3. D'Alessandro AM, *et al.* Successful treatment of severe cytomegalovirus infections with ganciclovir and CMV hyperimmune globulin in liver transplant recipients. *Transplant Proc* 1989; **21:** 3560–1.
4. Salmela K, *et al.* Ganciclovir in the treatment of severe cytomegalovirus disease in liver transplant patients. *Transplant Proc* 1990; **22:** 238–40.
5. Emanuel D, *et al.* Cytomegalovirus pneumonia after bone marrow transplantation successfully treated with the combination of ganciclovir and high-dose intravenous immune globulin. *Ann Intern Med* 1988; **109:** 777–82.
6. Studies of Ocular Complications of AIDS Research Group, in Collaboration with the AIDS Clinical Trials Group. Combination foscarnet and ganciclovir therapy vs monotherapy for the treatment of relapsed cytomegalovirus retinitis in patients with AIDS: the Cytomegalovirus Retreatment Trial. *Arch Ophthalmol* 1996; **114:** 23–33.
7. Mylonakis E, *et al.* Combination antiviral therapy for ganciclovir-resistant cytomegalovirus infection in solid-organ transplant recipients. *Clin Infect Dis* 2002; **34:** 1337–41.
8. Anand R, *et al.* Control of cytomegalovirus retinitis using sustained release of intraocular gancyclovir. *Arch Ophthalmol* 1993; **111:** 223–7.
9. Martin DF, *et al.* Treatment of cytomegalovirus retinitis with an intraocular sustained-release ganciclovir implant: a randomized controlled clinical trial. *Arch Ophthalmol* 1994; **112:** 1531–9.
10. Musch DC, *et al.* Treatment of cytomegalovirus retinitis with a sustained-release ganciclovir implant. *N Engl J Med* 1997; **337:** 83–90.
11. Ausayakhun S, *et al.* Treatment of cytomegalovirus retinitis in AIDS patients with intravitreal ganciclovir. *J Med Assoc Thai* 2005; **88** (suppl 9): S15–S20.
12. Velez G, *et al.* High-dose intravitreal ganciclovir and foscarnet for cytomegalovirus retinitis. *Am J Ophthalmol* 2001; **131:** 396–7.
13. Martin DF, *et al.* Oral ganciclovir for patients with cytomegalovirus retinitis treated with a ganciclovir implant. *N Engl J Med* 1999; **340:** 1063–70.
14. Lalezari JP, *et al.* High dose oral ganciclovir treatment for cytomegalovirus retinitis. *J Clin Virol* 2002; **24:** 67–77.
15. Goodrich JM, *et al.* Ganciclovir prophylaxis to prevent cytomegalovirus disease after allogeneic marrow transplant. *Ann Intern Med* 1993; **118:** 173–8.
16. Winston DJ, *et al.* Ganciclovir prophylaxis of cytomegalovirus infection and disease in allogeneic bone marrow transplant recipients. *Ann Intern Med* 1993; **118:** 179–84.
17. Hibberd PL, *et al.* Preemptive ganciclovir therapy to prevent cytomegalovirus disease in cytomegalovirus antibody-positive renal transplant recipients: a randomized controlled trial. *Ann Intern Med* 1995; **123:** 18–26.
18. Winston DJ, *et al.* Randomised comparison of ganciclovir and high-dose acyclovir for long-term cytomegalovirus prophylaxis in liver-transplant recipients. *Lancet* 1995; **346:** 69–74.
19. Gane E, *et al.* Randomised trial of efficacy and safety of oral ganciclovir in the prevention of cytomegalovirus disease in liver-transplant recipients. *Lancet* 1997; **350:** 1729–33.
20. Singh N. Preemptive therapy versus universal prophylaxis with ganciclovir for cytomegalovirus in solid organ transplant recipients. *Clin Infect Dis* 2001; **32:** 742–51.
21. Paya CV, *et al.* Preemptive use of oral ganciclovir to prevent cytomegalovirus infection in liver transplant patients: a randomized, placebo-controlled trial. *J Infect Dis* 2002; **185:** 854–60.
22. Keven K, *et al.* Cytomegalovirus prophylaxis using oral ganciclovir or valganciclovir in kidney and pancreas-kidney transplantation under antibody preconditioning. *Transplant Proc* 2004; **36:** 3107–12.
23. Monforte V, *et al.* Preemptive therapy with intravenous ganciclovir for the prevention of cytomegalovirus disease in lung transplant recipients. *Transplant Proc* 2005; **37:** 4039–42.
24. McCarthy M. Oral ganciclovir fails to prevent CMV in HIV trial. *Lancet* 1995; **346:** 895.
25. Spector SA, *et al.* Oral ganciclovir for the prevention of cytomegalovirus disease in persons with AIDS. *N Engl J Med* 1996; **334:** 1491–7.
26. Michaels MG, *et al.* Treatment of children with congenital cytomegalovirus infection with ganciclovir. *Pediatr Infect Dis J* 2003; **22:** 504–8.
27. Kimberlin DW, *et al.* Effect of ganciclovir therapy on hearing in symptomatic congenital cytomegalovirus disease involving the central nervous system: a randomized, controlled trial. *J Pediatr* 2003; **143:** 16–25.

Epstein-Barr virus infections. There have been anecdotal reports[1-4] of some improvement in patients with Epstein-Barr virus (EBV) infection given ganciclovir, although no antiviral therapy is entirely satisfactory (p.854).

1. Pirsch JD, *et al.* Treatment of severe Epstein-Barr virus-induced lymphoproliferative syndrome with ganciclovir: two cases after solid organ transplantation. *Am J Med* 1989; **86:** 241–4.
2. Ishida Y, *et al.* Ganciclovir for chronic active Epstein-Barr virus infection. *Lancet* 1993; **341:** 560–1.
3. MacGinley R, *et al.* Epstein-Barr virus encephalitis in a renal allograft recipient diagnosed by polymerase chain reaction on cerebrospinal fluid and successfully treated with ganciclovir. *Nephrol Dial Transplant* 2001; **16:** 197–8.
4. Adams LA, *et al.* Ganciclovir and the treatment of Epstein-Barr virus hepatitis. *J Gastroenterol Hepatol* 2006; **21:** 1758–60.

Herpesvirus infections. Ganciclovir 0.15% gel is licensed in a number of countries for the treatment of superficial ocular infections with herpes simplex. In patients with herpes simplex keratitis it has been reported to be as effective as aciclovir 3% ointment,[1] the drug most commonly used in this infection (see Ocular Herpes Simplex Infections, p.854).

1. Hoh HB, *et al.* Randomised trial of ganciclovir and acyclovir in the treatment of herpes simplex dendritic keratitis: a multicentre study. *Br J Ophthalmol* 1996; **80:** 140–3.

Preparations

USP 31: Ganciclovir for Injection; Ganciclovir Oral Suspension.

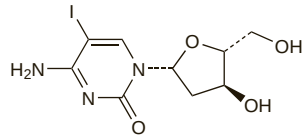
Proprietary Preparations (details are given in Part 3)
Arg.: Cigan clor; Cymevene; Cytovene†; Gasmilen; Grinevel; Virgan; ***Austral.:*** Cymevene; Vitrasert†; ***Austria:*** Cymevene; ***Belg.:*** Cymevene; Virgan; ***Braz.:*** Cymevene; Gancivir†; Ganvirax; ***Canad.:*** Cytovene; ***Chile:*** Cymevene; ***Cz.:*** Cymevene; Virgan; ***Denm.:*** Cymevene; ***Fin.:*** Cymevene; ***Fr.:*** Cymevan; Virgan; ***Ger.:*** Cymeven; ***Gr.:*** Cymevene; ***Hong Kong:*** Cymevene; ***Hung.:*** Cymevene; ***Indon.:*** Cymevene; ***Irl.:*** Cymevene; ***Israel:*** Cymevene; ***Ital.:*** Citovirax; Cymevene; ***Mex.:*** Cymevene; ***Neth.:*** Cymevene; ***Norw.:*** Cymevene; ***NZ:*** Cymevene; ***Philipp.:*** Cymevene; Virgan; ***Pol.:*** Cymevene; Virgan; ***Port.:*** Cymevene; Virgan; ***S.Afr.:*** Cymevene; ***Singapore:*** Cymevene; ***Spain:*** Cymevene; Vitrasert†; ***Swed.:*** Cymevene; ***Switz.:*** Cymevene; ***Thai.:*** Cymevene; ***Turk.:*** Cymevene; ***UK:*** Cymevene; Virgan†; ***USA:*** Cytovene; Vitrasert; ***Venez.:*** Cymevene.

Ibacitabine *(rINN)*

Ibacitabina; Ibacitabinum; Iododesoxycytidine. 2′-Deoxy-5-iodocytidine.

Ибацитабин

$C_9H_{12}IN_3O_4$ = 353.1.
CAS — 611-53-0.
ATC — D06BB08.
ATC Vet — QD06BB08.



Profile

Ibacitabine is an antiviral used topically as a 1% gel in the treatment of herpes labialis (p.854).

Preparations

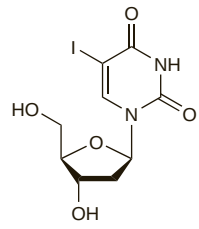
Proprietary Preparations (details are given in Part 3)
Fr.: Cuterpes.

Idoxuridine *(BAN, USAN, rINN)*

Allergan 211; GF-115; Idoksuridiini; Idoksuridinas; Idoxuridin; Idoxuridina; Idoxuridinum; IDU; 5-IDUR; 5-IUDR; NSC-39661; SKF-14287. 2′-Deoxy-5-iodouridine.

Идоксуридин

$C_9H_{11}IN_2O_5$ = 354.1.
CAS — 54-42-2.
ATC — D06BB01; J05AB02; S01AD01.
ATC Vet — QD06BB01; QJ05AB02; QS01AD01.



Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), *Int.*, *Jpn*, and *US.*
Ph. Eur. 6.2 (Idoxuridine). A white or almost white crystalline powder. M.p. about 180°, with decomposition. Slightly soluble in water and in alcohol; dissolves in dilute solutions of alkali hydroxides. A 0.1% solution in water has a pH of 5.5 to 6.5. Protect from light.
USP 31 (Idoxuridine). A white, practically odourless, crystalline powder. Slightly soluble in water and in alcohol; practically insoluble in chloroform and in ether. Store in airtight containers. Protect from light.

Stability. Iodine vapour is liberated on heating idoxuridine. It has been reported that some decomposition products such as iodouracil are more toxic than idoxuridine and reduce its antiviral activity.

Adverse Effects

Hypersensitivity reactions such as irritation, pain, and pruritus may occur occasionally when idoxuridine is applied to the eyes. Other adverse effects include stinging, conjunctivitis, oedema and inflammation of the eye or eyelids, photophobia, pruritus, and rarely, occlusion of the lachrymal duct. Prolonged or excessive use may damage the cornea.

Idoxuridine applied to the skin may produce irritation, stinging, and hypersensitivity reactions. Taste disturbance may also occur. Excessive application of topical idoxuridine to the skin may cause skin maceration.

Idoxuridine is a potential carcinogen and teratogen.

Carcinogenicity. Squamous carcinoma has been reported in association with topical idoxuridine treatment.[1]

1. Koppang HS, Aas E. Squamous carcinoma induced by topical idoxuridine therapy? *Br J Dermatol* 1983; **108:** 501–3.

Precautions

Idoxuridine should be used with caution in conditions where there is deep ulceration involving the stromal layers of the cornea, as delayed healing has resulted in corneal perforation. Prolonged topical use should be avoided.

The potential teratogenicity of idoxuridine should be taken into account when treating pregnant patients or patients likely to become pregnant. Corticosteroids should be applied with caution in patients also receiving idoxuridine as they may accelerate the spread of viral infection.

Interactions

Preparations containing boric acid should not be applied to the eye in patients also receiving ocular preparations of idoxuridine as irritation ensues.

Antiviral Action

After intracellular phosphorylation to the triphosphate, idoxuridine is incorporated into viral DNA instead of thymidine so inhibiting replication of sensitive viral strains. Idoxuridine is also incorporated into mammalian DNA. Idoxuridine is active against herpes simplex and varicella zoster viruses. It has also been shown to inhibit vaccinia virus, CMV, and adenovirus.

Pharmacokinetics

Penetration of idoxuridine into the cornea and skin is reported to be poor. Idoxuridine is rapidly metabolised in the body to iodouracil, uracil, and iodide, which are excreted in the urine.

Uses and Administration

Idoxuridine is a pyrimidine nucleoside structurally related to thymidine. It is used topically in the treatment of herpes simplex keratitis and cutaneous infections with herpes simplex (p.854) and herpes zoster (see Varicella-zoster Infections, p.855), but has generally been superseded by other antivirals.

In the treatment of herpes simplex keratitis, idoxuridine is applied as a 0.1% ophthalmic solution or a 0.5% eye ointment.

Idoxuridine 5% in dimethyl sulfoxide (to aid absorption) may be painted onto the lesions of cutaneous herpes simplex and herpes zoster four times daily for 4 days.

Preparations

BP 2008: Idoxuridine Eye Drops;
USP 31: Idoxuridine Ophthalmic Ointment; Idoxuridine Ophthalmic Solution.

Proprietary Preparations (details are given in Part 3)
Arg.: Idulea; ***Austral.:*** Herplex-D†; Stoxil; ***Belg.:*** Virexen†; ***Braz.:*** Herpesine; ***Canad.:*** Herplex; ***Ger.:*** Virunguent; Zostrum; ***Hung.:*** Oftan IDU†; ***India:*** Ridinox; ***Indon.:*** Isotic Ixodine; ***Irl.:*** Zostrum†; ***Israel:*** Virusan†; ***Ital.:*** Iducher; Idustatin; ***Malaysia:*** Virunguent†; ***Mex.:*** Idina†; ***Neth.:*** Virexen; ***NZ:*** Virasolve; ***Port.:*** Virexen†; Virunguent†; ***Rus.:*** Oftan IDU (Офтан ИДУ); ***Singapore:*** Virunguent; ***Spain:*** Virexen; ***Switz.:*** Iderpes†; Virunguent; ***UK:*** Herpid; ***Venez.:*** Herpidum†.

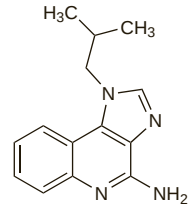
Multi-ingredient: ***Arg.:*** Itro†; ***Austral.:*** Virasolve; ***Ger.:*** Virunguent P†; ***Hong Kong:*** Virasolve†.

Imiquimod *(BAN, USAN, rINN)*

Imikimod; Imikimodi; Imiquimodum; R-837; S-26308. 4-Amino-1-isobutyl-1*H*-imidazo[4,5-*c*]quinoline.

Имихимод

$C_{14}H_{16}N_4$ = 240.3.
CAS — 99011-02-6.
ATC — D06BB10.
ATC Vet — QD06BB10.



Adverse Effects

Adverse effects after topical application of imiquimod include local skin erosion, erythema, excoriation, flaking, and oedema. There have been reports of localised hypopigmentation and hyperpigmentation. Skin reactions away from the site of application have been reported. Systemic effects after topical application include headache, flu-like symptoms, and myalgia.

Hypotension has occurred after repeated ingestion.

Hypersensitivity. Angioedema, initially of both the hands and feet and later the tongue, occurred in a 61-year-old man 3 weeks after starting treatment with a 5% imiquimod cream for squamous cell carcinoma *in situ* (Bowen's disease).[1]

1. Barton JC. Angioedema associated with imiquimod. *J Am Acad Dermatol* 2004; **51:** 477–8.

Uses and Administration

Imiquimod is an immune response modifier used topically in the treatment of external genital and perianal warts (p.1584), superficial basal cell carcinomas, and actinic keratoses (see below). For the treatment of genital and perianal **warts**, it is applied as a

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.

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).

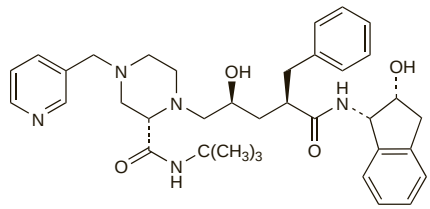
Индинавира Сульфат

$C_{36}H_{47}N_5O_4,H_2SO_4$ = 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]

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