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.

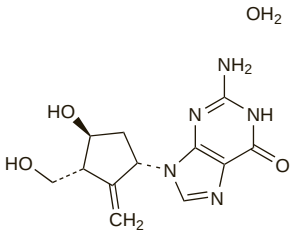
Энтекавир

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

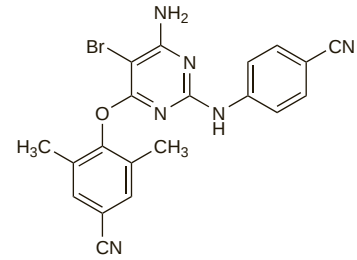
Etravirine *(USAN, rINN)*

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