Administration in renal impairment. Dosage reduction according to creatinine clearance (CC) is recommended for patients receiving oral stavudine who have renal impairment:

- CC 26 to 50 mL/minute: 20 mg every 12 hours (those weighing 60 kg or more) or 15 mg every 12 hours (those weighing less than 60 kg)
- CC below 26 mL/minute: 20 mg every 24 hours (those weighing 60 kg or more) or 15 mg every 24 hours (those weighing less than 60 kg)

Preparations

USP 31: Stavudine Capsules; Stavudine for Oral Solution.

Proprietary Preparations (details are given in Part 3)
Arg.: Biract†; Lion; Revixil†; Stamar; Stavubergen; Stelea†; STV; Tonavir; Zerit; ***Austral.:*** Zerit; ***Austria:*** Zerit; ***Belg.:*** Zerit; ***Braz.:*** Svudin†; Zeritavir; ***Canad.:*** Zerit; ***Chile:*** Zerit; ***Cz.:*** Zerit; ***Denm.:*** Zerit; ***Fin.:*** Zerit; ***Fr.:*** Zerit; ***Ger.:*** Zerit; ***Gr.:*** Zerit; ***Hong Kong:*** Zerit; ***Hung.:*** Zerit; ***India:*** Stavir; ***Indon.:*** Zerit; ***Irl.:*** Zerit; ***Israel:*** Zerit†; ***Ital.:*** Zerit; ***Jpn:*** Zerit; ***Malaysia:*** Virostav; Zerit†; ***Mex.:*** Apostavina†; Landstav; Pravidine; Ranstar; Zerit; ***Neth.:*** Zerit; ***Norw.:*** Zerit; ***NZ:*** Zerit; ***Pol.:*** Zerit; ***Port.:*** Zerit; ***Rus.:*** Actastav (Актастав); Zerit (Зерит); ***S.Afr.:*** Stavir; Zerit; ***Singapore:*** Zerit; ***Spain:*** Zerit; ***Swed.:*** Zerit; ***Switz.:*** Zerit; ***Thai.:*** Zerit; ***Turk.:*** Zerit; ***UK:*** Zerit; ***USA:*** Zerit; ***Venez.:*** Stavir; Zerit.

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

Telbivudine *(BAN, USAN, rINN)*

L-dT; Epavudine; LDT-600; NV-02B; Telbivudina; Telbivudinum. 2′-Deoxy-L-thymidine; 1-(2-Deoxy-β-L-*erythro*-pentofuranosyl)-5-methylpyrimidine-2,4(1*H*,3*H*)-dione.

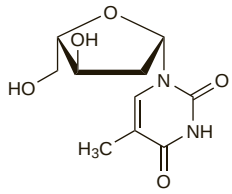
Тельбивудин

$C_{10}H_{14}N_2O_5$ = 242.2.

CAS — 3424-98-4.

ATC — J05AF11.

ATC Vet — QJ05AF11.



Adverse Effects

The most common adverse effects reported for telbivudine are cough, dizziness, fatigue, gastrointestinal effects including abdominal pain, diarrhoea, and nausea, and rash. There have also been reports of arthralgia, myalgia, myopathy, and malaise. Serum amylase, lipase and creatine phosphokinase levels may be increased. Raised serum alanine aminotransferase concentrations may occur and exacerbation of hepatitis has been reported after stopping treatment with telbivudine. There have been occasional reports of peripheral neuropathy, particularly when given with peginterferon alfa-2a.

Lactic acidosis, usually associated with severe hepatomegaly and steatosis, has been associated with treatment with nucleoside analogues (see Zidovudine, p.914).

Precautions

Telbivudine should be given with caution to patients with cirrhosis, hepatomegaly, or other risk factors for liver disease and should be withdrawn if there is a rapid increase in aminotransferase concentrations, progressive hepatomegaly or steatosis, or metabolic or lactic acidosis of unknown aetiology. Exacerbation of hepatitis B has been reported both during and after stopping treatment with telbivudine. Liver function should be monitored closely during treatment and for several months after treatment is stopped. Patients taking telbivudine should be monitored for peripheral neuropathy and treatment should be stopped if myopathy or peripheral neuropathy is diagnosed. Dosage reduction may be necessary in patients with renal impairment.

Interactions

Caution should be exercised when telbivudine is given with other drugs that alter renal function; serum concentrations of either drug may be affected. Telbivudine should be given with caution to patients taking other drugs associated with myopathy (such as azole antifungals, ciclosporin, corticosteroids, erythromycin, fibrates, HMG-CoA reductase inhibitors, penicillamine, and zidovudine).

Interferons. For mention of an increased risk of peripheral neuropathy in patients given both telbivudine and *peginterferon alfa-2a*, see Adverse Effects, above.

Antiviral Action

Telbivudine is phosphorylated intracellularly to the active triphosphate form, which competes with thymidine 5'-triphosphate, the natural substrate of hepatitis B virus reverse transcriptase, thereby causing DNA chain termination and inhibiting hepatitis B viral replication.

Telbivudine has no activity against HIV.

Pharmacokinetics

Telbivudine is absorbed from the gastrointestinal tract after oral doses. Peak plasma concentrations occur after about 3 hours. Absorption is not affected when given with food. Binding of telbivudine to plasma proteins is about 3.3% *in vitro*. Telbivudine is not metabolised by the cytochrome P450 system. It is mainly excreted renally by glomerular filtration as unchanged drug, with a terminal elimination half-life of 30 to 53.6 hours. Telbivudine is partially removed by haemodialysis.

Uses and Administration

Telbivudine is an orally bioavailable L-nucleoside analogue with specific activity against the hepatitis B virus. It is given orally for the treatment of chronic hepatitis B (p.851) in patients with compensated liver disease and evidence of active viral replication, persistently raised serum alanine aminotransferase concentrations, and histological evidence of active liver inflammation and fibrosis. The usual dose of telbivudine is 600 mg once daily. For details of dosage modification in patients with renal impairment, see below.

◊ References.

1. Lai CL, *et al.* A dose-finding study of once-daily oral telbivudine in HBeAg-positive patients with chronic hepatitis B virus infection. *Hepatology* 2004; **40:** 719–26.
2. Lai CL, *et al.* A 1-year trial of telbivudine, lamivudine, and the combination in patients with hepatitis B e antigen-positive chronic hepatitis B. *Gastroenterology* 2005; **129:** 528–36.
3. Kim JW, *et al.* Telbivudine: a novel nucleoside analog for chronic hepatitis B. *Ann Pharmacother* 2006; **40:** 472–8.
4. Jones R, Nelson M. Novel anti-hepatitis B agents: a focus on telbivudine. *Int J Clin Pract* 2006; **60:** 1295–9.
5. Keam SJ. Telbivudine. *Drugs* 2007; **67:** 1917–29.

Administration in renal impairment. The dosage of telbivudine should be reduced in patients with renal impairment by modifying the dosing interval according to the creatinine clearance (CC) of the patient:

- CC 50 mL or more per minute: 600 mg once daily
- CC 30 to 49 mL/minute: 600 mg every 48 hours
- CC less than 30 mL/minute (and not on dialysis): 600 mg every 72 hours
- end stage renal disease: 600 mg every 96 hours

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

Preparations

Proprietary Preparations (details are given in Part 3)
Cz.: Sebivo; ***Indon.:*** Sebivo; ***Malaysia:*** Sebivo; ***Port.:*** Sebivo; ***UK:*** Sebivo; ***USA:*** Tyzeka.

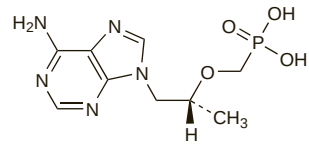
Tenofovir *(BAN, USAN, rINN)*

GS-1278; PMPA; (*R*)-PMPA; Ténofovir; Tenofovirum. 9-[(*R*)-2-(Phosphonomethoxy)propyl]adenine monohydrate; {[(*R*)-2-(6-Amino-9*H*-purin-9-yl)-1-methylethoxy]methyl}phosphonic acid monohydrate.

Тенофовир

$C_9H_{14}N_5O_4P,H_2O$ = 305.2.

CAS — 147127-20-6 (anhydrous tenofovir); 206184-49-8 (tenofovir monohydrate).



(anhydrous tenofovir)

Tenofovir Disoproxil Fumarate *(BANM, USAN, rINNM)*

Fumarato de disoproxilo de tenofovir; GS-4331/05; Ténofovir Disoproxil. Fumarate de; Tenofovirum Disoproxilum Fumaras. 9-{(*R*)-2-[(Bis{[(isopropoxycarbonyl)oxy]methoxy}phosphinyl)methoxy]propyl}adenine fumarate (1:1).

Тенофовир Дизопроксил Фумарат

$C_{19}H_{30}N_5O_{10}P,C_4H_4O_4$ = 635.5.

CAS — 202138-50-9.

ATC — J05AF07.

ATC Vet — QJ05AF07.

Adverse Effects

Adverse effects commonly associated with tenofovir disoproxil fumarate either as monotherapy for the treatment of chronic hepatitis B or with other antiretrovirals for the treatment of HIV are mild to moderate gastrointestinal events such as anorexia, abdominal pain, diarrhoea, dyspepsia, flatulence, nausea, and vomiting. Other commonly reported adverse effects are dizziness, fatigue, and headache. Skin rashes may occur. Hypophosphataemia is also common. Serum-amylase concentrations may be raised and pancreatitis has been reported rarely. There have also been reports of raised liver enzymes, hepatitis, nephritis, nephrogenic diabetes insipidus, renal impairment, acute renal failure, and effects on the renal proximal tubules, including Fanconi syndrome.

Lactic acidosis, usually associated with severe hepatomegaly and steatosis, has been associated with treatment with nucleoside reverse transcriptase inhibitors.

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 tenofovir disoproxil fumarate, 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 tenofovir disoproxil fumarate. Metabolic abnormalities such as hypertriglyceridaemia, hypercholesterolaemia, insulin resistance, hyperglycaemia, and hyperlactataemia have also been reported. NRTIs have also been associated with mitochondrial dysfunction manifesting as abnormal behaviour, anaemia, convulsions, hyperlipasaemia, hypertonia, and neutropenia. Elevated creatine phosphokinase, myalgia, myositis, and rarely rhabdomyolysis have been reported, particularly when nucleoside analogues have been given with HIV-protease inhibitors. 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 NRTIs see Zidovudine, p.914.

Effects on the kidney. Use of tenofovir in patients with HIV infection has been associated with renal toxicity,[1] including Fanconi syndrome,[2] interstitial nephritis,[3] and acute renal failure.[4,5] The mechanism of acute renal failure appears to be tubular necrosis, which may not resolve on withdrawal of the drug.[6] Some studies have indicated that glomerular filtration rate or creatinine clearance was consistently decreased in patients given tenofovir-containing regimens;[7,8] it has been reported that this is greater if combined with HIV-protease inhibitors than NNRTIs.[8] Other studies have not found renal toxicity to be a significant problem.[9,10]

1. Gitman MD, *et al.* Tenofovir-induced kidney injury. *Expert Opin Drug Saf* 2007; **6:** 155–64.

2. Gupta SK. Tenofovir-associated Fanconi syndrome: review of the FDA adverse event reporting system. *AIDS Patient Care STDS* 2008; **22:** 99–103.
3. Schmid S, *et al.* Acute interstitial nephritis of HIV-positive patients under atazanavir and tenofovir therapy in a retrospective analysis of kidney biopsies. *Virchows Arch* 2007; **450:** 665–70.
4. Hynes P, *et al.* Acute renal failure after initiation of tenofovir disoproxil fumarate. *Ren Fail* 2007; **29:** 1063–6.
5. Kapitsinou PP, Ansari N. Acute renal failure in an AIDS patient on tenofovir: a case report. *J Med Case Reports* 2008; **2:** 94.
6. Zimmermann AE, *et al.* Tenofovir-associated acute and chronic kidney disease: a case of multiple drug interactions. *Clin Infect Dis* 2006; **42:** 283–90.
7. Fux CA, *et al.* Tenofovir use is associated with a reduction in calculated glomerular filtration rates in the Swiss HIV Cohort Study. *Antivir Ther* 2007; **12:** 1165–73.
8. Goicoechea M, *et al.* Greater tenofovir-associated renal function decline with protease inhibitor-based versus nonnucleoside reverse-transcriptase inhibitor-based therapy. *J Infect Dis* 2008; **197:** 102–8.
9. Viganò A, *et al.* Renal safety of tenofovir in HIV-infected children: a prospective, 96-week longitudinal study. *Clin Drug Investig* 2007; **27:** 573–81.
10. Madeddu G, *et al.* Tenofovir renal safety in HIV-infected patients: results from the SCOLTA Project. *Biomed Pharmacother* 2008; **62:** 6–11.

Precautions

Treatment with tenofovir disoproxil fumarate should be stopped if there is a rapid increase in aminotransferase concentrations, progressive hepatomegaly or steatosis, or metabolic or lactic acidosis of unknown aetiology. It should be given with caution to patients with hepatomegaly or other risk factors for liver disease. In particular, extreme caution should be exercised in patients with co-existing hepatitis C infection who are receiving interferon alfa and ribavirin. In patients co-infected with hepatitis B, there is a risk of severe acute exacerbation of hepatitis when tenofovir is stopped, and liver function should be monitored closely in such patients for at least several months.

Tenofovir should be used with caution, and doses modified, in patients with renal impairment. Renal function and serum phosphates should be monitored before treatment is started, every 4 weeks during the first year of therapy, and then every 3 months; in patients with a history of renal impairment or who are particularly at risk, more frequent monitoring may be needed. If serum-phosphate concentrations fall markedly or if creatinine clearance is below 50 mL/minute, renal function should be evaluated within a week, and the dose interval may need to be adjusted or treatment interrupted. Tenofovir disoproxil fumarate may be associated with reduction in bone density and patients should be observed for evidence of bone abnormalities; bone monitoring should be considered for patients with a history of bone fractures or those at risk of osteopenia.

Interactions

Use of tenofovir disoproxil fumarate with nephrotoxic drugs or with other drugs eliminated by active tubular secretion is not recommended; if such use is unavoidable, renal function should be monitored weekly. Tenofovir increases the plasma concentrations of didanosine (see p.871). Once daily triple nucleoside regimens of tenofovir and lamivudine with either abacavir or didanosine are associated with a high level of treatment failure and of emergence of resistance, and should be avoided. Decreased plasma concentrations of atazanavir and increased plasma concentrations of tenofovir occur when tenofovir is given with atazanavir; the effect is significantly reduced when ritonavir is added as a booster. Use of ritonavir-boosted lopinavir with tenofovir modestly increases the plasma concentrations of tenofovir.

Antidiabetics. Fatal lactic acidosis has been reported[1] in a patient given *metformin* with didanosine, stavudine, and tenofovir.

1. Worth L, *et al.* A cautionary tale: fatal lactic acidosis complicating nucleoside analogue and metformin therapy. *Clin Infect Dis* 2003; **37:** 315–16.

Antiviral Action

Tenofovir is converted intracellularly to the diphosphate. This diphosphate halts the DNA synthesis of HIV through competitive inhibition of reverse transcriptase and incorporation into viral DNA. Tenofovir-resistant strains of HIV have been identified and cross-resistance to other reverse transcriptase inhibitors may occur.

Pharmacokinetics

Tenofovir disoproxil fumarate is rapidly absorbed and converted to tenofovir after oral doses, with peak plasma concentrations occurring after 1 to 2 hours. Bioavailability in fasting patients is about 25%, but this is enhanced when tenofovir disoproxil fumarate is taken with a high fat meal. Tenofovir is widely distributed into body tissues, particularly the kidneys and liver. Binding to plasma proteins is less than 1% and that to serum proteins about 7%. The terminal elimination half-life of tenofovir is 12 to 18 hours. Tenofovir is excreted mainly in the urine by both active tubular secretion and glomerular filtration. It is removed by haemodialysis.

◊ Reviews.

1. Kearney BP, *et al.* Tenofovir disoproxil fumarate: clinical pharmacology and pharmacokinetics. *Clin Pharmacokinet* 2004; **43:** 595–612.
2. Kearney BP, *et al.* Pharmacokinetics and dosing recommendations of tenofovir disoproxil fumarate in hepatic or renal impairment. *Clin Pharmacokinet* 2006; **45:** 1115–24.

Uses and Administration

Tenofovir is a nucleotide reverse transcriptase inhibitor with antiviral activity against HIV-1 and hepatitis B. It is used in the treatment of HIV infection and AIDS (p.856) and chronic hepatitis B infection (p.851). Viral resistance emerges rapidly when tenofovir is used alone in the treatment of HIV infection, and it is therefore used with other antiretrovirals.

It is given orally as the disoproxil fumarate ester. Tenofovir disoproxil fumarate 300 mg is equivalent to about 245 mg of tenofovir disoproxil and to about 136 mg of tenofovir. For the treatment of either HIV or chronic hepatitis B infection the usual dose is 300 mg of the disoproxil fumarate ester once daily with food.

For details of doses of tenofovir disoproxil fumarate to be used in patients with renal impairment, see below.

Fixed-dose combination products for the treatment of HIV infection and AIDS have been developed in order to improve patient adherence and avoid monotherapy, thereby decreasing the risk of acquired drug resistance. Products containing tenofovir disoproxil fumarate in combination with emtricitabine, and with efavirenz plus emtricitabine are available in some countries.

A gel containing tenofovir is under investigation as a topical microbicide in the prevention of HIV infection.

◊ Reviews.

1. Grim SA, Romanelli F. Tenofovir disoproxil fumarate. *Ann Pharmacother* 2003; **37:** 849–59.
2. Gallant JE, Deresinski S. Tenofovir disoproxil fumarate. *Clin Infect Dis* 2003; **37:** 944–50.
3. Dando TM, Wagstaff AJ. Emtricitabine/tenofovir disoproxil fumarate. *Drugs* 2004; **64:** 2075–82.
4. Lyseng-Williamson KA, *et al.* Tenofovir disoproxil fumarate: a review of its use in the management of HIV infection. *Drugs* 2005; **65:** 413–32.
5. Wong SN, Lok AS. Tenofovir disoproxil fumarate: role in hepatitis B treatment. *Hepatology* 2006; **44:** 309–13.
6. Reijnders JGP, Janssen HLA. Potency of tenofovir in chronic hepatitis B: mono or combination therapy? *J Hepatol* 2008; **48:** 383–6.
7. Stephan C. Experience with tenofovir disoproxil fumarate for antiretroviral therapy. *Expert Opin Pharmacother* 2008; **9:** 1197–209.
8. Pozniak A. Tenofovir: what have over 1 million years of patient experience taught us? *Int J Clin Pract* 2008; **62:** 1285–93.

Administration in renal impairment. Doses of tenofovir disoproxil fumarate should be modified by adjustment of the dosing interval in patients with renal impairment according to their creatinine clearance (CC):

- CC 50 mL or more per minute: usual once-daily dosage (above)
- CC 30 to 49 mL/minute: every 48 hours
- CC 10 to 29 mL/minute: every 72 to 96 hours
- haemodialysis patients: a dose every 7 days or after a cumulative total of 12 hours of dialysis

Preparations

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

Multi-ingredient: ***Arg.:*** Truvada; ***Austral.:*** Truvada; ***Cz.:*** Truvada; ***Fin.:*** Truvada; ***Fr.:*** Truvada; ***Ger.:*** Truvada; ***Gr.:*** Truvada; ***Irl.:*** Truvada; ***Ital.:*** Truvada; ***Mex.:*** Truvada; ***Neth.:*** Truvada; ***NZ:*** Truvada; ***Port.:*** Truvada; ***Spain:*** Truvada; ***Swed.:*** Truvada; ***UK:*** Atripla; Truvada; ***USA:*** Atripla; Truvada.

Tipranavir *(rINN)*

PNU-140690; Tipranavirum; U-140690. 3′-{(1*R*)-1-[(6*R*)-5,6-Dihydro-4-hydroxy-2-oxo-6-phenethyl-6-propyl-2*H*-pyran-3-yl]propyl}-5-(trifluoromethyl)-2-pyridinesulfonanilide.

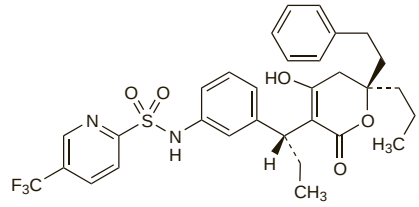
Типранавир

$C_{31}H_{33}F_3N_2O_5S$ = 602.7.

CAS — 174484-41-4.

ATC — J05AE09.

ATC Vet — QJ05AE09.



NOTE. Tipranavir Disodium is USAN.

Tipranavir Sodium *(BANM, rINNM)*

Natrii Tipranavirum; PNU-140690E; Tipranavir Disodium *(USAN)*; Tipranavir sodico; Tipranavir Sodique.

Натрий Типранавир

$C_{31}H_{31}F_3N_2Na_2O_5S$ = 646.6.

CAS — 191150-83-1.

ATC — J05AE09.

ATC Vet — QJ05AE09.

Adverse Effects

The most common adverse effects associated with antiretroviral regimens containing tipranavir are gastrointestinal disturbances (abdominal pain, diarrhoea, dyspepsia, flatulence, nausea, and vomiting), anorexia, fatigue, and headache. Serious adverse effects reported include increased risk of bleeding, lipid abnormalities (hyperlipidaemia and hypertriglyceridaemia), and severe hepatotoxicity (hepatitis and hepatic decompensation) and intracranial haemorrhage including some fatalities. Rashes, generally occurring after about 2 months of treatment and lasting about 3 weeks have been reported; rashes are sometimes accompanied by joint pain, stiffness, throat tightness, or generalised pruritus.

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 tipranavir, 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 tipranavir. 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.