200 mg daily in divided doses. In elderly patients the usual daily dose is 100 mg. A dosage reduction is also necessary in patients with severe renal or severe hepatic impairment (see below).

For details of doses in children, see below.

◊ Reviews.

1. Jefferson T, *et al.* Amantadine and rimantadine for influenza A in adults. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2006 (accessed 13/06/08).

Administration in children. For the prophylaxis of influenza A in children from 1 year of age, an oral dose of 5 mg/kg daily, up to a maximum daily dose of 150 mg, may be given. Although not licensed for the treatment of influenza A some experts consider that it may be given to children from 1 year of age.

Administration in hepatic or renal impairment. The usual oral dose of rimantadine in patients with severe renal or severe hepatic impairment and in elderly nursing home patients is 100 mg daily.

Preparations

USP 31: Rimantadine Hydrochloride Tablets.

Proprietary Preparations (details are given in Part 3)
Arg.: Germic†; Oclovir†; ***Cz.:*** Maridin; ***Mex.:*** Gabirol; ***Rus.:*** Algirem (Альгирем); ***USA:*** Flumadine.

Ritonavir *(BAN, USAN, rINN)*

A-84538; Abbott-84538; ABT-538; Ritonaviiri; Ritonavirum. 5-Thiazolylmethyl {(αS)-α-[(1S,3S)-1-hydroxy-3-((2S)-2-{3-[(2-isopropyl-4-thiazolyl)methyl]-3-methylureido}-3-methylbutyramido)-4-phenylbutyl]phenethyl}carbamate; N^1-[(1S,3S,4S)-1-Benzyl-3-hydroxy-5-phenyl-4-(1,3-thiazol-5-ylmethoxycarbonylamino)pentyl]-N^2-{[(2-isopropyl-1,3-thiazol-4-yl)methyl](methyl)carbamoyl}-L-valinamide.

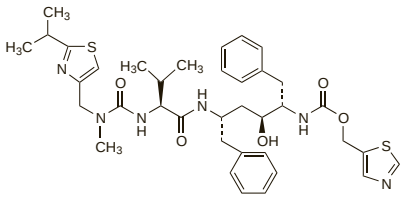
Ритонавир

$C_{37}H_{48}N_6O_5S_2$ = 720.9.

CAS — 155213-67-5.

ATC — J05AE03.

ATC Vet — QJ05AE03.



Pharmacopoeias. In *Eur.* (see p.vii), *Int.*, and *US.*
Ph. Eur. 6.2 (Ritonavir). A white or almost white powder. Practically insoluble in water; freely soluble in methyl alcohol and in dichloromethane; very slightly soluble in acetonitrile. It exhibits polymorphism. Protect from light.
USP 31 (Ritonavir). Practically insoluble in water; very soluble in acetonitrile; freely soluble in dichloromethane and in methyl alcohol. Store in airtight containers at a temperature between 5° and 30°. Protect from light.

Adverse Effects

The most common adverse effects associated with antiretroviral regimens containing ritonavir are asthenia, gastrointestinal effects (abdominal pain, anorexia, diarrhoea, nausea, and vomiting), headache, taste disorder, and numbness around the mouth. One of the more serious adverse effects of ritonavir is potentially fatal pancreatitis. Other commonly reported adverse effects include anxiety, dizziness, insomnia, fever, other gastrointestinal effects (dry mouth, dyspepsia, flatulence, local throat irritation), hyperaesthesia, mouth ulcer, malaise, pharyngitis, pruritus, rash, sweating, vasodilatation, and weight loss. Allergic reactions include urticaria, mild skin eruptions, bronchospasm, angioedema, and rarely anaphylaxis. A possible association with Stevens-Johnson syndrome has been reported with ritonavir. Reported abnormal laboratory results are decreased haemoglobin levels, increased eosinophil counts, raised liver enzymes and uric acid concentrations, and decreased free and total thyroxine concentrations; white blood cell and neutrophil counts may be reduced or increased.

Adverse effects associated with the use of ritonavir as a pharmacokinetic booster are dependent on the other HIV-protease inhibitor.

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 ritonavir, 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 ritonavir. 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

Ritonavir (as an antiviral agent or as a pharmacokinetic enhancer) should not be used in patients with decompensated liver disease. Caution is advised in patients with severe hepatic impairment (Child-Pugh Grade C) without decompensation, when ritonavir is used as a pharmacokinetic booster with another HIV-protease inhibitor, although specific recommendations depend on the other drug. 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 with haemophilia A and B as reports of spontaneous bleeding have been associated with the use of HIV-protease inhibitors. Patients should be monitored for signs and symptoms of pancreatitis (abdominal pain, nausea, vomiting, and increased serum lipase or amylase levels) and ritonavir treatment should be stopped in patients developing pancreatitis.

Interactions

Ritonavir is reported to have a high affinity for several cytochrome P450 isoenzymes with the following ranked order:

CYP3A > CYP2D6 > CYP2C9

Consequently ritonavir may compete with other drugs metabolised by this system, potentially resulting in mutually increased plasma concentrations and toxicity. Ritonavir also has a high affinity for P-glycoprotein and may inhibit this transporter; it may also induce glucuronidation and oxidation by CYP1A2 and CYP2C19.

Oral liquid formulations of ritonavir currently contain alcohol and use with disulfiram or metronidazole should be avoided.

Ritonavir 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 the alpha-adrenergic antagonist alfuzosin, antiarrhythmics (amiodarone, bepridil, encainide, flecainide, propafenone, and quinidine), antifungals (voriconazole), antihistamines (astemizole and terfenadine), ergot derivatives (dihydroergotamine, ergometrine, ergotamine, and methylergometrine), gastrointestinal prokinetics (cisapride), antipsychotics (clozapine and pimozide), sedatives and hypnotics (midazolam and triazolam), and statins (lovastatin and simvastatin). St John's wort decreases the concentration of ritonavir; use with the antiretroviral is not recommended due to the possible loss of its activity and development of resistance. UK licensed product information also contra-indicates the use of ritonavir with the analgesics pethidine, piroxicam, and dextropropoxyphene, bupropion, fusidic acid, rifabutin, and some other sedatives and hypnotics (clorazepate, diazepam, estazolam, and flurazepam).

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

Antiviral Action

Ritonavir is a selective, competitive, reversible inhibitor of HIV protease. It is active against HIV-1 and, to a lesser extent, HIV-2. It interferes with the formation of essential viral proteins making them incapable of infecting other cells. Ritonavir is also a potent inhibitor of the cytochrome P450 subfamily CYP3A (chiefly the isoenzyme CYP3A4), and low-dose ritonavir is used with other HIV-protease inhibitors to decrease their metabolism and thus increase plasma concentrations of the other protease inhibitor; such use is referred to as ritonavir pharmacokinetic enhancement or ritonavir-boosted therapy. 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; in general the greater the number of mutations, the higher the level of resistance. Cross-resistance between HIV-protease inhibitors and NRTIs or NNRTIs is considered unlikely.

Pharmacokinetics

Ritonavir is absorbed after oral doses and peak plasma concentrations occur in about 2 to 4 hours. Absorption is enhanced when ritonavir is taken with food, and is dose-related. Protein binding is reported to be about 98% and penetration into the CNS is minimal. Ritonavir is extensively metabolised in the liver mainly by cytochrome P450 isoenzymes CYP3A4 and to a lesser extent by CYP2D6. Five metabolites have been identified and the major metabolite has antiviral activity, but concentrations in plasma are low. Studies in HIV-infected children 2 to 14 years of age indicate that ritonavir clearance is 1.5 to 1.7 times greater than in adults. About 86% of a dose is eliminated through the faeces (both as unchanged drug and as metabolites) and about 11% is excreted in the urine (3.5% as unchanged drug). The elimination half-life is 3 to 5 hours.

◊ References.

1. Hsu A, *et al.* Multiple-dose pharmacokinetics of ritonavir in human immunodeficiency virus-infected subjects. *Antimicrob Agents Chemother* 1997; **41:** 898–905.
2. Hsu A, *et al.* Ritonavir: clinical pharmacokinetics and interactions with other anti-HIV agents. *Clin Pharmacokinet* 1998; **35:** 275–91.

Uses and Administration

Ritonavir is an HIV-protease inhibitor with antiviral activity against HIV. It is used in the treatment of HIV infection and AIDS (p.856). Viral resistance emerges rapidly when ritonavir is used alone, and it is therefore given with other antiretrovirals.

Ritonavir is given orally in an adult dose of 600 mg twice daily with food. In order to minimise nausea, ritonavir may be started at a dose of 300 mg twice daily and gradually increased over a period of up to 14 days by 100 mg twice daily to a total of 600 mg twice daily.

For details of doses in children, see below.

When used as a pharmacokinetic enhancer ritonavir is given in doses of 100 to 200 mg once or twice daily with other HIV-protease inhibitors.

◊ Reviews.

1. Lea AP, Faulds D. Ritonavir. *Drugs* 1996; **52:** 541–6.
2. Cooper CL, *et al.* A review of low-dose ritonavir in protease inhibitor combination therapy. *Clin Infect Dis* 2003; **36:** 1585–92.

Administration. Adjusting the dosage of ritonavir from 600 mg twice daily to 300 mg every 6 hours improved tolerability in 2 patients who would otherwise have stopped the drug.[1]

1. Merry C, *et al.* Improved tolerability of ritonavir derived from pharmacokinetic principles. *Br J Clin Pharmacol* 1996; **42:** 787.

Administration in children. For the treatment of HIV infection in children, ritonavir is given daily with other antiretroviral drugs. US licensed product information permits the use of oral ritonavir in infants over 1 month of age, whereas in the UK it is recommended from 2 years of age. The dose given should not exceed the maximum adult dose of 600 mg twice daily.

The recommended dose regimen is an initial dose of 250 mg/m^2 twice daily increasing by 50 mg/m^2 twice daily at 2- or 3-day intervals up to 350 to 400 mg/m^2 twice daily.

Molluscum contagiosum. Intractable molluscum contagiosum, a viral skin infection, resolved when a patient was given ritonavir for treatment of HIV infection.[1]

1. Hicks CB, *et al.* Resolution of intractable molluscum contagiosum in a human immunodeficiency virus-infected patient after institution of antiretroviral therapy with ritonavir. *Clin Infect Dis* 1997; **24:** 1023–5.

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Rifaxi; ***Austral.:*** Norvir; ***Belg.:*** Norvir; ***Braz.:*** Ritovir†; ***Canad.:*** Norvir; ***Chile:*** Norvir; ***Cz.:*** Norvir; ***Denm.:*** Norvir; ***Fin.:*** Norvir; ***Fr.:*** Norvir; ***Ger.:*** Norvir; ***Gr.:*** Norvir; ***Hong Kong:*** Norvir; ***Hung.:*** Norvir; ***India:*** Ritomune; ***Indon.:*** Norvir; ***Irl.:*** Norvir; ***Israel:*** Norvir; ***Ital.:*** Norvir; ***Jpn:*** Norvir; ***Malaysia:*** Norvir; ***Mex.:*** Norvir; ***Neth.:*** Norvir; ***Norw.:*** Norvir; ***NZ:*** Norvir; ***Pol.:*** Norvir; ***Port.:*** Norvir; ***Rus.:*** Norvir (Норвир)†; ***S.Afr.:*** Norvir; ***Spain:*** Norvir; ***Swed.:*** Norvir; ***Switz.:*** Norvir; ***Thai.:*** Norvir; ***Turk.:*** Norvir; ***UK:*** Norvir; ***USA:*** Norvir; ***Venez.:*** Norvir.

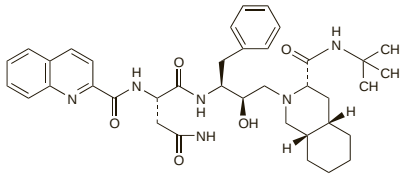
Multi-ingredient: ***Arg.:*** Kaletra; ***Austral.:*** Kaletra; ***Austria:*** Kaletra; ***Belg.:*** Kaletra; ***Braz.:*** Kaletra; ***Canad.:*** Kaletra; ***Chile:*** Kaletra; ***Cz.:*** Kaletra; ***Denm.:*** Kaletra; ***Fin.:*** Kaletra; ***Fr.:*** Kaletra; ***Ger.:*** Kaletra; ***Gr.:*** Kaletra; ***Hong Kong:*** Kaletra; ***Hung.:*** Kaletra; ***India:*** Ritomax-L; ***Israel:*** Kaletra; ***Ital.:*** Kaletra; ***Malaysia:*** Kaletra; ***Mex.:*** Kaletra; ***Neth.:*** Kaletra; ***Norw.:*** Kaletra; ***NZ:*** Kaletra; ***Pol.:*** Kaletra; ***Port.:*** Kaletra; ***Rus.:*** Kaletra (Калетра); ***S.Afr.:*** Kaletra; ***Singapore:*** Kaletra; ***Spain:*** Kaletra; ***Swed.:*** Kaletra; ***Switz.:*** Kaletra; ***Thai.:*** Kaletra; ***Turk.:*** Kaletra; ***UK:*** Kaletra; ***USA:*** Kaletra; ***Venez.:*** Kaletra.

Saquinavir *(BAN, USAN, rINN)*

Ro-31-8959; Sakinavir; Saquinavirum. N^1-{(1*S*,2*R*)-1-Benzyl-3-[(3*S*,4a*S*,8a*S*)-3-(*tert*-butylcarbamoyl)perhydroisoquinolin-2-yl]-2-hydroxypropyl}-N^2-(2-quinolylcarbonyl)-L-aspartamide; (*S*)-*N*-[(α*S*)-α-{(1*R*)-2-[(3*S*,4a*S*,8a*S*)-3-(*tert*-Butylcarbamoyl)octahydro-2(1*H*)-isoquinolyl]-1-hydroxyethyl}phenethyl]-2-quinaldamidosuccinamide.

Саквинавир

$C_{38}H_{50}N_6O_5$ = 670.8.
CAS — 127779-20-8.
ATC — J05AE01.
ATC Vet — QJ05AE01.



Pharmacopoeias. In *Int.*

Saquinavir Mesilate *(BANM, rINNM)*

Mesilato de saquinavir; Ro-31-8959/003; Sakinaviirimesilaatti; Sakinavirmesilat; Saquinavir, mésilate de; Saquinavir Mesylate *(USAN)*; Saquinaviri mesilas. Saquinavir methanesulfonate.

Саквинавира Мезилат

$C_{38}H_{50}N_6O_5,CH_4O_3S$ = 766.9.
CAS — 149845-06-7.
ATC — J05AE01.
ATC Vet — QJ05AE01.

Pharmacopoeias. In *Int.* and *US.*
USP 31 (Saquinavir Mesylate). Store in airtight containers.

Adverse Effects

The most common adverse effects associated with antiretroviral regimens containing saquinavir are gastrointestinal disorders (abdominal pain, diarrhoea, flatulence, nausea, vomiting) and fatigue. Other commonly reported adverse effects include alopecia, anaemia, anorexia, increased appetite, asthenia, constipation, dizziness, dry lips, mouth and skin, dyspepsia, dyspnoea, eczema, headache, hypersensitivity, decreased libido, malaise, muscle spasm, paraesthesia, peripheral neuropathy, pruritus, rash, sleep disturbances, and taste disorders. Commonly reported laboratory abnormalities include raised liver enzyme values, increased blood amylase, bilirubin, and creatinine, and lowered haemoglobin and platelet, lymphocyte, and white blood cell count. Rare but serious adverse effects that may be associated with saquinavir include acute myeloid leukaemia, haemolytic anaemia, allergic reactions, ascites, bullous skin eruptions, intestinal obstruction, jaundice, nephrolithiasis, pancreatitis, polyarthritis, portal hypertension, seizures, Stevens-Johnson syndrome, attempted suicide, and thrombocytopenia (occasionally fatal).

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 saquinavir, 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 saquinavir. 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

Ritonavir-boosted saquinavir should not be used in patients with decompensated liver disease and should be used with caution in patients with moderate hepatic or severe renal impairment. 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 with haemophilia A and B as reports of spontaneous bleeding have been associated with the use of HIV-protease inhibitors.

Interactions

Saquinavir is reported to be metabolised by the cytochrome P450 system, with the specific isoenzyme CYP3A4 responsible for more than 90% of the hepatic metabolism. Saquinavir is also a substrate and an inhibitor of P-glycoprotein. Drugs that affect this isoenzyme and/or P-glycoprotein may modify saquinavir plasma concentrations. Saquinavir may alter the pharmacokinetics of other drugs that are metabolised by this enzyme system or that are substrates for P-glycoprotein.

Saquinavir 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, propafenone, and quinidine), antihistamines (astemizole and terfenadine), antimycobacterial (rifampicin), ergot derivatives (dihydroergotamine, ergometrine, ergotamine, methylergometrine), gastrointestinal prokinetics (cisapride), antipsychotics (pimozide), sedatives and hypnotics (midazolam and triazolam), and statins (simvastatin and lovastatin). St John's wort decreases the concentration of saquinavir; 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

Saquinavir is a selective, competitive, reversible inhibitor of HIV-1 and HIV-2 protease. It interferes with the formation of essential viral proteins making them incapable of infecting other cells. Viral resistance develops rapidly when HIV-protease inhibitors are given alone and therefore they are used with other antiretrovirals. HIV isolates resistant to saquinavir have been reported and variable cross-resistance with other HIV-protease inhibitors has been seen. Cross-resistance between saquinavir and NRTIs or NNRTIs is unlikely because these drugs have different target enzymes.

Pharmacokinetics

Saquinavir is absorbed to a limited extent (about 30%) after oral doses of the mesilate and undergoes extensive first-pass hepatic metabolism, resulting in a bioavailability of 4% when taken with food. Bioavailability was found to be greater from a soft gelatin capsule formulation of saquinavir base in a suitable vehicle (*Fortovase, Roche*) than from a hard capsule formulation (*Invirase, Roche*). Bioavailability is substantially less when saquinavir is taken in the fasting state. Plasma concentrations are reported to be higher in HIV-infected patients than in healthy subjects. Saquinavir is about 98% bound to plasma proteins and extensively distributed into the tissues, although CSF concentrations are reported to be negligible. It is rapidly metabolised by the cytochrome P450 system (specifically the isoenzyme CYP3A4) to a number of inactive monohydroxylated and dihydroxylated compounds. It is excreted mainly in the faeces with a reported terminal elimination half-life of 13.2 hours.

◊ References.

1. Regazzi MB, *et al.* Pharmacokinetic variability and strategy for therapeutic drug monitoring of saquinavir (SQV) in HIV-1 infected individuals. *Br J Clin Pharmacol* 1999; **47:** 379–82.
2. Grub S, *et al.* Pharmacokinetics and pharmacodynamics of saquinavir in pediatric patients with human immunodeficiency virus infection. *Clin Pharmacol Ther* 2002; **71:** 122–30.
3. Acosta EP, *et al.* Pharmacokinetics of saquinavir plus low-dose ritonavir in human immunodeficiency virus-infected pregnant women. *Antimicrob Agents Chemother* 2004; **48:** 430–6.

Uses and Administration

Saquinavir is an HIV-protease inhibitor with antiviral activity against HIV. It is used in the treatment of HIV infection and AIDS (p.856). Viral resistance emerges rapidly when saquinavir is used alone, and it is therefore used with other antiretrovirals, including low-dose ritonavir which is given as a pharmacokinetic enhancer (ritonavir-boosted saquinavir).

Saquinavir is given orally as the mesilate but doses are expressed in terms of the base; 229 mg of saquinavir mesilate is equivalent to about 200 mg of saquinavir. The dose is 1 g twice daily given with ritonavir 100 mg twice daily with or after food.

◊ Reviews.

1. Vella S, Floridia M. Saquinavir: clinical pharmacology and efficacy. *Clin Pharmacokinet* 1998; **34:** 189–201.
2. Figgitt DP, Plosker GL. Saquinavir soft-gel capsule: an updated review of its use in the management of HIV infection. *Drugs* 2000; **60:** 481–516.
3. Plosker GL, Scott LJ. Saquinavir: a review of its use in boosted regimens for treating HIV infection. *Drugs* 2003; **63:** 1299–1324.

Preparations

USP 31: Saquinavir Capsules.

Proprietary Preparations (details are given in Part 3)
Arg.: Fortovase; Proteovir; ***Austral.:*** Fortovase; Invirase; ***Austria:*** Fortovase; Invirase; ***Belg.:*** Fortovase†; Invirase; ***Braz.:*** Fortovase; Invirase; Svir†; ***Canad.:*** Fortovase; Invirase; ***Chile:*** Fortovase†; Invirase; ***Cz.:*** Fortovase†; Invirase; ***Denm.:*** Fortovase; Invirase; ***Fin.:*** Fortovase†; Invirase; ***Fr.:*** Fortovase; Invirase; ***Ger.:*** Fortovase†; Invirase; ***Gr.:*** Fortovase; Invirase; ***Hong Kong:*** Fortovase†; Invirase; ***Hung.:*** Invirase; ***Irl.:*** Fortovase†; Invirase; ***Israel:*** Fortovase; Invirase; ***Ital.:*** Fortovase; Invirase; ***Jpn:*** Fortovase; Invirase; ***Mex.:*** Fortovase; Invirase; ***Neth.:*** Fortovase; Invirase; ***Norw.:*** Fortovase; Invirase; ***NZ:*** Fortovase; Invirase; ***Philipp.:*** Invirase; ***Pol.:*** Invirase; ***Port.:*** Fortovase†; Invirase; ***S.Afr.:*** Fortovase†; Invirase; ***Spain:*** Fortovase; Invirase; ***Swed.:*** Fortovase†; Invirase; ***Switz.:*** Fortovase†; Invirase; ***Thai.:*** Fortovase; ***UK:*** Fortovase†; Invirase; ***USA:*** Fortovase†; Invirase; ***Venez.:*** Fortovase.