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.

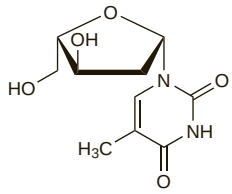
Тельбивудин

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

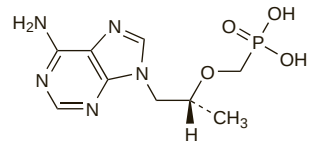
Tenofovir *(BAN, USAN, rINN)*

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.