atic review[71] was unable to come to a conclusion about safety and efficacy, noting that publication bias posed a problem.

Conventional treatments are only partially effective and may produce adverse effects, and many patients with MS try alternative therapies. The most common *dietary interventions* are supplementation with polyunsaturated fatty acids (such as omega-3 and omega-6 fatty acids, often as fish, evening primrose, or sunflower oils), allergen-free diets, vitamins, and micronutrients and antoxidants (such as selenium, ginkgo biloba extracts, and coenzyme Q10). A review of the relationship between these dietary interventions and MS concluded that there was insufficient evidence to determine their benefits or risks.[72] Polyunsaturated fatty acids seem to have no major effect on disease progression and recurrence of exacerbations over 2 years. Research into the value of vitamin D is ongoing after findings that higher levels of serum vitamin D are associated with a lower risk of MS.[73]

The use of *hyperbaric oxygen* therapy in MS was a matter of debate for many years. Some workers reported benefit, especially in bladder and bowel function or in cerebellar function whereas others were unable to substantiate any long-term benefit and reviews have concluded that there is no convincing evidence that hyperbaric oxygen therapy is useful.[74,75]

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Rheumatoid arthritis. Preliminary studies suggested that interferon beta might have a beneficial effect on rheumatoid arthritis,[1] the conventional management of which is described on p.11. However, a subsequent randomised, double-blind study[2] found that adding subcutaneous interferon beta to methotrexate treatment in patients with rheumatoid arthritis had no clinical or radiological benefit over adding placebo.

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2. van Holten J, *et al.* A multicentre, randomised, double blind, placebo controlled phase II study of subcutaneous interferon beta-1a in the treatment of patients with active rheumatoid arthritis. *Ann Rheum Dis* 2005; **64:** 64–9.

Warts. For the use of interferon beta in the management of warts, see Interferon Alfa, p.891.

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Avonex; Betaferon; Blastoferon; Rebif; ***Austral.:*** Avonex; Betaferon; Rebif; ***Austria:*** Avonex; Betaferon; Rebif; ***Belg.:*** Avonex; Betaferon; Rebif; ***Braz.:*** Avonex; Betaferon; Rebif; Serobif; ***Canad.:*** Avonex; Betaseron; Rebif; ***Chile:*** Avonex; Betaferon; Rebif†; ***Cz.:*** Avonex; Betaferon; Rebif; ***Denm.:*** Avonex; Betaferon; Rebif; ***Fin.:*** Avonex; Betaferon; Rebif; ***Fr.:*** Avonex; Betaferon; Rebif; ***Ger.:*** Avonex; Betaferon; Fiblaferon; Rebif; ***Gr.:*** Avonex; Betaferon; Rebif; ***Hong Kong:*** Betaferon; Rebif; ***Hung.:*** Avonex; Betaferon; Rebif; ***India:*** Betaferon; Rebif; ***Indon.:*** Rebif; ***Irl.:*** Avonex; Betaferon; Rebif; ***Israel:*** Avonex; Betaferon; Rebif; ***Ital.:*** Avonex; Betaferon; Betron R†; Rebif; Serobif; ***Jpn:*** Feron; ***Malaysia:*** Betaferon; Rebif; ***Mex.:*** Avonex; Betaferon; Rebif; Unibeta; ***Neth.:*** Avonex; Betaferon; Rebif; ***Norw.:*** Avonex; Betaferon; Rebif; ***NZ:*** Avonex; Betaferon; Rebif; ***Philipp.:*** Betaferon; Rebif; ***Pol.:*** Avonex†; Betaferon; Rebif; ***Port.:*** Avonex; Betaferon; Rebif; ***Rus.:*** Avonex (Авонекс); Betaferon (Бетаферон); Rebif (Ребиф); ***S.Afr.:*** Avonex; Betaferon; Rebif; ***Singapore:*** Betaferon; Rebif; ***Spain:*** Avonex; Betaferon; Rebif; ***Swed.:*** Avonex; Betaferon; Rebif; ***Switz.:*** Avonex; Betaferon; Rebif; ***Thai.:*** Betaferon; Rebif; ***Turk.:*** Avonex; Betaferon; Rebif; ***UK:*** Avonex; Betaferon; Rebif; ***USA:*** Avonex; Betaseron; Rebif; ***Venez.:*** Avonex; Rebif.

Interferon Gamma *(BAN, rINN)*

IFN-γ; Interferón-γ; Interferon-γ; Interféron gamma; Interferón gamma; Interferoni gamma; Interferonigamma; Interferonum Gamma.

Интерферон Гамма

CAS — 98059-18-8 (interferon gamma-1a); 98059-61-1 (interferon gamma-1b).
ATC — L03AB03.
ATC Vet — QL03AB03.

NOTE. Interferon gamma was previously known as immune interferon.
Interferon gamma-1b is *USAN* and was previously known as interferon gamma-2a.

Pharmacopoeias. *Eur.* (see p.vii) includes Interferon Gamma-1b Concentrated Solution.
Ph. Eur. 6.2 (Interferon Gamma-1b Concentrated Solution; Interferoni Gamma-1b Solutio Concentrata). It is a solution of the *N*-terminal methionyl form of interferon gamma. It is produced by a method based on recombinant DNA technology using bacteria as host cells. It is a clear, colourless or slightly yellowish liquid. The pH of the solution is 4.5 to 5.5. Store in airtight containers at a temperature of –70°. Protect from light.

Nomenclature. Interferon gamma may be derived from immunologically stimulated T-lymphocytes (hence its former name of immune interferon) or produced by recombinant DNA technology. Similarly to interferon alfa, protein variants of interferon gamma are designated by a number and further qualified by a letter to indicate the amino-acid sequences at terminal positions 1 and 139:

- interferon gamma-1a has at position 1 hydrogen, cysteine, tyrosine, and cysteine and at position 139 arginine, alanine, serine, glutamine, and a hydroxyl group
- interferon gamma-1b, formerly known as interferon gamma-2a, has at position 1 hydrogen and methionine and at position 139 a hydroxyl group

Interferon gamma derived through recombinant DNA technology is labelled (rbe).

Adverse Effects

As for interferons in general (see Interferon Alfa, p.885)

Precautions

As for interferons in general (see Interferon Alfa, p.887). Interferon gamma in high doses has been shown to increase the incidence of abortions in *primates* and should be avoided during pregnancy.

Interactions

As for interferons in general (see Interferon Alfa, p.888).

Antiviral Action

As for interferons in general (see Interferon Alfa, p.888).

Pharmacokinetics

Interferons are not absorbed from the gastrointestinal tract. Peak plasma concentrations of interferon gamma-1b occur about 4 hours after intramuscular injection and about 7 to 8 hours after subcutaneous injection. Half-lives of 38 minutes (intravenous dosage), 2.9 hours (intramuscular dosage), and 4.9 to 5.9 hours (subcutaneous dosage) have been reported.

Uses and Administration

Interferon gamma is a cytokine with antiviral and immunomodulating effects. Interferon gamma-1b is used for its action as a macrophage-stimulating factor as an adjunct to antimicrobial therapy in chronic granulomatous disease. It is also used to delay time to disease progression and reduce the frequency of serious infections in patients with severe malignant osteopetrosis.

Interferon gamma-1b is given in a dose of 50 micrograms/m^2 body-surface (1 million units/m^2) three times weekly by subcutaneous injection. Patients with a body-surface less than 0.5 m^2 should receive 1.5 micrograms/kg body-weight three times weekly.

Interferon gamma-1b is also under investigation for the treatment of cryptogenic fibrosing alveolitis (see below).

Interferon gamma-n1 has also been used for the treatment of cutaneous T-cell lymphomas.

◊ Reviews.

1. Marciano BE, *et al.* Long-term interferon-γ therapy for patients with chronic granulomatous disease. *Clin Infect Dis* 2004; **39:** 692–9.

Bacterial infections. In addition to its use to control infections in chronic granulomatous disease, interferon gamma was used with some success as an adjunct to antibacterials in a patient with Whipple's disease[1] but was of no benefit in a study in burn-related infections.[2] For the conventional management of these infections, see Whipple's Disease, p.200 and Skin Infections, p.194.

1. Schneider T, *et al.* Treatment of refractory Whipple disease with interferon-γ. *Ann Intern Med* 1998; **129:** 875–7.
2. Wasserman D, *et al.* Interferon-γ in the prevention of severe burn-related infections: a European phase III multicenter trial. *Crit Care Med* 1998; **26:** 434–9.

MYCOBACTERIAL INFECTIONS. Experience with interferons for *nontuberculous mycobacterial infections* in patients with AIDS is limited. Interferon gamma given with antimycobacterials produced beneficial responses in 3 patients with *Mycobacterium avium* complex infections, but produced no response or only a transient response in 3 others given interferon gamma alone.[1,2]

Beneficial responses have also been reported after use of interferon alfa[3] or gamma[4] as an adjunct to antimycobacterial therapy in HIV-negative patients with mycobacterial infections unresponsive to conventional therapy. Interferon alfa has been tried as an adjunct to conventional therapy in *multibacillary leprosy.*[5]

Inhaled interferon alfa[6] or gamma[7] may be a useful adjunct to conventional antimycobacterial treatment for *pulmonary tuberculosis.*

For discussion of these infections and their standard treatment, see Leprosy, p.176, Nontuberculous Mycobacterial Infections, p.181, and Tuberculosis, p.196.

1. Squires KE, *et al.* Interferon-γ and Mycobacterium avium-intracellulare infection. *J Infect Dis* 1989; **159:** 599–600.
2. Squires KE, *et al.* Interferon-γ treatment for Mycobacterium avium-intracellulare complex bacillemia in patients with AIDS. *J Infect Dis* 1992; **166:** 686–7.
3. Maziarz RT, *et al.* Reversal of infection with Mycobacterium avium intracellulare by treatment with alpha-interferon in a patient with hairy cell leukemia. *Ann Intern Med* 1988; **109:** 292–4.
4. Holland SM, *et al.* Treatment of refractory disseminated nontuberculous mycobacterial infection with interferon gamma: a preliminary report. *N Engl J Med* 1994; **330:** 1348–55.
5. Ganapati R, *et al.* A multicenter study of recombinant interferon-alpha2b in the treatment of multibacillary leprosy. *Int J Lepr* 1997; **65:** 495–7.
6. Giosuè S, *et al.* Effects of aerosolized interferon-α in patients with pulmonary tuberculosis. *Am J Respir Crit Care Med* 1998; **158:** 1156–62.
7. Condos R, *et al.* Treatment of multidrug-resistant pulmonary tuberculosis with interferon-γ via aerosol. *Lancet* 1997; **349:** 1513–15.

Cryptogenic fibrosing alveolitis. In a preliminary study[1] in patients with cryptogenic fibrosing alveolitis (CFA; idiopathic pulmonary fibrosis—see Diffuse Parenchymal Lung Disease, p.1502) who had not responded to treatment with corticosteroids or to other immunosuppressive therapy, lung capacity increased in 9 patients given interferon gamma-1b with prednisolone for 12 months, but deteriorated in 9 who were treated with prednisolone alone for the same period. The study was, however, criticised for its methodology and the statistical significance of its findings questioned.[2] A later study[3] involving 330 patients with CFA found that interferon gamma 1-b did not affect progression-free survival or pulmonary function; however, a trend toward lower mortality was seen in patients who received interferon gamma-1b compared with those given placebo. A subsequent study[4] to characterise the molecular effects of subcutaneous interferon gamma-1b versus placebo reported that interferon gamma-1b affected CFA through multiple pathways and could be of potential benefit. A randomised, prospective study[5] comparing interferon gamma-1b and colchicine (given for 24 months) in patients with mild-to-moderate CFA reported that 15.6% of patients treated with interferon gamma-1b and 38.8% of those given colchicine died. Patients treated with interferon gamma-1b also showed a higher forced vital capacity after 24 months of treatment. A review[6] of the use of interferon gamma-1b in the management of CFA found that efficacy of interferon gamma-1b was inconsistent with regard to changes in pulmonary function and mortality, although studies suggested that interferon gamma-1b may be of benefit in earlier-stage disease. A meta-analysis[7] of randomised controlled studies evaluating the use of interferon gamma-1b in the treatment of CFA concluded that interferon gamma-1b therapy was associated with reduced mortality.

1. Ziesche R, *et al.* A preliminary study of long-term treatment with interferon gamma-1b and low-dose prednisolone in patients with idiopathic pulmonary fibrosis. *N Engl J Med* 1999; **341:** 1264–9.
2. King TE. Interferon gamma-1b for the treatment of idiopathic pulmonary fibrosis. *N Engl J Med* 2000; **342:** 974–5.
3. Raghu G, *et al.* A placebo-controlled trial of interferon gamma-1b in patients with idiopathic pulmonary fibrosis. *N Engl J Med* 2004; **350:** 125–33.
4. Strieter RM, *et al.* Effects of interferon-γ 1b on biomarker expression in patients with idiopathic pulmonary fibrosis. *Am J Respir Crit Care Med* 2004; **170:** 133–40.
5. Antoniou KM, *et al.* Long-term clinical effects of interferon gamma-1b and colchicine in idiopathic pulmonary fibrosis. *Eur Respir J* 2006; **28:** 496–504.
6. Pacanowski MA, Amsden GW. Interferon gamma-1b in the treatment of idiopathic pulmonary fibrosis. *Ann Pharmacother* 2005; **39:** 1678–86.
7. Bajwa EK, *et al.* Interferon-γ1b therapy in idiopathic pulmonary fibrosis: a metaanalysis. *Chest* 2005; **128:** 203–6.

Leishmaniasis. Interferon gamma has been tried both systemically and locally as an adjunct to standard treatment of leishmaniasis (p.824) with encouraging results. A review[1] of the use of interferon gamma in non-viral infections concluded that interferon gamma was effective when combined with antimony compounds for treatment failures in visceral leishmaniasis and could enhance the response to initial therapy in untreated patients. However, the response to adjunctive interferon gamma was limited in patients with a high degree of resistance to antimony compounds.[2] For cutaneous infections, intralesional interferon gamma has been shown to be effective[3] but less so than intralesional antimony compounds.[4] Subcutaneous interferon gamma (with antimony given intravenously) was no more effective than antimony alone when given as a short course over 10 days.[5] However, encouraging responses have been reported in patients who have failed to respond to antimony compounds alone.[6]

1. Murray HW. Interferon-gamma and host antimicrobial defense: current and future clinical applications. *Am J Med* 1994; **97:** 459–67.
2. Sundar S, *et al.* Response to interferon-γ plus pentavalent antimony in Indian visceral leishmaniasis. *J Infect Dis* 1997; **176:** 1117–19.
3. Harms G, *et al.* Effects of intradermal gamma-interferon in cutaneous leishmaniasis. *Lancet* 1989; **i:** 1287–92.
4. Harms G, *et al.* A randomized trial comparing a pentavalent antimonial drug and recombinant interferon-γ in the local treatment of cutaneous leishmaniasis. *Trans R Soc Trop Med Hyg* 1991; **85:** 214–16.
5. Arana BA, *et al.* Efficacy of a short course (10 days) of high-dose meglumine antimonate with or without interferon-γ in treating cutaneous leishmaniasis in Guatemala. *Clin Infect Dis* 1994; **18:** 381–4.
6. Falcoff E, *et al.* Clinical healing of antimony-resistant cutaneous or mucocutaneous leishmaniasis following the combined administration of interferon-γ and pentavalent antimonial compounds. *Trans R Soc Trop Med Hyg* 1994; **88:** 95–7.

Osteopetrosis. Interferon gamma has been tried in the treatment of malignant osteopetrosis (p.1509). A study[1] in 14 patients found that interferon gamma-1b increased bone resorption. In 11 who received this treatment for 18 months there was stabilisation or improvement in clinical condition and a reduction in the frequency of serious infection.

1. Key LL, *et al.* Long-term treatment of osteopetrosis with recombinant human interferon gamma. *N Engl J Med* 1995; **332:** 1594–9.

Skin disorders. Interferons have been tried in skin disorders in which IgE levels are raised. Subcutaneous interferon gamma improved *eczema* and reduced serum-IgE concentration in one patient, but the condition gradually returned within a week of stopping treatment.[1] In two studies[2,3] subcutaneous interferon gamma given to patients with severe atopic dermatitis and raised serum-IgE concentrations resulted in improvement of the skin condition; IgE concentrations were reduced in one study[2] but remained high in the other.[3] Subcutaneous interferon alfa, however, was unsuccessful in 2 patients with very severe atopic dermatitis; serum-IgE concentrations and severity of the skin condition remained unaffected.[4] Interferon alfa has been tried in subacute *cutaneous lupus erythematosus*[5,6] and *discoid lupus erythematosus.*[6] Although marked improvement generally occurred, the condition tended to recur within several weeks of stopping treatment. For discussion of the conventional treatment of eczema, see p.1579 and of lupus erythematosus, see Systemic Lupus Erythematosus, p.1513.

There have been reports[7,8] of the successful use of interferon alfa to control the symptoms of *urticaria* associated with mastocytosis (p.1138).

Interferons have also been proposed for antifibrotic therapy in the management of diffuse *scleroderma* (see p.1817). A multicentre study of interferon gamma in scleroderma[9] found that cutaneous symptoms might be improved but that treatment was associated with an unacceptable incidence of adverse effects. Interferon gamma has also been tried in *eosinophilic pustular folliculitis.*[10]

Interferons have also been used for the treatment of warts (see under Interferon Alfa, p.891).

1. Souillet G, *et al.* Alpha-interferon treatment of patient with hyper IgE syndrome. *Lancet* 1989; **i:** 1384.
2. Reinhold U, *et al.* Recombinant interferon-γ in severe atopic dermatitis. *Lancet* 1990; **335:** 1282.
3. Boguniewicz M, *et al.* Recombinant gamma interferon in treatment of patients with atopic dermatitis and elevated IgE levels. *Am J Med* 1990; **88:** 365–70.
4. MacKie RM. Interferon-α for atopic dermatitis. *Lancet* 1990; **335:** 1282–3.
5. Nicolas J-F, Thivolet J. Interferon alfa therapy in severe unresponsive subacute cutaneous lupus erythematosus. *N Engl J Med* 1989; **321:** 1550–1.
6. Thivolet J, *et al.* Recombinant interferon α2a is effective in the treatment of discoid and subacute cutaneous lupus erythematosus. *Br J Dermatol* 1990; **122:** 405–9.
7. Kolde G, *et al.* Treatment of urticaria pigmentosa using interferon alpha. *Br J Dermatol* 1995; **133:** 91–4.
8. Lippert U, Henz BM. Long-term effect of interferon alpha treatment in mastocytosis. *Br J Dermatol* 1996; **134:** 1164–5.
9. Polisson RP, *et al.* A multicenter trial of recombinant human interferon gamma in patients with systemic sclerosis: effects on cutaneous fibrosis and interleukin 2 receptor levels. *J Rheumatol* 1996; **23:** 654–8.
10. Fushimi M, *et al.* Eosinophilic pustular folliculitis effectively treated with recombinant interferon-γ: suppression of mRNA expression of interleukin 5 in peripheral blood mononuclear cells. *Br J Dermatol* 1996; **134:** 766–72.

Preparations

Proprietary Preparations (details are given in Part 3)

Arg.: Imufor†; Imukin; ***Austral.:*** Imukin; ***Austria:*** Imukin; ***Belg.:*** Immukine; ***Cz.:*** Imukin; ***Denm.:*** Imukin; ***Fin.:*** Imukin; ***Fr.:*** Imukin; ***Ger.:*** Imukin; ***Gr.:*** Imukin; ***Hong Kong:*** Immukin; ***Irl.:*** Immukin; ***Ital.:*** Gammakine†; Imukin; ***Jpn:*** Biogamma; Ogamma†; ***Neth.:*** Immukine; ***Norw.:*** Imukin; ***NZ:*** Imukin; ***Port.:*** Imukin; ***Spain:*** Imukin; ***Swed.:*** Imukin; ***Switz.:*** Imukin; ***UK:*** Immukin; ***USA:*** Actimmune.

Lamivudine *(BAN, USAN, rINN)*

3TC; (–)-2′-Deoxy-3′-thiacytidine; GR-109714X; Lamivudiini; Lamivudin; Lamivudina; Lamivudinum; Lamiwudyna; Lavmivudin. (–)-1-[(2R,5S)-2-(Hydroxymethyl)-1,3-oxathiolan-5-yl]cytosine.

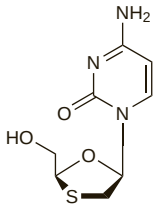
Ламивудин

$C_8H_{11}N_3O_3S$ = 229.3.

CAS — 131086-21-0; 134678-17-4.

ATC — J05AF05.

ATC Vet — QJ05AF05.



Pharmacopoeias. In *Eur.* (see p.vii) and *US.*
Ph. Eur. 6.2 (Lamivudine). A white or almost white powder. It exhibits polymorphism. Soluble in water, slightly soluble in alcohol; sparingly soluble in methyl alcohol. Protect from light.
USP 31 (Lamivudine). A white to off-white solid. Soluble in water. Protect from light.

Adverse Effects

Adverse effects commonly associated with lamivudine either as monotherapy or with other antiretrovirals for the treatment of HIV include abdominal pain, nausea, vomiting, diarrhoea, headache, fever, rash, alopecia, malaise, insomnia, cough, nasal symptoms, arthralgia, and musculoskeletal pain. There have also been reports of pancreatitis, anaemia, neutropenia, and thrombocytopenia. Increases in liver enzymes and serum amylase may occur. Lactic acidosis, usually associated with severe hepatomegaly and steatosis, has been reported during treatment with nucleoside reverse transcriptase inhibitors.

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 lamivudine, 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 lamivudine. Metabolic abnormalities such as hypertriglyceridaemia, hypercholesterolaemia, insulin resistance, hyperglycaemia, and hyperlactataemia have also been reported. NRTIs have also been associated with mitochondrial dysfunction manifesting as abnormal behaviour, anaemia, convulsions, hyperlipasaemia, hypertonia, and neutropenia. Elevated creatine phosphokinase, myalgia, myositis, and rarely rhabdomyolysis have been reported, particularly when nucleoside analogues have been given with HIV-protease inhibitors. 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 NRTIs see Zidovudine, p.914.

Patients taking a lower dose of lamivudine for the treatment of chronic hepatitis B often have abdominal discomfort and pain, diarrhoea, fatigue, headache, nausea, malaise, respiratory-tract infections, and vomiting. The most frequently reported laboratory abnormalities are elevated creatine phosphokinase, increases in serum lipase, and raised liver enzymes, in particular alanine aminotransferase. There have been rare reports of lactic acidosis, pancreatitis, and muscle disorders such as cramps, myalgia, and rhabdomyolysis.

Effects on the blood. Although anaemia associated with lamivudine usually occurs when it is used with zidovudine, there has been a report[1] of severe anaemia in a 62-year-old HIV-infected man given lamivudine alone.

1. Weitzel T, *et al.* Severe anaemia as a newly recognized side-effect caused by lamivudine. *AIDS* 1999; **13:** 2309–11.

Effects on the hair. Hair loss was associated with lamivudine treatment in 5 patients.[1]

1. Fong IW. Hair loss associated with lamivudine. *Lancet* 1994; **344:** 1702.

Effects on the nervous system. Exacerbation of peripheral neuropathy has been reported in a patient after substitution of lamivudine for zalcitabine.[1]

1. Cupler EJ, Dalakas MC. Exacerbation of peripheral neuropathy by lamivudine. *Lancet* 1995; **345:** 460–1.

Hypersensitivity. Angioedema, urticaria, and anaphylactoid reaction occurred in a patient 30 minutes after receiving the first dose of lamivudine.[1]

1. Kainer MA, Mijch A. Anaphylactoid reaction, angioedema, and urticaria associated with lamivudine. *Lancet* 1996; **348:** 1519.

Precautions

Lamivudine therapy should be stopped in patients who develop abdominal pain, nausea, or vomiting or with abnormal biochemical test results until pancreatitis has been excluded.

Treatment with lamivudine may be associated with lactic acidosis and should be stopped if there is a rapid increase in aminotransferase concentrations, progressive hepatomegaly, or metabolic or lactic acidosis of unknown aetiology. Lamivudine should be used with caution in patients with hepatomegaly or other risk factors for hepatic disease. Patients co-infected with HIV and chronic hepatitis B or C and treated with combination antiretroviral therapy are at increased risk for severe and potentially fatal hepatic adverse events. In patients with chronic hepatitis B, there is a risk of rebound hepatitis when lamivudine is stopped, and liver function should be monitored in such patients. The possibility of HIV infection should be excluded before beginning lamivudine therapy for hepatitis B, since the lower doses used to treat the latter may permit the development of lamivudine-resistant strains of HIV.

Dosage reduction may be necessary in patients with impaired renal function.

Interactions

The renal excretion of lamivudine may be inhibited by other drugs mainly eliminated by active renal secretion, for example trimethoprim. Usual prophylactic doses of trimethoprim are unlikely to necessitate reductions in lamivudine dosage unless the patient has renal impairment, but the co-administration of lamivudine with the high doses of trimethoprim (as co-trimoxazole) used in pneumocystis pneumonia and toxoplasmosis should be avoided. Although there is usually no clinically significant interaction with zidovudine, severe anaemia has occasionally been reported in patients given lamivudine with zidovudine (see Zidovudine, Interactions, p.915). Lamivudine may antagonise the antiviral action of zalcitabine and the two drugs should not be used together. Once daily triple nucleoside regimens of lamivudine and tenofovir with either abacavir or didanosine are associated with a high level of treatment failure and of emergence of resistance, and should be avoided.

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

Antiviral Action

Lamivudine is converted intracellularly in stages to the triphosphate. This triphosphate halts the DNA synthesis of retroviruses, including HIV, through competitive inhibition of reverse transcriptase and incorporation into viral DNA. Lamivudine is also active against hepatitis B virus. Resistance to lamivudine has been reported in isolates of HIV and hepatitis B virus.

Pharmacokinetics

Lamivudine is rapidly absorbed after oral doses and peak plasma concentrations are achieved in about 1 hour. Absorption is delayed, but not reduced, by ingestion with food. Bioavailability is between 80 and 87%. Binding to plasma protein is reported to be up to 36%. Lamivudine crosses the blood-brain barrier with a ratio of CSF to serum concentrations of about 0.12. It crosses the placenta and is distributed into breast milk.

Lamivudine is metabolised intracellularly to the active antiviral triphosphate. Hepatic metabolism is low and it is cleared mainly unchanged by active renal excretion. An elimination half-life of 5 to 7 hours has been reported after a single dose.

◊ References.

1. Mueller BU, *et al.* Serum and cerebrospinal fluid pharmacokinetics of intravenous and oral lamivudine in human immunodeficiency virus-infected children. *Antimicrob Agents Chemother* 1998; **42:** 3187–92.
2. Johnson MA, *et al.* Clinical pharmacokinetics of lamivudine. *Clin Pharmacokinet* 1999; **36:** 41–66.
3. Bruno R, *et al.* Comparison of the plasma pharmacokinetics of lamivudine during twice and once daily administration in patients with HIV. *Clin Pharmacokinet* 2001; **40:** 695–700.
4. Asari A, *et al.* Pharmacokinetics of lamivudine in subjects receiving peritoneal dialysis in end-stage renal failure. *Br J Clin Pharmacol* 2007; **64:** 738–44.
5. Burger DM, *et al.* Age-dependent pharmacokinetics of lamivudine in HIV-infected children. *Clin Pharmacol Ther* 2007; **81:** 517–20.
6. Tremoulet AH, *et al.* Pediatric AIDS Clinical Trials Group. Population pharmacokinetics of lamivudine in human immunodeficiency virus-exposed and -infected infants. *Antimicrob Agents Chemother* 2007; **51:** 4297–4302.

Uses and Administration

Lamivudine is a nucleoside reverse transcriptase inhibitor structurally related to cytosine with antiviral activity against HIV-1 and hepatitis B virus. It is used in the treatment of HIV infection and AIDS, (p.856) and chronic hepatitis B infection (p.851). Viral resistance emerges rapidly when lamivudine is used alone in the treatment of HIV infection, and it is therefore used with other antiretrovirals.

For HIV infection, the dose of lamivudine for adults is 300 mg by mouth daily as a single dose or in two divided doses.

For chronic hepatitis B, the adult dose is 100 mg once daily by mouth. In patients with concomitant HIV and hepatitis B infection the dosage regimen appropriate for HIV should be used.

For details of doses in infants, children, and adolescents see below.

Reduction of dosage is recommended for patients with renal impairment (see below).

Fixed-dose combination products for the treatment of HIV infection and AIDS have been developed in order to improve patient adherence and avoid monotherapy, thereby decreasing the risk of acquired drug resistance. Products containing lamivudine in combination with zidovudine or abacavir and with abacavir plus zidovudine are available in some countries.

◊ Reviews.

1. Dando TM, Scott LJ. Abacavir plus lamivudine: a review of their combined use in the management of HIV infection. *Drugs* 2005; **65:** 285–302.

Administration in children. For the treatment of HIV infection in infants and children lamivudine is given orally either as tablets or a solution, together with other antiretroviral drugs. Doses are based on body-weight:

- in infants and children over 3 months of age and weighing less than 14 kg or in those unable to swallow tablets the oral solution may be given in a dose of 4 mg/kg twice daily to a maximum daily dose of 300 mg
- in children weighing 14 to 21 kg the tablet formulation may be given in a dose of 75 mg twice daily
- in children weighing 21 to 30 kg the tablet formulation may be given in a dose of 75 mg in the morning and 150 mg at night
- in children weighing over 30 kg the tablet formulation may be given in a dose of 150 mg twice daily

Dosage of lamivudine should be reduced in HIV-infected patients (at least 3 months of age and weighing less than 30 kg) with moderate to severe renal impairment (creatinine clearance (CC) below 50 mL/minute):

- CC 30 to 49 mL/minute: 4 mg/kg for the first dose then 4 mg/kg once daily
- CC 15 to 29 mL/minute: 4 mg/kg for the first dose then 2.6 mg/kg once daily