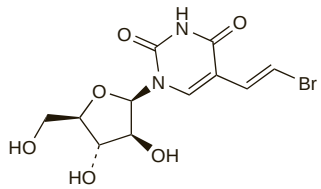
Sorivudine *(BAN, USAN, rINN)*

Bravavir; Bromovinylarauracil; Brovavir; BV-araU; BVAU; Sorivudina; Sorivudinum; SQ-32756; YN-72. (*E*)-1-β-D-Arabinofuranosyl-5-(2-bromovinyl)uracil.

Соривудин

$C_{11}H_{13}BrN_2O_6$ = 349.1.

CAS — 77181-69-2.



Profile

Sorivudine is a synthetic thymidine derivative with antiviral activity against varicella-zoster virus. It has been investigated for the treatment of herpes zoster but was withdrawn from the market in Japan after deaths in patients also given fluorouracil.

◊ References.

1. Yawata M. Deaths due to drug interaction. *Lancet* 1993; **342:** 1166.
2. Diasio RB. Sorivudine and 5-fluorouracil: a clinically significant drug-drug interaction due to inhibition of dihydropyrimidine dehydrogenase. *Br J Clin Pharmacol* 1998; **46:** 1–4.

Stavudine *(BAN, USAN, pINN)*

BMY-27857; d4T; Estavudina; Stavudiini; Stavudin; Stavudinas; Stavudinum. 1-(2,3-Dideoxy-β-D-*glycero*-pent-2-enofuranosyl)-thymine.

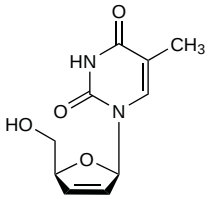
Ставудин

$C_{10}H_{12}N_2O_4$ = 224.2.

CAS — 3056-17-5.

ATC — J05AF04.

ATC Vet — QJ05AF04.



Pharmacopoeias. In *Eur.* (see p.vii) and *US.*

Ph. Eur. 6.2 (Stavudine). A white or almost white powder. It exhibits polymorphism. Soluble in water; sparingly soluble in alcohol; slightly soluble in dichloromethane. Protect from light and humidity.

USP 31 (Stavudine). A white to off-white, crystalline powder. Soluble in water, in dimethylacetamide, and in dimethyl sulfoxide; sparingly soluble in alcohol, in acetonitrile, and in methyl alcohol; slightly soluble in dichloromethane; insoluble in petroleum spirit. Store in airtight containers at a temperature of 25°, excursions permitted between 15° and 30°. Protect from light.

Adverse Effects

The most common adverse effect reported with stavudine either as monotherapy or with other antiretrovirals is peripheral neuropathy; it occurs more frequently in patients taking stavudine with didanosine and hydroxycarbamide. Other common adverse effects include abdominal pain, nausea, diarrhoea, dyspepsia, fatigue, dizziness, depression, headache, insomnia, sleep disturbances, pruritus, and rash. Abnormal liver function tests may occur and hepatitis, hepatic failure, and pancreatitis have been reported rarely; fatalities have occurred and were reported most often in patients taking stavudine with didanosine and hydroxycarbamide. Lactic acidosis, usually associated with severe hepatomegaly and steatosis, has been associated with treatment with NRTIs. There have been reports of motor weakness associated with stavudine, occurring particularly in association with lactic acidosis.

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 stavudine, 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 stavudine. 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 nervous system. Peripheral neuropathy is a well recognised adverse effect of stavudine and has been the subject of a review.[1]

1. Moyle GJ, Sadler M. Peripheral neuropathy with nucleoside antiretrovirals: risk factors, incidence and management. *Drug Safety* 1998; **19:** 481–94.

Gynaecomastia. Bilateral gynaecomastia was associated with stavudine use in a patient with HIV infection who was also receiving lamivudine and co-trimoxazole.[1] Symptoms resolved when stavudine was stopped. Four other cases of gynaecomastia were reported in HIV-infected patients given HAART regimens containing stavudine.[2]

1. Melbourne KM, *et al.* Gynecomastia with stavudine treatment in an HIV-positive patient. *Ann Pharmacother* 1998; **32:** 1108.
2. Manfredi R, *et al.* Gynecomastia associated with highly active antiretroviral therapy. *Ann Pharmacother* 2001; **35:** 438–9.

Precautions

Stavudine should be used with caution in patients with a history of peripheral neuropathy and treatment suspended if peripheral neuropathy develops; if symptoms resolve on withdrawal, stavudine may be resumed at half the previous dose. Treatment with stavudine may be associated with lactic acidosis and should be stopped if there is a rapid increase in aminotransferase concentrations, progressive hepatomegaly or steatosis, or metabolic or lactic acidosis of unknown aetiology. Stavudine should be given with caution to patients with hepatomegaly or other risk factors for liver disease. If liver enzymes increase to 5 times the upper limit of normal during treatment then stavudine should be stopped. Patients co-infected with chronic hepatitis B or C who are being treated with combination antiretroviral therapy are at an increased risk of severe and potentially fatal hepatic adverse events. Patients with a history of pancreatitis should also be observed carefully for signs of pancreatitis during stavudine treatment. Use with other drugs likely to cause peripheral neuropathy or pancreatitis should be avoided if possible. Stavudine should be used with caution and doses reduced in patients with renal impairment.

Interactions

The intracellular activation of stavudine and hence its antiviral effect may be inhibited by zidovudine, doxorubicin, and ribavirin.

Use of stavudine with other drugs known to cause pancreatitis or peripheral neuropathy should be avoided if possible. The combination of hydroxycarbamide and didanosine if given with stavudine, may carry a higher risk of adverse effects including hepatotoxicity, peripheral neuropathy, and pancreatitis (fatal and non-fatal).

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.

Antivirals. Reference to *in-vivo* antagonism of the antiretroviral effect of stavudine when used with *zidovudine*.[1]

1. Havlir DV, *et al.* In vivo antagonism with zidovudine plus stavudine combination therapy. *J Infect Dis* 2000; **182:** 321–5.

Phenylpropanolamine. Hypertensive crisis associated with use of phenylpropanolamine and clemastine occurred in a patient receiving HIV prophylaxis with indinavir, lamivudine, and stavudine.[1] The most likely cause was an interaction between phenylpropanolamine and stavudine, although interactions with the other antiretrovirals could not be ruled out.

1. Khurana V, *et al.* Hypertensive crisis secondary to phenylpropanolamine interacting with triple-drug therapy for HIV prophylaxis. *Am J Med* 1999; **106:** 118–19.

Antiviral Action

Stavudine is converted intracellularly in stages to the triphosphate. This triphosphate halts the DNA synthesis of retroviruses, including HIV, through competitive inhibition of reverse transcriptase and incorporation into viral DNA. Stavudine-resistant strains of HIV have been identified and cross-resistance to other nucleoside reverse transcriptase inhibitors may occur.

Pharmacokinetics

Stavudine is absorbed rapidly after oral doses producing peak plasma concentrations within 1 hour and with a reported bioavailability of about 86%. Giving it with food delays but does not reduce absorption. Stavudine crosses the blood-brain barrier producing a CSF to plasma ratio of about 0.4 after 4 hours. Binding to plasma proteins is negligible. Stavudine is metabolised intracellularly to the active antiviral triphosphate. The elimination half-life is reported to be about 1 to 1.5 hours after single or multiple doses. The intracellular half-life of stavudine triphosphate has been estimated to be 3.5 hours *in vitro*. About 40% of a dose is excreted in the urine by active tubular secretion and glomerular filtration. Stavudine is removed by haemodialysis.

◊ References.

1. Rana KZ, Dudley MN. Clinical pharmacokinetics of stavudine. *Clin Pharmacokinet* 1997; **33:** 276–84.
2. Kaul S, *et al.* Effect of food on bioavailability of stavudine in subjects with human immunodeficiency virus infection. *Antimicrob Agents Chemother* 1998; **42:** 2295–8.
3. Grasela DM, *et al.* Pharmacokinetics of single-dose oral stavudine in subjects with renal impairment and in subjects requiring hemodialysis. *Antimicrob Agents Chemother* 2000; **44:** 2149–53.

Uses and Administration

Stavudine is a nucleoside reverse transcriptase inhibitor related to thymidine with antiviral activity against HIV-1. It is used in the treatment of HIV infection and AIDS (p.856). Viral resistance emerges rapidly when stavudine is used alone, and it is therefore used with other antiretrovirals. Stavudine is given orally, usually as a capsule or solution. Usual adult doses of stavudine are 40 mg every 12 hours for patients weighing 60 kg or more or 30 mg every 12 hours for patients weighing less than 60 kg.

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

For details of reduced doses of stavudine to be used in patients with renal impairment, see below.

◊ Reviews.

1. Hurst M, Noble S. Stavudine: an update of its use in the treatment of HIV infection. *Drugs* 1999; **58:** 919–49.
2. Cheer SM, Goa KL. Stavudine once daily. *Drugs* 2002; **62:** 2667–74.

Administration in children. For the treatment of HIV infection in infants, children, and adolescents stavudine is given orally with other antiretroviral drugs. Doses are based on body-weight:

- in neonates from birth to 13 days old a dose of 500 micrograms/kg every 12 hours may be given
- in infants at least 14 days old and those weighing less than 30 kg the dose is 1 mg/kg every 12 hours
- in children and adolescents weighing 30 kg or more, the adult dose is given (see above)

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.

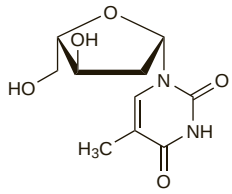
Тельбивудин

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

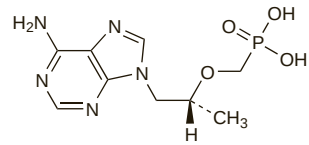
Tenofovir *(BAN, USAN, rINN)*

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.