин

$C_{20}H_{15}BrN_6O$ = 435.3.

CAS — 269055-15-4.



Adverse Effects

The most common adverse effects associated with antiretroviral regimens containing etravirine are nausea and skin rash (usually mild to moderate) and generally appearing in the second week of treatment and resolving within 1 to 2 weeks. Severe skin reactions, including erythema multiforme and Stevens-Johnson syndrome, have occurred. Additional adverse events of moderate to severe intensity reported by at least 2% of patients receiving etravirine in clinical studies included gastrointestinal complaints (abdominal pain, diarrhoea, nausea, and vomiting), fatigue, headache, hypertension, and peripheral neuropathy. Raised liver enzyme values, glucose levels, and serum-cholesterol and -triglyceride concentrations have 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 etravirine, 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 etravirine.

Precautions

Etravirine should be stopped if a severe skin rash develops. Patients co-infected with chronic hepatitis B or C have experienced worsening of hepatitis-related symptoms when treated with etravirine. Patients who have virologic failure on a NNRTI-containing regimen

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.

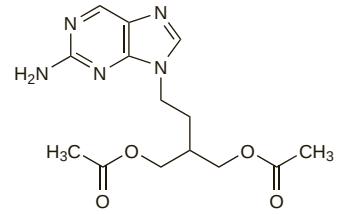
Фамцикловир

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