5% cream three times each week for up to 16 weeks and is left on the skin for 6 to 10 hours. For the management of superficial **basal cell carcinoma**, a 5% cream is applied 5 times each week for 6 weeks and left on the skin for about 8 hours. For the treatment of **actinic keratoses** on the face or scalp, a 5% cream is also used and is again left on the skin for 8 hours. In the UK, this is applied 3 times each week for 4 weeks, repeated after a 4-week break for a further 4 weeks if necessary; in the USA, application twice a week for 16 weeks is recommended.

Imiquimod is also under investigation for the treatment of other squamous cell carcinomas.

◊ Reviews.


1. Tyring S, *et al.* Imiquimod; an international update on therapeutic uses in dermatology. *Int J Dermatol* 2002; **41:** 810–16.
2. Garland SM. Imiquimod. *Curr Opin Infect Dis* 2003; **16:** 85–9.
3. Wagstaff AJ, Perry CM. Topical imiquimod: a review of its use in the management of anogenital warts, actinic keratoses, basal cell carcinoma and other skin lesions. *Drugs* 2007; **67:** 2187–2210.
4. Schön MP, Schön M. Imiquimod: mode of action. *Br J Dermatol* 2007; **157** (suppl 2): 8–13.


**Leishmaniasis.** Evidence from small studies[1,2] suggests that topical imiquimod 5 or 7.5% cream, in combination with parenteral meglumine antimoniate (p.828) may be of use in the management of cutaneous leishmaniasis (p.824).


1. Miranda-Verástegui C, *et al.* Randomized, double-blind clinical trial of topical imiquimod 5% with parenteral meglumine antimoniate in the treatment of cutaneous leishmaniasis in Peru. *Clin Infect Dis* 2005; **40:** 1395–1403.
2. Arevalo I, *et al.* Role of imiquimod and parenteral meglumine antimoniate in the initial treatment of cutaneous leishmaniasis. *Clin Infect Dis* 2007; **44:** 1549–54.


**Malignant neoplasms of the skin.** Imiquimod is indicated in the treatment of actinic keratosis[1-4] and basal cell carcinoma (p.673).[5-8] It is under investigation for the treatment of Bowen's disease.[9] It has also been tried in lentigo maligna[10] and other forms of localised or *in-situ* melanoma,[11,12] and there are also reports of investigational use in the management of metastatic melanoma.[13,14] and in anal and vulvar intraepithelial neoplasia.[15,16]


1. Lebwohl M, *et al.* Imiquimod 5% cream for the treatment of actinic keratosis: results from two phase III, randomized, double-blind, parallel group, vehicle-controlled trials. *J Am Acad Dermatol* 2004; **50:** 714–21.
2. Korman N, *et al.* Dosing with 5% imiquimod cream 3 times per week for the treatment of actinic keratosis: results of two phase 3, randomized, double-blind, parallel-group, vehicle-controlled trials. *Arch Dermatol* 2005; **141:** 467–73.
3. Krawtchenko N, *et al.* A randomised study of topical 5% imiquimod vs topical 5-fluorouracil vs cryosurgery in immunocompetent patients with actinic keratoses: a comparison of clinical and histological outcomes including 1-year follow-up. *Br J Dermatol* 2007; **157** (suppl 2): 34–40.
4. Alomar A, *et al.* Vehicle-controlled, randomized, double-blind study to assess safety and efficacy of imiquimod 5% cream applied once daily 3 days per week in one or two courses of treatment of actinic keratoses on the head. *Br J Dermatol* 2007; **157:** 133–41.
5. Chen TM, *et al.* Treatment of a large superficial basal cell carcinoma with 5% imiquimod: a case report and review of the literature. *Dermatol Surg* 2002; **28:** 344–6.
6. Drehs MM, *et al.* Successful treatment of multiple superficial basal cell carcinomas with topical imiquimod: case report and review of the literature. *Dermatol Surg* 2002; **28:** 427–9.
7. Schulze HJ, *et al.* Imiquimod 5% cream for the treatment of superficial basal cell carcinoma: results from a randomized vehicle-controlled phase III study in Europe. *Br J Dermatol* 2005; **152:** 939–47.
8. Bath-Hextall FJ, *et al.* Interventions for basal cell carcinoma of the skin. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2007 (accessed 13/06/08).
9. Mackenzie-Wood A, *et al.* Imiquimod 5% cream in the treatment of Bowen's disease. *J Am Acad Dermatol* 2001; **44:** 462–70.
10. Rajpar SF, Marsden JR. Imiquimod in the treatment of lentigo maligna. *Br J Dermatol* 2006; **155:** 653–6.
11. Lonsdale-Eccles AA, *et al.* Successful treatment of vulval melanoma in situ with topical 5% imiquimod cream. *Br J Dermatol* 2006; **155:** 215–17.
12. Spieth K, *et al.* Topical imiquimod: effectiveness in intraepithelial melanoma of oral mucosa. *Lancet Oncol* 2006; **7:** 1036–7.
13. Zeitouni NC, *et al.* Treatment of cutaneous metastatic melanoma with imiquimod 5% cream and the pulsed-dye laser. *Br J Dermatol* 2005; **152:** 376–7.
14. Utikal J, *et al.* Complete remission of multiple satellite and intransit melanoma metastases after sequential treatment with isolated limb perfusion and topical imiquimod. *Br J Dermatol* 2006; **155:** 488–91.
15. Wieland U, *et al.* Imiquimod treatment of anal intraepithelial neoplasia in HIV-positive men. *Arch Dermatol* 2006; **142:** 1438–44.
16. van Seters M, *et al.* Treatment of vulvar intraepithelial neoplasia with topical imiquimod. *N Engl J Med* 2008; **358:** 1465–73.


### Preparations

**Proprietary Preparations** (details are given in Part 3)

***Arg.:*** Aldara; Imimore; Miquimod; ***Austral.:*** Aldara; ***Belg.:*** Aldara; ***Braz.:*** Aldara; ***Canad.:*** Aldara; ***Chile:*** Aldara; Imimor; Labimiq; Tocasol; ***Cz.:*** Aldara; ***Denm.:*** Aldara; ***Fin.:*** Aldara; ***Fr.:*** Aldara; ***Ger.:*** Aldara; ***Gr.:*** Aldara; ***Hong Kong:*** Aldara; ***Hung.:*** Aldara; ***Irl.:*** Aldara; ***Israel:*** Aldara; ***Ital.:*** Aldara; ***Malaysia:*** Aldara; ***Mex.:*** Aldara; ***Neth.:*** Aldara; ***Norw.:*** Aldara; ***NZ:*** Aldara; ***Philipp.:*** Aldara; ***Pol.:*** Aldara; ***Port.:*** Aldara; ***S.Afr.:*** Aldara; ***Singapore:*** Aldara; ***Spain:*** Aldara; ***Swed.:*** Aldara; ***Switz.:*** Aldara; ***Thai.:*** Aldara; ***UK:*** Aldara; ***USA:*** Aldara.

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## Indinavir Sulfate *(USAN, pINNM)*

Indinavir; sulfate d'; Indinavir Sulphate *(BANM)*; Indinaviri sulfas; L-735524; MK-0639; MK-639; Sulfato de indinavir. (α*R*,γ*S*,2*S*)-α-Benzyl-2-(*tert*-butylcarbamoyl)-γ-hydroxy-*N*-[(1*S*,2*R*)-2-hydroxy-1-indanyl]-4-(3-pyridylmethyl)-1-piperazinevaleramide sulfate (1:1).

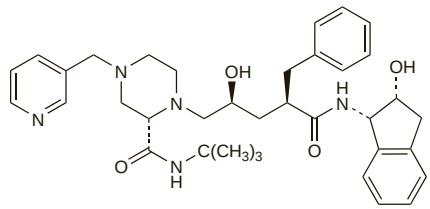
Индинавира Сульфат

$C_{36}H_{47}N_5O_4,H_2SO_4$ = 711.9.

*CAS — 150378-17-9 (indinavir); 157810-81-6 (indinavir sulfate).*

*ATC — J05AE02.*

*ATC Vet — QJ05AE02.*



*(indinavir)*

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

**Ph. Eur. 6.2** (Indinavir Sulphate). A white or almost white, hygroscopic powder. Freely soluble in water; soluble in methyl alcohol; practically insoluble in heptane. Store in airtight containers. Protect from light.

**USP 31** (Indinavir Sulfate). Store in airtight containers at a temperature of 25°, excursions permitted between 15° and 30°. Protect from moisture.

### Adverse Effects

The most commonly reported adverse effects associated with antiretroviral regimens containing indinavir include gastrointestinal disturbances (abdominal pain, diarrhoea, dyspepsia, nausea and vomiting), taste disturbances, headache, and dizziness. Nephrolithiasis, often with flank pain and occurring with or without haematuria, is the most frequently reported serious adverse effect. It appears to be dose-related and is more frequent in patients taking more than 2.4 g daily; it also occurs more often in children. Temporarily stopping treatment and giving fluids often resolve the symptoms, but interstitial nephritis and acute renal failure have been reported. Dry skin and skin rashes occur commonly and may occasionally be severe. Cases of Stevens-Johnson syndrome and erythema multiforme have also been reported. Hypersensitivity reactions, including vasculitis and sometimes anaphylaxis, have been associated with indinavir. Hepatitis, including cases resulting in hepatic failure and death has occurred. Cases of acute haemolytic anaemia have been reported again with some fatalities. Other commonly reported adverse effects are dry mouth, dysuria, fatigue, flatulence, hypoaesthesia, insomnia, paraesthesia, pruritus, and acid regurgitation. Neutrophil counts may be reduced and mean corpuscular volume increased. Abnormal laboratory test results associated with indinavir-containing regimens have included crystalluria, haematuria, proteinuria, raised liver enzymes, and asymptomatic hyperbilirubinaemia.

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 indinavir, 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 observed in patients receiving antiretroviral therapy, including indinavir. 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.

◊ Reviews.


1. Moyle GJ, Gazzard BG. A risk-benefit assessment of HIV protease inhibitors. *Drug Safety* 1999; **20:** 299–321.


**Effects on carbohydrate and lipid metabolism.** HIV-protease inhibitors have been associated with a lipodystrophy syndrome characterised by peripheral fat wasting, central adiposity and the so called 'buffalo hump', hyperlipidaemia, and insulin resistance.[1]

A survey of 113 HIV-infected patients receiving HIV-protease inhibitors found lipodystrophy in 83% (severe in 11%) and impaired glucose tolerance in 23% (including diabetes mellitus in 7%) after a mean of 21 months of therapy.[2]

A systematic review[3] of published material has concluded that use of HIV-protease inhibitors is associated with increased concentrations of total cholesterol, triglycerides, and low-density lipoprotein; that use is often associated with morphological signs of cardiovascular disease such as increased carotid intima thickness or atherosclerotic lesions; and that there is some evidence of an increased risk of myocardial infarction. Comparison of the effect of specific protease inhibitors showed that ritonavir was consistently associated with elevated lipids and that, although some studies showed that saquinavir was associated with elevated lipids, it was to a lesser degree than other drugs. Guidelines[4] have been published outlining the management, including drug therapy, of antiretroviral-induced lipid disorders in HIV-infected patients.

Impaired glucose tolerance has been linked to reduction in insulin sensitivity[5] and has responded to treatment with sulfonylureas or insulin.[6]


1. Carr A, *et al.* Pathogenesis of HIV-1-protease inhibitor-associated peripheral lipodystrophy, hyperlipidaemia, and insulin resistance. *Lancet* 1998; **351:** 1881–3.
2. Carr A, *et al.* Diagnosis, prediction, and natural course of HIV-1 protease-inhibitor-associated lipodystrophy, hyperlipidaemia, and diabetes mellitus: a cohort study. *Lancet* 1999; **353:** 2093–9.
3. Rhew DC, *et al.* Association between protease inhibitor use and increased cardiovascular risk in patients infected with human immunodeficiency virus: a systematic review. *Clin Infect Dis* 2003; **37:** 959–72.
4. Dubé MP, *et al.* Guidelines for the evaluation and management of dyslipidemia in human immunodeficiency virus (HIV)-infected adults receiving antiretroviral therapy: recommendations of the HIV Medicine Association of the Infectious Disease Society of America and the Adult AIDS Clinical Trials Group. *Clin Infect Dis* 2003; **37:** 613–27. Also available at: http://www.journals.uchicago.edu/doi/pdf/10.1086/378131 (accessed 28/08/08)
5. Walli R, *et al.* Impaired glucose tolerance and protease inhibitors. *Ann Intern Med* 1998; **129:** 837–8.
6. Dubé MP, *et al.* Protease inhibitor-associated hyperglycaemia. *Lancet* 1997; **350:** 713–14.


**Effects on the cardiovascular system.** For adverse effects of HIV-protease inhibitors on carbohydrate and lipid metabolism that increase the risk of coronary vascular disease, see above.

**Effects on the kidneys.** Nephrolithiasis has been reported in about 10% of patients receiving indinavir, and the incidence may be higher in patients with haemophilia or hepatitis C infection.[1] Both asymptomatic[2] and symptomatic[3,4] crystalluria have been reported in patients receiving indinavir, with symptomatic urinary-tract disease in 8%. Indinavir has been identified as the major constituent of both urinary crystals[2] and calculi.[5] In addition there have been reports of acute interstitial nephritis associated with indinavir[6] and deterioration of renal function associated with both indinavir[7] and ritonavir.[8,9] Renal atrophy was associated with long-term treatment with indinavir.[10,11]


1. Brodie SB, *et al.* Variation in incidence of indinavir-associated nephrolithiasis among HIV-positive patients. *AIDS* 1998; **12:** 2433–7.
2. Kopp JB, *et al.* Crystalluria and urinary tract abnormalities associated with indinavir. *Ann Intern Med* 1997; **127:** 119–25.
3. Hachey DM, *et al.* Indinavir crystalluria in an HIV-positive man. *Ann Pharmacother* 2000; **34:** 403.
4. Famularo G, *et al.* Symptomatic crystalluria associated with indinavir. *Ann Pharmacother* 2000; **34:** 1414–18.
5. Daudon M, *et al.* Urinary stones in HIV-1-positive patients treated with indinavir. *Lancet* 1997; **349:** 1294–5.
6. Marroni M, *et al.* Acute interstitial nephritis secondary to the administration of indinavir. *Ann Pharmacother* 1998; **32:** 843–4.
7. Boubaker K, *et al.* Changes in renal function associated with indinavir. *AIDS* 1998; **12:** F249–F254.

8. Duong M, *et al.* Renal failure after treatment with ritonavir. *Lancet* 1996; **348:** 693–4.
9. Chugh S, *et al.* Ritonavir and renal failure. *N Engl J Med* 1997; **336:** 138.
10. Hanabusa H, *et al.* Renal atrophy associated with long-term treatment with indinavir. *N Engl J Med* 1999; **340:** 392–3.
11. Cattelan AM, *et al.* Severe hypertension and renal atrophy associated with indinavir. *Clin Infect Dis* 2000; **30:** 619–21.

**Effects on the liver.** The use of indinavir with other antiretroviral drugs has been associated with the development of severe hepatitis.[1,2]

Hepatic failure was attributed to ritonavir in a patient receiving combination therapy for AIDS.[3]

1. Bräu N, *et al.* Severe hepatitis in three AIDS patients treated with indinavir. *Lancet* 1997; **349:** 924–5.
2. Matsuda J, *et al.* Severe hepatitis in patients with AIDS and haemophilia B treated with indinavir. *Lancet* 1997; **350:** 364.
3. Picard O, *et al.* Hepatotoxicity associated with ritonavir. *Ann Intern Med* 1998; **129:** 670–1.

**Effects on the menstrual cycle.** Irregular, prolonged, or heavy menstruation[1] in 4 patients receiving ritonavir subsequently returned to normal in the 3 who were transferred to a different HIV-protease inhibitor.

1. Nielsen H. Hypermenorrhoea associated with ritonavir. *Lancet* 1999; **353:** 811–12.

**Effects on mental state.** Acute paranoid reactions occurred on two occasions in a patient receiving saquinavir.[1]

1. Finlayson JA, Laing RBS. Acute paranoid reaction to saquinavir. *Am J Health-Syst Pharm* 1998; **55:** 2016–17.

**Effects on the pancreas.** Pancreatitis was associated with use of ritonavir with saquinavir in 1 patient,[1] and with ritonavir (other drugs unspecified) in 2 others,[2] and was believed to be secondary to hyperlipidaemia (see Effects on Carbohydrate and Lipid Metabolism, above).

1. McBride M, *et al.* Lipid lowering therapy in patients with HIV infection. *Lancet* 1998; **352:** 1782–3.
2. Di Perri G, *et al.* HIV-protease inhibitors. *N Engl J Med* 1998; **339:** 773–4.

**Effects on sexual function.** Sexual dysfunction has been reported in patients given combination therapy with HIV-protease inhibitors and reverse transcriptase inhibitors.[1,2]

1. Martínez E, *et al.* Sexual dysfunction with protease inhibitors. *Lancet* 1999; **353:** 810–11.
2. Colebunders R, *et al.* Sexual dysfunction with protease inhibitors. *Lancet* 1999; **353:** 1802.

**Effects on the skin.** Skin rashes have been reported in about 20% of patients receiving indinavir and in 3 to 5% of patients receiving nelfinavir or saquinavir. Rash is described as a frequent adverse effect of ritonavir. In patients taking indinavir who reported rashes,[1] the rash commonly appeared within 2 weeks of starting treatment, was frequently accompanied by pruritus, and was usually self-limiting, commonly resolving within 4 weeks.

Paronychia and pyogenic granuloma of the great toes has been reported in patients receiving indinavir.[2]

1. Gajewski LK, *et al.* Characterization of rash with indinavir in a national patient cohort. *Ann Pharmacother* 1999; **33:** 17–21.
2. Bouscarat F, *et al.* Paronychia and pyogenic granuloma of the great toes in patients treated with indinavir. *N Engl J Med* 1998; **338:** 1776–7.

## Precautions

Indinavir is primarily metabolised in the liver and therefore caution and possible dosage reduction are required in hepatic 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.

Although renal excretion is a relatively minor route of elimination, adequate hydration is recommended to reduce the risk of nephrolithiasis; monitoring is advised in the presence of renal impairment. Treatment may need to be temporarily interrupted or stopped completely in patients developing nephrolithiasis. 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.

**Mycobacterial infections.** Patients with a previously unsuspected *Mycobacterium avium* complex infection experienced a severe febrile syndrome with inflammatory lymphadenitis after starting indinavir treatment.[1] The reaction resolved with appropriate antimycobacterial therapy.

1. Race EM, *et al.* Focal mycobacterial lymphadenitis following initiation of protease-inhibitor therapy in patients with advanced HIV-1 disease. *Lancet* 1998; **351:** 252–5.

**Pregnancy.** A retrospective survey[1] involving 89 women who received HIV-protease inhibitors during pregnancy indicated that these antivirals appeared generally safe.

1. Morris AB, *et al.* Multicenter review of protease inhibitors in 89 pregnancies. *J Acquir Immune Defic Syndr* 2000; **25:** 306–11.

## Interactions

Indinavir is metabolised mainly by the cytochrome P450 isoenzyme CYP3A4. It may compete for the same metabolic pathways with a wide range of drugs that are metabolised similarly, often resulting in mutually increased plasma concentrations. A drug that is a significant inducer of microsomal enzymes, particularly CYP3A4, may reduce plasma concentrations of indinavir. HIV-protease inhibitors may themselves induce metabolism and may reduce plasma concentrations of other drugs.

Indinavir is contraindicated 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 include antiarrhythmics (amiodarone and flecainide), antihistamines (astemizole and terfenadine), ergot derivatives (dihydroergotamine, ergometrine, ergotamine, and methylergometrine), gastrointestinal prokinetics (cisapride), antipsychotics (pimozide), sedatives and hypnotics (alprazolam, midazolam, and triazolam), and statins (lovastatin and simvastatin). Rifampicin and St John's wort decrease the concentration of indinavir; use with the antiretroviral is not recommended due to the possible loss of its activity and development of resistance. Use of indinavir with atazanavir is contra-indicated as both drugs have been associated with indirect hyperbilirubinaemia.

Other HIV-protease inhibitors may have similar interactions. The principal interactions that have been reported as a risk for one or more of the various HIV-protease inhibitors are listed below. For further information on drug interactions of HIV-protease inhibitors see Table 1, p.917.

◊ References to interactions associated with HIV-protease inhibitors.

1. Eagling VA, *et al.* Differential inhibition of cytochrome P450 isoforms by the protease inhibitors, ritonavir, saquinavir and indinavir. *Br J Clin Pharmacol* 1997; **44:** 190–4.
2. von Moltke LL, *et al.* Protease inhibitors as inhibitors of human cytochromes P450: high risk associated with ritonavir. *J Clin Pharmacol* 1998; **38:** 106–11.
3. Malaty LI, Kuper JJ. Drug interactions of HIV protease inhibitors. *Drug Safety* 1999; **20:** 147–69.

**Amfetamines.** For mention of interactions, including a fatal serotonergic reaction, with *methylenedioxymethamfetamine* (Ecstasy) in patients receiving ritonavir, see p.2159.

**Analgesics.** Ritonavir and possibly other HIV-protease inhibitors produce complex and potentially serious interactions with some opioids (see p.103). Interactions between ritonavir and *dextropropoxyphene* (p.41) or *pethidine* (p.114) are considered to be especially hazardous. Ritonavir might also prolong *fentanyl*-induced respiratory depression (see p.57). Amprenavir, nelfinavir, ritonavir, and ritonavir-boosted HIV-protease inhibitors may reduce plasma concentrations of *methadone* (see p.84). For the effect of some HIV-protease inhibitors on the pharmacokinetics of *buprenorphine*, see p.30.

Use of ritonavir with *piroxicam* can result in potentially toxic concentrations of piroxicam (see p.118).

**Antiarrhythmics.** Use of HIV-protease inhibitors with the antiarrhythmics *amiodarone*, *encainide*, *flecainide*, *propafenone*, or *quinidine* may result in potentially toxic plasma concentrations of these drugs with an increased risk of ventricular arrhythmias.

**Antibacterials.** Plasma concentrations of HIV-protease inhibitors may be reduced to subtherapeutic levels by *rifabutin* or *rifampicin*. In addition, plasma concentrations of rifabutin may be increased, with a consequent risk of uveitis. In general, HIV-protease inhibitors should not be used with rifampicin (p.327) and dosage modifications may be necessary if used with rifabutin; licensed product information for indinavir recommends increasing the dose of the antiretroviral to 1 g every 8 hours and halving the dose of rifabutin. Further information is given in Rifabutin under Interactions, p.324 and Uses, Tuberculosis and HIV Infection, p.325.

HIV-protease inhibitors may inhibit the metabolism of *clarithromycin* (p.249) and possibly other macrolides.

**Antidepressants.** HIV-protease inhibitors may inhibit the metabolism of *desipramine* and other tricyclic antidepressants (p.380). Interactions may also occur between HIV-protease inhibitors and SSRIs such as *fluoxetine* (p.396), and have also occurred with *bupropion* (p.384).

Plasma concentrations of HIV-protease inhibitors may be reduced by *St John's wort* as a result of induction of cytochrome P450; concomitant use should be avoided.[1]

1. Piscitelli SC, *et al.* Indinavir concentrations and St John's wort. *Lancet* 2000; **355:** 547–8. Correction. *ibid.* 2001; **357:** 1210.

**Antiepileptics.** Reduced plasma concentrations of HIV-protease inhibitors may be anticipated if the enzyme inducers *carbamazepine*, *phenobarbital*, or *phenytoin* are given concurrently. Nelfinavir has been reported to reduce the plasma concentration of phenytoin (p.499); a similar effect may occur with ritonavir. In addition, carbamazepine concentrations have been reported to be increased by ritonavir (p.475).

**Antifungals.** Plasma concentrations of HIV-protease inhibitors may be increased by azole antifungals. Licensed product information recommends that the dose of indinavir should be reduced to 600 mg every 8 hours when given with *itraconazole* 200 mg twice daily. A dose reduction is not considered necessary by the UK licensed product information when indinavir is given with *ketoconazole*, but the US product information recommends a reduction to indinavir 600 mg every 8 hours.

Conversely, plasma concentrations of ketoconazole are increased by ritonavir.

**Antihistamines.** HIV-protease inhibitors inhibit the metabolism of non-sedating antihistamines such as *astemizole* and *terfenadine* resulting in increased plasma concentrations of these drugs and an increased risk of serious ventricular arrhythmias. Such combinations should be avoided.

**Antipsychotics.** Ritonavir and possibly other HIV-protease inhibitors may increase plasma concentrations of *clozapine* (but see p.984), *pimozide* (p.1018), and *sertindole* (p.1028) resulting in increased toxicity. Concomitant use should be avoided. Plasma concentrations of *thioridazine* may also be increased when given with some HIV-protease inhibitors.

**Antivirals.** HIV-protease inhibitors can inhibit metabolism of other drugs from the same class and increases in adverse effects have resulted.

Plasma concentrations of atazanavir, indinavir,[1] and lopinavir-ritonavir may be reduced by *nevirapine*; the UK licensed product information for indinavir recommends a dose increase of indinavir to 1 g every 8 hours be considered.

Plasma concentrations of indinavir[2] and saquinavir may be increased by *delavirdine*; the UK licensed product information for indinavir recommends a dose reduction of indinavir to 400 to 600 mg every 8 hours in patients receiving delavirdine and the UK licensed information for saquinavir recommends that liver function should be monitored if saquinavir is given with delavirdine.

Plasma concentrations of amprenavir, atazanavir, indinavir, *lopinavir*, and saquinavir are decreased when given with *efavirenz*. The use of efavirenz with ritonavir is associated with an increased frequency of adverse effects, presumably due to competitive inhibition of metabolism, and liver enzymes should be monitored in patients receiving this combination. Plasma concentrations of nelfinavir are increased when given with efavirenz, but the combination is usually well tolerated at standard doses.

Although there is no direct interaction between HIV-protease inhibitors and *didanosine*, the buffer included in the didanosine formulation can impair their absorption; doses should be separated by at least 1 to 2 hours from didanosine doses, which should be given on an empty stomach.

For a report of reduced area under the plasma concentration-time curve for *zidovudine* in patients receiving ritonavir, see p.915.

1. Murphy RL, *et al.* Antiviral effect and pharmacokinetic interaction between nevirapine and indinavir in persons infected with human immunodeficiency virus type 1. *J Infect Dis* 1999; **179:** 1116–23.
2. Ferry JJ, *et al.* Pharmacokinetic drug-drug interaction study of delavirdine and indinavir in healthy subjects. *J Acquir Immune Defic Syndr Hum Retrovirol* 1998; **18:** 252–9.

**Benzodiazepines.** For the effect of HIV-protease inhibitors on benzodiazepines, see Diazepam, p.990.

**Cardiac glycosides.** For details of a possible interaction between ritonavir and *digoxin*, see p.1262.

**Ciclosporin.** Mutual increases in the area under the plasma concentration-time curves for saquinavir and ciclosporin were reported in a kidney transplant recipient.[1] The resultant adverse effects subsided when doses of both drugs were reduced by half. Similar interactions with other HIV-protease inhibitors are possible.

1. Brinkman K, *et al.* Pharmacokinetic interaction between saquinavir and cyclosporine. *Ann Intern Med* 1998; **129:** 914–15.

**Corticosteroids.** Corticosteroids, in particular *dexamethasone*, may induce the metabolism of HIV-protease inhibitors resulting in reduced plasma concentrations. For the effect of ritonavir on plasma concentrations of *fluticasone*, see p.1495

**Ergot alkaloids.** For reports of ergotism in patients receiving HIV-protease inhibitors and ergot alkaloids, see Ergotamine, p.621.

**Gastrointestinal drugs.** The antidiarrhoeal *loperamide* markedly reduced exposure to saquinavir in 12 healthy subjects given a single dose of both drugs.[1] Exposure was reduced by about 54%, a reduction of the same order of magnitude as seen with enzyme inducers such as rifampicin, although the mechanism in this case was thought likely to be impaired absorption of the antiviral. Prolonged use of loperamide might lead to substantial reductions in saquinavir plasma concentrations, and reduced clinical efficacy. Plasma concentrations of loperamide were also increased, and those of its metabolite desmethylloperamide correspondingly reduced, but this was thought unlikely to be of clinical significance.

Atazanavir and indinavir depend on acid pH in the stomach for adequate absorption, and acid-suppressive therapies such as *histamine $H_2$-antagonists* and *proton pump inhibitors* may significantly reduce their absorption; if acid-suppressive therapy is necessary, these HIV-protease inhibitors should be boosted with low-dose ritonavir to ensure adequate antiretroviral activity.[2]

For the effect of HIV-protease inhibitors on *cisapride*, see p.1721.

1. Mikus G, *et al.* Reduction of saquinavir exposure by coadministration of loperamide: a two-way pharmacokinetic interaction. *Clin Pharmacokinet* 2004; **43:** 1015–24.
2. Fulco PP, *et al.* Acid suppressive therapy and the effects on protease inhibitors. *Ann Pharmacother* 2006; **40:** 1974–83.

**Grapefruit.** Exposure to saquinavir was increased by 50% when taken with grapefruit juice;[1] however, licensed product information does not recommend any adjustment of dosage of saquinavir.

1. Kupferschmidt HHT, *et al.* Grapefruit juice enhances the bioavailability of the HIV protease inhibitor saquinavir in men. *Br J Clin Pharmacol* 1998; **45:** 355–9.

**Hormonal contraceptives.** For the effect of HIV-protease inhibitors on hormonal contraceptives, see p.2068.

**Interleukin-2.** Plasma concentrations of indinavir were increased[1] during use with interleukin-2.

1. Piscitelli SC, *et al.* Alteration in indinavir clearance during interleukin-2 infusions in patients infected with the human immunodeficiency virus. *Pharmacotherapy* 1998; **18:** 1212–16.

**Paclitaxel.** For the effect of HIV-protease inhibitors on paclitaxel, see Interactions, Antivirals, p.759.

**Phenylpropanolamine.** For a possible interaction between phenylpropanolamine and antiretrovirals including indinavir, see Stavudine, p.907.

**Sildenafil.** For the effect of HIV-protease inhibitors on sildenafil, including a report of fatal myocardial infarction after sildenafil in a patient receiving ritonavir and saquinavir, see p.2194.

**Statins.** HIV-protease inhibitors may inhibit the metabolism of statins metabolised by CYP3A4 isoenzymes resulting in an increased risk of myopathy. Although those statins less dependent on CYP3A4 for metabolism may be used in certain circumstances to manage HIV-protease inhibitor-induced lipid disorders, use with lovastatin or simvastatin should be avoided, and HIV-protease inhibitors should be given with caution in patients receiving atorvastatin or rosuvastatin.

**Tacrolimus.** HIV-protease inhibitors may inhibit the metabolism of tacrolimus (see Antivirals, p.1845).

**Theophylline.** For a potential effect of ritonavir on theophylline, see p.1144.

**Warfarin.** For the effect of HIV-protease inhibitors on warfarin, see p.1430.

## Antiviral Action

Indinavir is a selective, competitive, reversible inhibitor of HIV-1 and HIV-2 proteases with a tenfold greater selectivity for HIV-1 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. Various degrees of cross-resistance between HIV-protease inhibitors may occur.

## Pharmacokinetics

Indinavir is rapidly absorbed after oral doses producing peak plasma concentrations in 0.8 hours (range 0.5 to 1.1 hours). Bioavailability is about 65% after a single 800-mg dose. Absorption is reduced if given with a meal high in calories, fat, and protein but is less affected by a light meal (for the effect of pH see Gastrointestinal Drugs under Interactions, above). At doses up to 1 g, increases in plasma concentration are proportionately greater than increases in dose. Plasma protein binding is about 60%. Indinavir is reported to cross the blood-brain barrier. It undergoes oxidative metabolism by cytochrome P450 isoenzyme CYP3A4 and glucuronidation. At least seven metabolites (1 glucuronide and 6 oxidative metabolites) have been identified. The elimination half-life is 1.8 hours. Less than 20% of the absorbed dose is excreted in the urine, about half of this as unchanged drug. The remainder is excreted in the faeces.

◊ References.

1. Ståhle L, *et al.* Indinavir in cerebrospinal fluid of HIV-1-infected patients. *Lancet* 1997; **350:** 1823.
2. Bernard L, *et al.* Indinavir concentrations in hair from patients receiving highly active antiretroviral therapy. *Lancet* 1998; **352:** 1757–8.
3. Wintergerst U, *et al.* Use of saliva specimens for monitoring indinavir therapy in human immunodeficiency virus-infected patients. *Antimicrob Agents Chemother* 2000; **44:** 2572–4.
4. Haas DW, *et al.* Steady-state pharmacokinetics of indinavir in cerebrospinal fluid and plasma among adults with human immunodeficiency virus type 1 infection. *Clin Pharmacol Ther* 2000; **68:** 367–74.
5. Burger DM, *et al.* Pharmacokinetics of the protease inhibitor indinavir in human immunodeficiency virus type 1-infected children. *Antimicrob Agents Chemother* 2001; **45:** 701–5.
6. Kappelhoff BS, *et al.* Population pharmacokinetics of indinavir alone and in combination with ritonavir in HIV-1-infected patients. *Br J Clin Pharmacol* 2005; **60:** 276–86.
7. Unadkat JD, *et al.* Pharmacokinetics and safety of indinavir in human immunodeficiency virus-infected pregnant women. *Antimicrob Agents Chemother* 2007; **51:** 783–6.

## Uses and Administration

Indinavir 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 indinavir is used alone, and it is therefore used with other antiretrovirals.

Indinavir is given orally as the sulfate, but doses are expressed in terms of the base; 116 mg of indinavir sulfate is equivalent to about 100 mg of indinavir. It is given in a usual adult dose of 800 mg every 8 hours. For the *reduced* doses recommended in patients taking azole antifungals or the NNRTI delavirdine, and *increased* doses in those also taking rifabutin or nevirapine, see Antibacterials, Antifungals, and Antivirals, under Interactions, above. Indinavir should be given either 1 hour before or 2 hours after meals, or with a light, low-fat meal. Adequate hydration should be maintained. Treatment may have to be interrupted if acute episodes of nephrolithiasis occur.

For details of doses in children and adolescents, see below. For details of modified dosage to be used in patients with hepatic impairment, see below.

**Administration in children.** For the treatment of HIV infection in children 4 years of age and older indinavir is given orally with other antiretroviral drugs. A dose of 500 mg/m$^2$ every 8 hours is recommended; doses should not exceed the adult dose (see above).

**Administration in hepatic impairment.** A reduction in the oral dose of indinavir to 600 mg every 8 hours is recommended for patients with mild to moderate hepatic insufficiency due to cirrhosis.

## Preparations

**Proprietary Preparations** (details are given in Part 3)
***Arg.:*** Avural; Crixivan; Elvenavir; Forli; Indilea; Inhibisam; ***Austral.:*** Crixivan; ***Austria:*** Crixivan; ***Belg.:*** Crixivan; ***Braz.:*** Crixivan; Dinavir†; Indinax; ***Canad.:*** Crixivan; ***Chile:*** Crixivan; ***Cz.:*** Crixivan; ***Denm.:*** Crixivan; ***Fin.:*** Crixivan; ***Fr.:*** Crixivan; ***Ger.:*** Crixivan; ***Gr.:*** Crixivan; ***Hong Kong:*** Crixivan; ***Hung.:*** Crixivan; ***India:*** Indivan; ***Irl.:*** Crixivan; ***Israel:*** Crixivan; ***Ital.:*** Crixivan; ***Jpn:*** Crixivan; ***Malaysia:*** Crixivan; ***Mex.:*** Crixivan; Indilan; ***Neth.:*** Crixivan; ***Norw.:*** Crixivan; ***NZ:*** Crixivan; ***Philipp.:*** Crixivan; ***Pol.:*** Crixivan; ***Port.:*** Crixivan; ***Rus.:*** Crixivan (Криксиван); ***S.Afr.:*** Crixivan; ***Singapore:*** Crixivan; ***Spain:*** Crixivan; ***Swed.:*** Crixivan; ***Switz.:*** Crixivan; ***Thai.:*** Crixivan; ***Turk.:*** Crixivan; ***UK:*** Crixivan; ***USA:*** Crixivan; ***Venez.:*** Crixivan; Indivan.

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## Inosine Pranobex *(BAN)*

Inosine Dimepranol Acedoben *(pINNM)*; Inosin Pranobeks; Inosina Dimepranol Acedobén; Inosine Acédobène Diméprano; Inosinum Dimepranolum Acedobenum; Inosinum pranobexum; Inosiplex; Isoprinosine; Methisoprinol; NP-113; NPT-10381. Inosine 2-hydroxypropyldimethylammonium 4-acetamidobenzoate (1:3).

Инозин Димепранол Ацедобен

$C_{10}H_{12}N_4O_5$:$C_{14}H_{22}N_2O_4$ (1:3) = 1115.2.

*CAS — 36703-88-5.*

*ATC — J05AX05.*

*ATC Vet — QJ05AX05.*

NOTE. Dimepranol Acedoben is *pINN* and *USAN*.

## Adverse Effects and Precautions

Some patients have had transient nausea, vomiting, headaches, arthralgia, fatigue, vertigo, raised liver enzymes, pruritus, and skin rashes. Metabolism of the inosine content of inosine pranobex leads to increased serum and urine concentrations of uric acid; caution is therefore recommended in treating patients with renal impairment, gout, or hyperuricaemia.

## Antiviral Action

Inosine pranobex appears to owe its activity in viral infections more to its capacity to modify or stimulate cell-mediated immune processes than to a direct action on the virus.

## Pharmacokinetics

Inosine pranobex is reported to be rapidly absorbed from the gastrointestinal tract with peak plasma concentrations occurring 1 hour after an oral dose. It is also rapidly metabolised with a plasma half-life of 50 minutes, the inosine portion of the complex yielding uric acid; the other components undergo oxidation and glucuronidation. The metabolites are excreted in the urine.

◊ References.

1. Nielsen P, Beckett AH. The metabolism and excretion in man of NN-dimethylamino-isopropanol and p-acetamido-benzoic acid after administration of isoprinosine. *J Pharm Pharmacol* 1981; **33:** 549–50.

## Uses and Administration

Inosine pranobex is a complex of inosine (p.2325) with dimepranol acedoben ((±)-1-(dimethylamino)-2-propanol *p*-acetamidobenzoate). It has been used in the treatment of various viral infections (see below), including herpes simplex, genital warts, and subacute sclerosing panencephalitis, although other treatments or measures are preferred. The oral dose in mucocutaneous herpes simplex is 1 g four times daily for 7 to 14 days. An oral dose of 1 g three times daily is given for 14 to 28 days as an adjunct to standard topical treatment for genital warts. In subacute sclerosing panencephalitis, the oral dose is 50 to 100 mg/kg daily in divided doses given every 4 hours.

◊ Reviews.

1. Campoli-Richards DM, *et al.* Inosine pranobex: a preliminary review of its pharmacodynamic and pharmacokinetic properties, and therapeutic efficacy. *Drugs* 1986; **32:** 383–424.

**Alopecia.** Oral inosine pranobex (50 mg/kg daily in 5 divided doses for 12 weeks) has been investigated[1] with some apparent benefit in the treatment of recalcitrant alopecia areata (p.1577).

1. Georgala S, *et al.* Inosiplex for treatment of alopecia areata: a randomized placebo-controlled study. *Acta Derm Venereol* 2006; **86:** 422–4.

**Subacute sclerosing panencephalitis.** Inosine pranobex has been tried[1,2] in the treatment of subacute sclerosing panencephalitis, a complication of measles (p.860), but the results of clinical studies have been equivocal. Some success has been reported when inosine pranobex has been given with interferons and other antivirals. However, a randomised study involving 121 patients, of whom 67 completed analysis, was unable to show any difference between an oral regimen of inosine pranobex 100 mg/kg daily in 3 divided doses (up to a maximum of 3 g daily) for 6 months, and the same dose combined with intraventricular interferon alfa, although the outcomes, which were considered satisfactory in about 35% of cases, were better than the 10% remission rate in historical controls, implying some benefit with either treatment.[3]

1. Haddad FS, Risk WS. Isoprinosine treatment in 18 patients with subacute sclerosing panencephalitis: a controlled study. *Ann Neurol* 1980; **7:** 185–8.
2. Jones CE, *et al.* Inosiplex therapy in subacute sclerosing panencephalitis: a multicentre, non-randomised study in 98 patients. *Lancet* 1982; **i:** 1034–7.
3. Gascon GG. International Consortium on Subacute Sclerosing Panencephalitis. Randomized treatment study of inosiplex versus combined inosiplex and intraventricular interferon-α in subacute sclerosing panencephalitis (SSPE): international multicenter study. *J Child Neurol* 2003; **18:** 819–27. Correction. *ibid.* 2004; **19:** 342.

**Warts.** Although of no apparent benefit in the treatment of palmar/plantar warts,[1] oral inosine pranobex has been shown to be of value in the treatment of refractory genital warts (p.1584) in the cervix,[2] as well as producing some apparent epithelial morphological improvement in women with subclinical human papillomavirus infection of the vulva.[3]

1. Berth-Jones J, Hutchinson PE. Modern treatment of warts: cure rates at 3 and 6 months. *Br J Dermatol* 1992; **127:** 262–5.
2. Georgala S, *et al.* Oral inosiplex in the treatment of cervical condylomata acuminata: a randomised placebo-controlled trial. *BJOG* 2006; **113:** 1088–91.
3. Tay SK. Efficacy of inosine pranobex oral therapy in subclinical human papillomavirus infection of the vulva: a randomized double-blinded placebo controlled study. *Int J STD AIDS* 1996; **7:** 276–80.

## Preparations

**Proprietary Preparations** (details are given in Part 3)
***Austria:*** Isoprinosin; ***Belg.:*** Isoprinosine; ***Canad.:*** Imunovir; ***Chile:*** Isoprinosine; ***Cz.:*** Isoprinosine; ***Fr.:*** Isoprinosine; ***Ger.:*** delimmun; Isoprinosine; ***Gr.:*** Isoprinosine; ***Hong Kong:*** Qualiprinol; ***Hung.:*** Isoprinosine; ***Indon.:*** Isprinol; ***Irl.:*** Imunovir; Isoprinosine; ***Ital.:*** Avirin†; Farviran†; Virustop†; Viruxan; ***Mex.:*** Isoprinosine; Pranosine; ***NZ:*** Imunovir; ***Philipp.:*** Immunosin; Isoprinosine; ***Pol.:*** Groprinosin; ***Port.:*** Isovir; ***Rus.:*** Isoprinosine (Изопринозин); ***Singapore:*** Imin; ***UK:*** Imunovir.