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4. Hynes P, *et al.* Acute renal failure after initiation of tenofovir disoproxil fumarate. *Ren Fail* 2007; **29:** 1063–6.
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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.
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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.

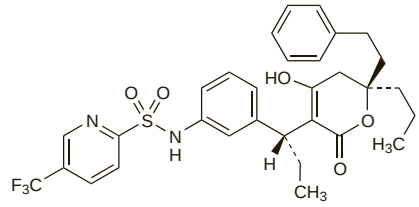
Типранавир

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