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.

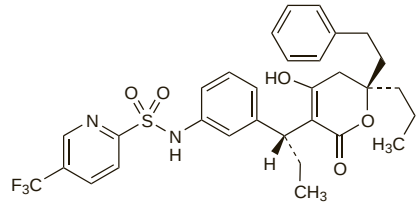
Типранавир

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

For further information on adverse effects associated with HIV-protease inhibitors see under Indinavir Sulfate, p.882.

Precautions

Tipranavir should not be used in patients with moderate to severe hepatic impairment (Child-Pugh class B or C), and should be used with caution in those with mild impairment (Child-Pugh A). Treatment should not be started in patients with pre-treatment liver enzyme values more than 5 times the upper limit of normal. Patients should be closely monitored for clinical signs and symptoms of hepatitis; monitoring of liver enzymes is recommended before and during treatment with tipranavir. In patients with mild hepatic impairment, chronic hepatitis, or other underlying liver disease more frequent monitoring is recommended. Treatment should be interrupted or stopped if liver function deteriorates and should be permanently stopped in those patients with liver enzyme values more than 10 times the upper limit of normal or in those who develop signs or symptoms of clinical hepatitis. Patients with pre-existing liver disease or co-infected with chronic hepatitis B or C and treated with combination antiretroviral therapy are at increased risk for severe and potentially fatal hepatic adverse events.

Caution is advised in treating patients who are at increased risk of bleeding such as those with haemophilia A and B or who are taking antiplatelet drugs or anticoagulants as reports of spontaneous bleeding have been associated with the use of HIV-protease inhibitors. Tipranavir oral solution contains vitamin E and patients given the oral solution should not take high doses of supplemental vitamin E.

Tipranavir contains a sulfonamide moiety and should be used with caution in patients with a known sulfonamide allergy.

Interactions

Tipranavir is both an inducer and an inhibitor of the cytochrome P450 isoenzyme CYP3A4 although when given with low-dose ritonavir there is a net inhibition of CYP3A4; there is therefore the potential for complex interactions with other drugs metabolised by this enzyme. Ritonavir-boosted tipranavir is also a net inducer of P-glycoprotein.

Tipranavir is contra-indicated with drugs that are highly dependent on CYP3A4 for clearance and for which elevated plasma concentrations are associated with serious or life-threatening events. These drugs include antiarrhythmics (amiodarone, bepridil, flecainide, metoprolol, propafenone, and quinidine), antihistamines (astemizole and terfenadine), ergot derivatives (dihydroergotamine, ergometrine, ergotamine, and methylergometrine), gastrointestinal prokinetics (cisapride), antipsychotics (pimozide), sedatives and hypnotics (midazolam and triazolam), and statins (simvastatin and lovastatin). Rifampicin and St John's wort decrease the concentration of tipranavir; use with the antiretroviral is not recommended due to the possible loss of its activity and development of resistance.

For further information on drug interactions of HIV-protease inhibitors see under Indinavir Sulfate, p.883 and Table 1, p.917.

Antiviral Action

Tipranavir is a non-peptide HIV-protease inhibitor. It interferes with the formation of essential viral proteins making them incapable of infecting other cells. HIV isolates resistant to tipranavir have been reported and viral resistance develops rapidly when HIV-protease inhibitors are given alone and therefore they are used with other antiretrovirals. Various degrees of cross-resistance between HIV-protease inhibitors may occur.

Pharmacokinetics

Tipranavir is absorbed to a limited extent after oral doses. Food improves the tolerability and bioavailability is increased with a high fat meal. Peak plasma concentrations are reached within 1 to 5 hours and steady state is usually reached after 7 to 10 days of treatment. Tipranavir is about 99.9% bound to plasma proteins. It is metabolised by the cytochrome P450 system (predominantly the isoenzyme CYP3A4), although when given with ritonavir metabolism is minimal with the majority of tipranavir being excreted unchanged in the faeces. The mean elimination half-life of tipranavir is 4.8 to 6 hours.

Uses and Administration

Tipranavir is a non-peptide HIV-protease inhibitor with antiviral activity against HIV. It is used for the treatment of HIV infection and AIDS (p.856) in treatment-experienced patients or in those with multidrug-resistant HIV infection. Viral resistance emerges rapidly when tipranavir is used alone, and it is therefore used with other antiretrovirals.

It is given with low-dose ritonavir, which acts as a pharmacokinetic enhancer (ritonavir-boosted tipranavir). The dose is tipranavir 500 mg (with ritonavir 200 mg) twice daily with food.

For details of doses in children see below.

No dose adjustment is required for patients with renal impairment or mild liver disease. Tipranavir should not be given to patients with moderate to severe liver disease.

◊ Reviews.

1. Croom KF, Keam SJ. Tipranavir: a ritonavir-boosted protease inhibitor. *Drugs* 2005; **65:** 1669–77.
2. Dong BJ, Cocohoba JM. Tipranavir: a protease inhibitor for HIV salvage therapy. *Ann Pharmacother* 2006; **40:** 1311–21.
3. King JR, Acosta EP. Tipranavir: a novel nonpeptidic protease inhibitor of HIV. *Clin Pharmacokinet* 2006; **45:** 665–82.
4. Temesgen Z, Feinberg J. Tipranavir: a new option for the treatment of drug-resistant HIV infection. *Clin Infect Dis* 2007; **45:** 761–9.
5. Orman JS, Perry CM. Tipranavir: a review of its use in the management of HIV infection. *Drugs* 2008; **68:** 1435–63.

Administration in children. For the treatment of HIV infection in children, tipranavir is given orally with other antiretroviral drugs. It is given with low-dose ritonavir, which acts as a pharmacokinetic enhancer. US licensed product information permits the use of oral tipranavir in children from 2 years of age. Doses are based on body-weight or body-surface and should not exceed the maximum adult dose (see above).

- The usual recommended dose in children is: tipranavir 14 mg/kg (with ritonavir 6 mg/kg) twice daily *or* tipranavir 375 mg/m^2 (with ritonavir 150 mg/m^2) twice daily
- children who are intolerant or develop toxicities to the usual dose may take a reduced dose: tipranavir 12 mg/kg (with ritonavir 5 mg/kg) twice daily *or* tipranavir 290 mg/m^2 (with ritonavir 115 mg/m^2) twice daily

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Aptivus; ***Belg.:*** Aptivus; ***Cz.:*** Aptivus; ***Fin.:*** Aptivus; ***Fr.:*** Aptivus; ***Gr.:*** Aptivus; ***Hung.:*** Aptivus; ***Irl.:*** Aptivus; ***Ital.:*** Aptivus; ***Mex.:*** Aptivus; ***Pol.:*** Aptivus; ***Port.:*** Aptivus; ***Swed.:*** Aptivus; ***UK:*** Aptivus; ***USA:*** Aptivus.

Trichosanthin

Compound Q; GLQ-223 (a purified form of trichosanthin); Tricosantina.

CAS — 60318-52-7 (trichosanthins); 116899-30-0 (Trichosanthes kirilowii); 160185-58-0 (Trichosanthes kirilowii root); 120947-28-6 (GLQ-223).

Profile

Trichosanthin is a polypeptide extracted from the tuber of the Chinese cucumber, *Trichosanthes kirilowii* (Cucurbitaceae). It has been investigated in the treatment of HIV infection and is used in China as an abortifacient.

HIV infection and AIDS. Trichosanthin has been given to patients with AIDS, AIDS-related complex, or HIV infection.[1,2] It has generally been given by intravenous injection, the use of the intramuscular route having been abandoned due to the occurrence of pain and necrosis at the injection site.[1] A common adverse effect with intravenous use was a flu-like syndrome with headache, myalgias, fever, and arthralgia and was generally mild to moderate,[3] although neurological effects progressing to coma with fatalities have been reported.[1,2] Improvements in surrogate markers for HIV infection have been reported including increases in CD4+ T lymphocyte counts in patients with moderate disease[3] and in patients failing to respond to reverse transcriptase inhibitors.[4]

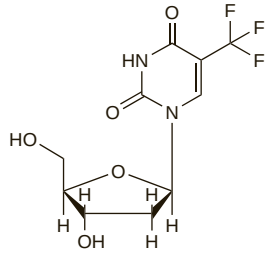
1. Byers VS, *et al.* A phase I/II study of trichosanthin treatment of HIV disease. *AIDS* 1990; **4:** 1189–96.
2. Kahn JO, *et al.* The safety and pharmacokinetics of GLQ223 in subjects with AIDS and AIDS-related complex: a phase I study. *AIDS* 1990; **4:** 1197–1204.
3. Kahn JO, *et al.* Safety, activity, and pharmacokinetics of GLQ223 in patients with AIDS and AIDS-related complex. *Antimicrob Agents Chemother* 1994; **38:** 260–7.
4. Byers VS, *et al.* A phase II study of effect of addition of trichosanthin to zidovudine in patients with HIV disease and failing antiretroviral agents. *AIDS Res Hum Retroviruses* 1994; **10:** 413–20.

Trifluridine *(USAN, rINN)*

F_3T; F_3TDR; NSC-75520; Trifluorothymidine; Trifluorothymidinum; Trifluorotymidiini; Trifluorotymidin; Trifluridiini; Trifluridin; Trifluridina; Trifluridinum. ααα-Trifluorothymidine; 2′-Deoxy-5-trifluoromethyluridine.

Трифлуридин

$C_{10}H_{11}F_3N_2O_5$ = 296.2.
CAS — 70-00-8.
ATC — S01AD02.
ATC Vet — QS01AD02.



Pharmacopoeias. In *US.*
USP 31 (Trifluridine). A white, odourless powder, appearing under the microscope as rod-like crystals. Store in airtight containers. Protect from light.

Adverse Effects

Adverse effects occurring after the use of trifluridine in the eyes are similar to those for idoxuridine (p.881) but have been reported to occur less frequently.

◊ References.

1. Udell IJ. Trifluridine-associated conjunctival cicatrization. *Am J Ophthalmol* 1985; **99:** 363–4.

Antiviral Action

Trifluridine acts similarly to idoxuridine to interfere with viral DNA synthesis after phosphorylation. It is reported to be active against herpes simplex viruses, some adenoviruses, vaccinia viruses, and CMV. Like idoxuridine it is incorporated into mammalian DNA.

Pharmacokinetics

Trifluridine is absorbed through the cornea after application to the eye and penetration may be increased in the presence of damage or inflammation. Systemic absorption does not appear to follow ocular administration.

Uses and Administration

Trifluridine is a pyrimidine nucleoside structurally related to thymidine. It is used in the treatment of primary keratoconjunctivitis and recurrent epithelial keratitis due to herpes simplex viruses (p.854). One drop of a 1% ophthalmic solution is instilled into the eye every 2 hours up to a maximum of 9 times daily until complete re-epithelialisation has occurred. Treatment is then reduced to one drop every 4 hours to a minimum of 5 drops daily for a further 7 days. Treatment should not be continued for more than a total of 21 days.

Trifluridine, alone or as a combined formulation with a thymidine phosphorylase inhibitor to reduce its metabolism (TAS-102), has been investigated in the treatment of malignant neoplasms.

◊ Reviews.

1. Heidelberger C, King DH. Trifluorothymidine. *Pharmacol Ther* 1979; **6:** 427–42.
2. Carmine AA, *et al.* Trifluridine: a review of its antiviral activity and therapeutic use in the topical treatment of viral eye infections. *Drugs* 1982; **23:** 329–53.
3. Temmink OH, *et al.* Therapeutic potential of the dual-targeted TAS-102 formulation in the treatment of gastrointestinal malignancies. *Cancer Sci* 2007; **98:** 779–89.

Preparations

Proprietary Preparations (details are given in Part 3)
Canad.: Viroptic; ***Cz.:*** Triherpine†; ***Fr.:*** Virophta; ***Ger.:*** Triflumann; ***Gr.:*** Thilol; ***Hong Kong:*** Triherpine†; ***Hung.:*** Triherpine†; ***Ital.:*** Triherpine; ***Neth.:*** TFT Ophtiole; ***Port.:*** Adrocil†; Viridin; ***S.Afr.:*** TFT; ***Spain:*** Viromidin; ***Switz.:*** Triherpine†; ***Thai.:*** Triherpine; ***Turk.:*** TFT-Thilo; ***USA:*** Viroptic.