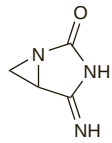
Imexon *(rINN)*

BM-06002; Imexón; Imexonum. (5*R*,*S*)-4-Amino-1,3-diazabicyclo[3.1.0]hex-3-en-2-one.

Имексон

$C_4H_5N_3O$ = 111.1.

CAS — 59643-91-3.



Profile

Imexon is a cyanoaziridine compound that appears to act as an antineoplastic in several ways, one of which is by causing mitochondrial disruption in the cancer cell, thus inducing apoptosis. It is under investigation for the treatment of malignant neoplasms, including ovarian cancer, pancreatic adenocarcinoma, multiple myeloma, and metastatic malignant melanoma.

Interleukin-2

BG-8301 (teceleukin); Epidermal Thymocyte Activating Factor; ETAF; IL-2; Interleucina 2; T-cell Growth Factor.

Description. Interleukin-2 is a naturally-occurring 133-amino-acid glycoprotein with a molecular weight of about 15 000. It is available from natural sources or as a product of recombinant DNA technology (rIL-2).

In addition to aldesleukin (below) modified forms of interleukin-2 produced by recombinant DNA technology have included celmoleukin and teceleukin.

Aldesleukin *(BAN, USAN, rINN)*

Aldesleukiini; Aldesleukina; Aldesleukine; Aldesleukinum; Aldeslökin; Des-alanyl-1, Serine-125 Human Interleukin-2; Recombinant Interleukin-2; 125-L-Serine-2–133-interleukin 2 (human reduced).

Альдеслейкин

CAS — 110942-02-4.

ATC — L03AC01.

ATC Vet — QL03AC01.

Description. Aldesleukin (modified human recombinant interleukin-2) is produced by recombinant DNA technology using an *Escherichia coli* strain containing an analogue of the human interleukin-2 gene. It differs from native interleukin-2 in that it is not glycosylated, it has no N-terminal alanine, and it has serine substituted for cysteine at position 125.

Incompatibility. Aldesleukin 33 800 units/mL in glucose 5% lost significant biological activity when mixed with other drugs including ganciclovir sodium, lorazepam, pentamidine isetionate, prochlorperazine edisilate, and promethazine hydrochloride.[1] However, the incompatibility was not detectable by spectrophotometric methods and only lorazepam was visually incompatible, suggesting that these methods may be invalid for assessing the compatibility of proteins.

1. Alex S, *et al.* Compatibility and activity of aldesleukin (recombinant interleukin-2) in presence of selected drugs during simulated Y-site administration: evaluation of three methods. *Am J Health-Syst Pharm* 1995; **52:** 2423–6.

Stability. Aldesleukin lost 75 to 100% of activity when reconstituted with glucose 5% or sodium chloride 0.9% in a plastic syringe and given over 24 hours with a syringe driver.[1,2] Loss of activity was not seen if aldesleukin was reconstituted with water alone[2] or with the addition of albumin.[1,2] It was suggested that loss of activity could be suspected because of lack of toxicity,[1,2] and that the lack of toxicity in some published studies could be due to this.[1,3] However, the authors of these studies indicated that they had reconstituted aldesleukin with albumin.[4,5] Reconstitution with low concentrations of albumin has been advocated to avoid bioavailability problems,[1,4,6] but is not recommended for currently licensed preparations. Vials of aldesleukin are reconstituted with water for injection.

However, UK licensed product information allows for further dilution of reconstituted aldesleukin with up to 500 mL of glucose 5%, containing human albumin 0.1%, when infused over a 24-hour period; the albumin should be added and mixed with the glucose before addition of the reconstituted aldesleukin.

For short intravenous infusion, the US licensed product information indicates that dilution in glucose 5% outside of a specified range (below 30 micrograms/mL and above 70 micrograms/mL) results in increased variability in drug delivery.

Reconstitution or dilution of aldesleukin preparations with sodium chloride 0.9% is not recommended because increased aggregation occurs.

1. Miles DW, *et al.* Reconstitution of interleukin 2 with albumin for infusion. *Lancet* 1990; **335:** 1602–3.
2. Vlasveld LT, *et al.* Reconstitution of interleukin-2. *Lancet* 1990; **336:** 446.
3. Miles DW, *et al.* Toxicity and reconstitution of recombinant interleukin-2 with albumin. *Lancet* 1991; **338:** 1464.
4. Franks CR. Reconstitution of interleukin-2. *Lancet* 1990; **336:** 445–6.
5. Hamblin T. Reconstitution of interleukin-2 with albumin for infusion. *Lancet* 1990; **336:** 251.
6. Lamers CHJ, *et al.* Bioavailability of interleukin-2 after reconstitution with albumin. *Lancet* 1992; **340:** 241.

Units

100 units of human interleukin-2 are contained in one ampoule of the first International Standard Preparation (1987). The activity of interleukin-2 has also been expressed in Nutley and Cetus units: 100 international units is reportedly equivalent to about 83.3 Nutley units and to about 16.7 Cetus units. US licensed product information states that 18 million international units of aldesleukin are equivalent to 1.1 mg of protein.

Adverse Effects and Treatment

Toxicity is related to dose and route and is often severe; fatalities have been recorded. Decreased vascular resistance and increased capillary permeability (the 'capillary leak syndrome') is common in patients given aldesleukin, and results in hypotension, reduced organ perfusion, and oedema. The incidence and severity of this syndrome is lower after subcutaneous than intravenous dosage. Fluid replacement may be necessary to treat the resultant hypovolaemia and dopamine or other pressor agents may be needed to help maintain organ perfusion. Capillary leak syndrome may also be associated with cardiac effects including tachycardia, angina, myocardial infarction; respiratory effects such as dyspnoea, pulmonary oedema, and respiratory failure; renal abnormalities including uraemia and oliguria or anuria; mental status changes including irritability, depression, confusion, and drowsiness. Therapy should be stopped if patients develop severe lethargy or somnolence, as continuing may result in coma. Raised liver enzymes, gastrointestinal disturbances, fever and flu-like symptoms (malaise, rigors, chills, arthralgia, and myalgia), rashes, pruritus, anaemia, leucopenia, and thrombocytopenia, are also relatively common. Paracetamol (but not NSAIDs, see Effects on the Kidneys, below) may be used prophylactically for fever. Pethidine may be used to control rigors. Antiemetics and antidiarrhoeals may also be required. Antihistamines may benefit some patients with pruritic rash. Injection site reactions are common after subcutaneous doses; necrosis has occurred. Aldesleukin therapy is associated with impaired neutrophil function, and an increased risk of bacterial infections (see below), including sepsis and bacterial endocarditis; this has been reported mainly after intravenous use, and antibacterial prophylaxis may be necessary.

◊ References.

1. Sundin DJ, Wolin MJ. Toxicity management in patients receiving low-dose aldesleukin therapy. *Ann Pharmacother* 1998; **32:** 1344–52.
2. Schwartzentruber DJ. Guidelines for the safe administration of high-dose interleukin-2. *J Immunother* 2001; **24:** 287–93.
3. Dutcher J, *et al.* Kidney cancer: the Cytokine Working Group experience (1986-2001): part II: management of IL-2 toxicity and studies with other cytokines. *Med Oncol* 2001; **18:** 209–19.
4. Schwartz RN, *et al.* Managing toxicities of high-dose interleukin-2. *Oncology (Huntingt)* 2002; **16** (suppl 13): 11–20.

Bacterial infections. The incidence of sepsis and bacteraemia is increased in patients receiving interleukin-2 via intravenous catheters,[1,2] and possibly subcutaneously,[3] although others have not found this to be the case.[4,5] The increased incidence of non-opportunistic bacterial infection may be a particular problem in patients with AIDS who are treated with interleukin-2.[6] The mechanism is uncertain, but may be related to impairment of neutrophil function by the cytokine.[7]

1. Snydman DR, *et al.* Nosocomial sepsis associated with interleukin-2. *Ann Intern Med* 1990; **112:** 102–7.
2. Shiloni E, *et al.* Interleukin-2 therapy, central venous catheters, and nosocomial sepsis. *Ann Intern Med* 1990; **112:** 882–3.
3. Jones AL, *et al.* Infectious complications of subcutaneous interleukin-2 and interferon-alpha. *Lancet* 1992; **339:** 181–2.
4. Buter J, *et al.* Infection after subcutaneous interleukin-2. *Lancet* 1992; **339:** 552.
5. Schomburg AG, *et al.* Cytokines and infection in cancer patients. *Lancet* 1992; **339:** 1061.
6. Murphy PM, *et al.* Marked disparity in incidence of bacterial infections in patients with the acquired immunodeficiency syndrome receiving interleukin-2 or interferon-γ. *Ann Intern Med* 1988; **108:** 36–41.
7. Klempner MS, *et al.* An acquired chemotactic defect in neutrophils from patients receiving interleukin-2 immunotherapy. *N Engl J Med* 1990; **322:** 959–65.

Effects on endocrine function. It has been suggested that patients with adrenal metastases may be particularly susceptible to adrenal haemorrhage and consequent failure during interleukin therapy.[1] Results also suggested that lack of endogenous steroid production may increase the risk of early severe interleukin-2 toxicity.[1]

Effects on thyroid function have also been reported, with the development of hypothyroidism[2-4] and goitre.[3]

1. VanderMolen LA, *et al.* Adrenal insufficiency and interleukin-2 therapy. *Ann Intern Med* 1989; **111:** 185.
2. Atkins MB, *et al.* Hypothyroidism after treatment with interleukin-2 and lymphokine-activated killer cells. *N Engl J Med* 1988; **318:** 1557–63.
3. van Liessum PA, *et al.* Hypothyroidism and goitre during interleukin-2 therapy without LAK cells. *Lancet* 1989; **i:** 224.
4. Sauter NP, *et al.* Transient thyrotoxicosis and persistent hypothyroidism due to acute autoimmune thyroiditis after interleukin-2 and interferon-α therapy for metastatic carcinoma: a case report. *Am J Med* 1992; **92:** 441–4.

Effects on the kidneys. Intravenous aldesleukin therapy was associated with varying degrees of acute renal dysfunction in almost all of 99 adult patients.[1] The clinical syndrome of hypotension, oliguria, fluid retention, and associated azotaemia with intense tubular avidity for filtered sodium all support prerenal acute renal failure as the cause of renal dysfunction. However, renal function values returned to baseline levels within 7 days in 62% of patients and in 95% by 30 days. Patients with elevated pretreatment serum-creatinine values, particularly those aged over 60 years, and those who had previously undergone a nephrectomy, were at risk of more severe and prolonged changes in renal function, and might be particularly vulnerable to the use of indometacin for associated fever and chills, which could potentiate renal impairment through its effects on intrarenal prostaglandin production. Similar effects were noted in a study[2] of 15 children given continuous infusion of aldesleukin. A further study[3] of the renal haemodynamic effects of aldesleukin infusion found it to have a specific renal vasoconstrictor effect; changes in renal prostaglandin synthesis contributed to the decreased renal blood flow.

1. Belldegrun A, *et al.* Effects of interleukin-2 on renal function in patients receiving immunotherapy for advanced cancer. *Ann Intern Med* 1987; **106:** 817–22.
2. Cochat P, *et al.* Renal effects of continuous infusion of recombinant interleukin-2 in children. *Pediatr Nephrol* 1991; **5:** 33–7.
3. Geertsen PF, *et al.* Renal haemodynamics, sodium and water reabsorption during continuous intravenous infusion of recombinant interleukin-2. *Clin Sci* 1998; **95:** 73–81.

Effects on the skin. Pseudosystemic sclerosis has been reported after use of aldesleukin; a reduction in skin thickening was seen after aldesleukin therapy was stopped and corticosteroids started.[1]

1. Marie I, *et al.* Pseudosystemic sclerosis as a complication of recombinant human interleukin 2 (aldesleukin) therapy. *Br J Dermatol* 2007; **156:** 182–3.

Precautions

Aldesleukin should be given with great care, if at all, to patients with pre-existing cardiac or pulmonary disease, and those with severe renal or hepatic impairment. It should be avoided in patients with CNS metastases or seizure disorders.

Risk factors for toxicity and poor response include restricted physical activity (Eastern Cooperative Oncology Group performance status of 1 or greater), 2 or more metastatic sites, and a period of less than 24 months between diagnosis of primary tumour and consideration for aldesleukin therapy. UK licensed product information states that aldesleukin should not be used to treat metastatic renal cell carcinoma in patients with all three of these risk factors.

Aldesleukin may worsen auto-immune diseases, and should be used with caution in patients with these conditions. Bacterial infections should be adequately treated before beginning therapy. Aldesleukin may increase effusions from serosal surfaces, and these should generally be treated before starting aldesleukin therapy.

Vital signs, blood counts, renal and hepatic function, serum electrolytes, and pulmonary and cardiac function should be monitored before starting treatment and then regularly during therapy.

Activity. For mention of the loss of activity when aldesleukin was given by continuous infusion without albumin, see Stability above.

Inflammatory bowel disease. Two patients with a history of Crohn's disease had a recurrence of the condition when given aldesleukin. It was suggested that interleukin-2 should be contraindicated in such patients.[1]

1. Sparano JA, *et al.* Symptomatic exacerbation of Crohn disease after treatment with high-dose interleukin-2. *Ann Intern Med* 1993; **118:** 617–18.

Psoriasis. Exacerbations of psoriasis developed in 3 patients during therapy with aldesleukin alone or with lymphokine-activated killer cells. The psoriatic symptoms remitted with topical therapy.[1]

1. Lee RE, *et al.* Interleukin 2 and psoriasis. *Arch Dermatol* 1988; **124:** 1811–15.

Interactions

Corticosteroids (which reduce some of the adverse effects of interleukin-2) may also reduce its antineoplastic properties: use together should generally be avoided. The use of iodinated contrast media after aldesleukin therapy may result in symptoms resembling the immediate adverse effects of aldesleukin. Although most events were reported to occur within 2 to 4 weeks of the last dose of aldesleukin, some occurred several months afterward.

Antivirals. For the effect of interleukin-2 on plasma concentrations of *indinavir*, see p.884.

NSAIDs. NSAIDs are effective in preventing or reducing fever and myalgia caused by interleukin-2. However, there is concern that they could exacerbate renal toxicity (see also Effects on the Kidneys, above). Use of *indometacin* in patients receiving interleukin-2 led to more severe weight gain, oliguria, and azotaemia in 1 study.[1] However, *ibuprofen* was used successfully to reduce interleukin-2 toxicity in another study.[2]

1. Sosman JA, *et al.* Repetitive weekly cycles of interleukin-2 II: clinical and immunologic effects of dose, schedule, and addition of indomethacin. *J Natl Cancer Inst* 1988; **80:** 1451–61.
2. Eberlein TJ, *et al.* Ibuprofen causes reduced toxic effects of interleukin 2 administration in patients with metastatic cancer. *Arch Surg* 1989; **124:** 542–7.

Pharmacokinetics

After intravenous bolus, the serum distribution and elimination half-lives of aldesleukin are 13 and 85 minutes, respectively. After subcutaneous doses, the absorption half-life is 45 minutes and the elimination half-life is 5.3 hours, while bioavailability ranges between 35 and 47%.

Aldesleukin is metabolised to amino acids by the kidneys.

◊ References.

1. Anderson PM, Sorenson MA. Effects of route and formulation on clinical pharmacokinetics of interleukin-2. *Clin Pharmacokinet* 1994; **27:** 19–31.
2. Piscitelli SC, *et al.* Pharmacokinetics and pharmacodynamics of subcutaneous interleukin-2 in HIV-infected patients. *Pharmacotherapy* 1996; **16:** 754–9.
3. Kirchner GI, *et al.* Pharmacokinetics of recombinant human interleukin-2 in advanced renal cell carcinoma patients following subcutaneous application. *Br J Clin Pharmacol* 1998; **46:** 5–10.

Uses and Administration

Interleukin-2 is a lymphokine which stimulates the proliferation of T-lymphocytes and thus amplifies immune response to an antigen; it also has actions on B-lymphocytes, and induces the production of interferon-γ and the activation of lymphokine-activated killer (LAK) cells and natural killer (NK) cells. Interleukin-2 is used in the immunotherapy of metastatic renal cell carcinoma in selected patients (see p.667). It is also used in metastatic melanoma (p.673), and has been tried in non-Hodgkin's lymphoma and acute myeloid leukaemia.

Interleukin-2 is usually given by intravenous infusion or subcutaneous injection of one of its recombinant forms, such as aldesleukin.

Many dosage regimens have been tried. In the UK, the recommended dose of aldesleukin for metastatic renal cell carcinoma is 18 million units given subcutaneously once daily for 5 days, followed by 2 days rest for the first week. For the next 3 weeks, 18 million units are then given on days 1 and 2 of each week, and 9 million units on days 3 to 5 of each week, followed by 2 days rest. This 4-week cycle may be repeated after an interval of 1 week. Doses may be delayed or reduced if the regimen is not tolerated.

Intravenous infusion of aldesleukin is now rarely used because of an association with capillary leak syndrome (see Adverse Effects and Treatment, above). If it is used, 18 million units/m^2 per 24 hours is given as a continuous intravenous infusion for 5 days, followed by 2 to 6 days of rest. Then another 5 days of infusion is given, followed by 3 weeks of rest. This constitutes one induction cycle; a second cycle may be given after the 3-week rest period of the first cycle. After either subcutaneous or intravenous use, up to 4 maintenance cycles may be given, at 4-week intervals, to patients who respond or whose disease stabilises. In the USA, aldesleukin is given by intravenous infusion for metastatic renal cell carcinoma or metastatic melanoma. The recommended dose is an infusion of 600 000 units/kg over 15 minutes, every 8 hours for up to 14 doses. This 5-day cycle is repeated after 9 days. Further courses may be given at intervals of at least 7 weeks in patients who respond. Doses should be withheld for toxicity.

Aldesleukin given by inhalation is being investigated in the treatment of renal cell carcinoma.

Interleukin-2 has also been given in adoptive immunotherapy with LAK cells or tumour-infiltrating lymphocytes (TIL), which are harvested from the patient, activated *ex vivo*, and then re-infused.

Interleukin-2 is also being tried in patients with HIV infection and AIDS in an attempt to restore immune response (see below) and has been given in some other infections or immune diseases.

Other interleukins are under investigation (see also Interleukin-1, p.2325). Conjugates of interleukin-2 with macrogol (PEG-IL2; pegaldesleukin) have also been investigated and liposome-encapsulated interleukin-2 has also been investigated for the treatment of renal, brain and CNS tumours.

A mixture of naturally occurring cytokines, including interleukins, interferons, chemokines, and colony-stimulating factors (Multikine®) is under investigation for neoadjuvant therapy in patients with squamous cell carcinoma of the head and neck.

◊ Reviews.

1. Noble S, Goa K. Aldesleukin (recombinant interleukin-2): a review of its pharmacological properties, clinical efficacy and tolerability in patients with metastatic melanoma. *BioDrugs* 1997; **7:** 394–422.
2. Atkins MB, *et al.* High-dose recombinant interleukin 2 therapy for patients with metastatic melanoma: analysis of 270 patients treated between 1985 and 1993. *J Clin Oncol* 1999; **17:** 2105–16.
3. Malaguarnera M, *et al.* Use of interleukin-2 in advanced renal carcinoma: meta-analysis and review of the literature. *Eur J Clin Pharmacol* 2001; **57:** 267–73.
4. Atkins MB, *et al.* Kidney cancer: the Cytokine Working Group experience (1986-2001): part I: IL-2-based clinical trials. *Med Oncol* 2001; **18:** 197–207.
5. Gaffen SL, Liu KD. Overview of interleukin-2 function, production and clinical applications. *Cytokine* 2004; **28:** 109–23.
6. Eklund JW, Kuzel TM. A review of recent findings involving interleukin-2-based cancer therapy. *Curr Opin Oncol* 2004; **16:** 542–6.
7. Eklund JW, Kuzel TM. Interleukin-2 in the treatment of renal cell carcinoma and malignant melanoma. *Cancer Treat Res* 2005; **126:** 263–87.
8. Porta C. Maintenance biotherapy with interleukin-2 and interferon for metastatic renal cell cancer. *Expert Rev Anticancer Ther* 2006; **6:** 141–52.
9. McDermott DF. Update on the application of interleukin-2 in the treatment of renal cell carcinoma. *Clin Cancer Res* 2007; **13:** 716s–720s.
10. Petrella T, *et al.* Single-agent interleukin-2 in the treatment of metastatic melanoma: a systematic review. *Cancer Treat Rev* 2007; **33:** 484–96.

HIV infection and AIDS. The immunodeficiency of HIV infection and AIDS (p.856) has been associated with a defect in interleukin-2 production. Interleukin-2 stimulates the proliferation of lymphocytes and activates natural killer cells and a number of studies have therefore examined the potential benefits of adding interleukin-2 to the treatment of patients with HIV infection.[1,2] Following earlier pilot studies, trials of antiretroviral therapy plus interleukin-2 have shown it to produce a much greater increase in CD4 cell counts than antiretroviral therapy alone,[3-7] even where therapy included HAART. Given the efficacy of current therapies, demonstrating additional benefits on survival or disease progression is difficult, although some studies have been undertaken.[1] In the interim, a pooled analysis[8] of earlier results showed a non-significant trend towards improved clinical outcome.

Although teceleukin has been tried[3] most studies of interleukin-2 therapy in HIV have used aldesleukin. Doses and routes have varied: in general doses seem to have ranged from 6 to 18 million units daily by intravenous infusion, or 3 to 30 million units daily subcutaneously, given in most cases for a 5-day cycle every 8 weeks. Subcutaneous dosage appears to be as effective as intravenous,[4,9] is more convenient,[4] and may be less toxic.[10] There is evidence that 5-day dose cycles of 3, 4.5 or 7.5 million units twice daily by subcutaneous injection are effective,[5,6,9,11-13] whereas cycles with a lower dose of 1.5 million units twice daily are not.[5,11,13] A meta-analysis[14] of 3 trials found that subcutaneous doses of 7.5 million units twice daily for 5 days every 8 weeks resulted in greater increases in CD4 cell counts after 3 cycles of therapy than doses of 4.5 million units or 1.5 million units. However, others have reported benefit from a dose as low as 3 million units daily when used with HAART in patients with advanced disease.[15] Continuous low-dose daily therapy appears to accelerate the normalisation of T-cell and natural killer cell concentrations over the course of several months.[10]

Adverse effects are common, particularly at higher doses and with intravenous infusion rather than subcutaneous use.[7,10] However, concerns about a potential stimulant effect on viral replication with a consequent increase in viral load do not seem to have been borne out.[4-7,9] Some studies have reported reduced viral loads in interleukin-treated patients,[6,16] including decreases in hepatitis C viral load in those HIV patients co-infected with hepatitis C.[9,17]

The macrogol conjugate of interleukin-2, PEG-IL2, has also been investigated in this context, but results have been disappointing, since it appears markedly less effective than aldesleukin in stimulating CD4 counts.[4,18]

1. Pau AK, Tavel JA. Therapeutic use of interleukin-2 in HIV-infected patients. *Curr Opin Pharmacol* 2002; **2:** 433–9.
2. Temesgen Z. Interleukin-2 for the treatment of human immunodeficiency virus infection. *Drugs Today* 2006; **42:** 791–801.
3. Bartlett JA, *et al.* Coadministration of zidovudine and interleukin-2 increases absolute CD4 cells in subjects with Walter Reed stage 2 human immunodeficiency virus infection: results of ACTG protocol 042. *J Infect Dis* 1998; **178:** 1170–3.
4. Levy Y, *et al.* Comparison of subcutaneous and intravenous interleukin-2 in asymptomatic HIV-1 infection: a randomised controlled trial. *Lancet* 1999; **353:** 1923–9.
5. Losso MH, *et al.* A randomized, controlled, phase II trial comparing escalating doses of subcutaneous interleukin-2 plus antiretrovirals versus antiretrovirals alone in human immunodeficiency virus-infected patients with CD4+ cell counts ≥350/mm . *J Infect Dis* 2000; **181:** 1614–21. Correction. *ibid.*; 2122.
6. Davey RT, *et al.* Immunologic and virologic effects of subcutaneous interleukin 2 in combination with antiretroviral therapy: a randomized controlled trial. *JAMA* 2000; **284:** 183–9.
7. Piscitelli SC, *et al.* A risk-benefit assessment of interleukin-2 as an adjunct to antiviral therapy in HIV infection. *Drug Safety* 2000; **22:** 19–31.
8. Emery S, *et al.* Pooled analysis of 3 randomized, controlled trials of interleukin-2 therapy in adult human immunodeficiency virus type 1 disease. *J Infect Dis* 2000; **182:** 428–34.
9. Tambussi G, *et al.* Efficacy of low-dose intermittent subcutaneous interleukin (IL)–2 in antiviral drug–experienced human immunodeficiency virus–infected persons with detectable virus load: a controlled study of 3 IL-2 regimens with antiviral drug therapy. *J Infect Dis* 2001; **183:** 1476–84.
10. Smith KA. Low-dose daily interleukin-2 immunotherapy: accelerating immune restoration and expanding HIV-specific T-cell immunity without toxicity. *AIDS* 2001; **15** (suppl 2): S28–S35.
11. Davey RT, *et al.* A randomized trial of high- versus low-dose subcutaneous interleukin-2 outpatient therapy for early human immunodeficiency virus type 1 infection. *J Infect Dis* 1999; **179:** 849–58.
12. David D, *et al.* Rapid effect of interleukin-2 therapy in human immunodeficiency virus–infected patients whose CD4 cell counts increase only slightly in response to combined antiretroviral treatment. *J Infect Dis* 2001; **183:** 730–5.
13. Ruxrungtham K, *et al.* A randomized, controlled 24-week study of intermittent subcutaneous interleukin-2 in HIV-1 infected patients in Thailand. *AIDS* 2000; **14:** 2509–13.
14. Arduino RC, *et al.* CD4 cell response to 3 doses of subcutaneous interleukin 2: meta-analysis of 3 Vanguard studies. *Clin Infect Dis* 2004; **39:** 115–22.
15. Arnó A, *et al.* Efficacy of low-dose subcutaneous interleukin-2 to treat advanced human immunodeficiency virus type 1 in persons with ≤250/microlitre CD4 T cells and undetectable plasma virus load. *J Infect Dis* 1999; **180:** 56–60.
16. Lafeuillade A, *et al.* Pilot study of a combination of highly active antiretroviral therapy and cytokines to induce HIV-1 remission. *J Acquir Immune Defic Syndr* 2001; **26:** 44–55.
17. Schlaak JF, *et al.* Sustained suppression of HCV replication and inflammatory activity after interleukin-2 therapy in patients with HIV/hepatitis C virus coinfection. *J Acquir Immune Defic Syndr* 2002; **29:** 145–8.
18. Carr A, *et al.* Outpatient continuous intravenous interleukin-2 or subcutaneous, polyethylene glycol-modified interleukin-2 in human immunodeficiency virus-infected patients: a randomized, controlled, multicenter study. *J Infect Dis* 1998; **178:** 992–9.

Postherpetic neuralgia. A 46-year-old HIV patient with chronic, treatment-resistant postherpetic neuralgia (p.9) received 1 cycle of subcutaneous interleukin-2 (7.5 million units twice daily for 5 consecutive days) within the context of a clinical HIV study. He reported immediate resolution of his postherpetic neuralgia, and no recurrence of pain occurred during 3 years of follow-up.[1]

1. Rotty J, *et al.* Interleukin-2: a potential treatment option for postherpetic neuralgia? *Clin Infect Dis* 2006; **43:** e109–e110.

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Ilgen; Proleukin; ***Austral.:*** Proleukin†; ***Austria:*** Proleukin; ***Belg.:*** Proleukin; ***Braz.:*** Proleukin; ***Canad.:*** Proleukin; ***Cz.:*** Proleukin; ***Denm.:*** Pro-

leukin; ***Fr.:*** Proleukin; ***Ger.:*** Proleukin; ***Gr.:*** Proleukin; ***Hong Kong:*** Proleukin; ***Hung.:*** Proleukin; ***Irl.:*** Proleukin; ***Israel:*** Proleukin; ***Ital.:*** Proleukin; ***Jpn:*** Celeuk; Imunace; ***Mex.:*** Proleukin; ***Neth.:*** Proleukin; ***NZ:*** Proleukin; ***Pol.:*** Proleukin; ***Port.:*** Proleukin; ***Rus.:*** Proleukin (Пролейкин); Roncoleukin (Ронколейкин); ***S.Afr.:*** Chiron IL-2; ***Singapore:*** Proleukin†; ***Spain:*** Proleukin; ***Switz.:*** Proleukin; ***Turk.:*** Proleukin; ***UK:*** Proleukin; ***USA:*** Proleukin.

Ipilimumab *(USAN, rINN)*

Ipilimumabum; MDX-010; MDX-CTA-4. Immunoglobulin G1, anti-(human CTLA-4 (antigen)) (human γ1-chain), disulfide with human κ-chain, dimer.

Ипилимумаб

CAS — 477202-00-9.

Profile

Ipilimumab is an antibody to the cytotoxic-T-lymphocyte-associated antigen 4 (CTLA-4), which is a cell surface receptor involved in the downregulation of T-cell activation. Ipilimumab is under investigation for the treatment of melanoma and various solid tumours. Adverse effects include enterocolitis, hypophysitis, dermatitis, arthritis, uveitis, hepatitis, nephritis, and aseptic meningitis.

◊ References.

1. Beck KE, *et al.* Enterocolitis in patients with cancer after antibody blockade of cytotoxic T-lymphocyte-associated antigen 4. *J Clin Oncol* 2006; **24:** 2283–9.
2. Weber J. Review: anti-CTLA-4 antibody ipilimumab: case studies of clinical response and immune-related adverse events. *Oncologist* 2007; **12:** 864–72.

Iratumumab *(USAN, rINN)*

Iratumumabum; MDX-060. Immunoglobulin G1, anti-(tumor necrosis factor ligand superfamily member 8 (CD30 ligand)) (human monoclonal MDX-060 heavy chain), disulfide with human monoclonal MDX-060 light chain, dimer.

Иратумумаб

CAS — 640735-09-7.

Profile

Iratumumab is an anti-CD30 monoclonal antibody that is under investigation for the treatment of Hodgkin's disease. Reported adverse effects include a rise in liver transaminases, and acute respiratory distress syndrome.

Irinotecan Hydrochloride

(BANM, USAN, rINNM)

Camptothecin 11 (irinotecan); CPT-11 (irinotecan); DQ-2805; Hidrocloruro de irinotecán; Irinotécan, Chlorhydrate d'; Irinotecani Hydrochloridum; Irinotekaanihydrokloridi; Irinotekan Hidroklorür; Irinotekanhydroklorid; U-101440E. (+)-7-Ethyl-10-hydroxycamptothecine 10-[1,4′-bipiperidine]-1′-carboxylate hydrochloride trihydrate; (*S*)-4,11-Diethyl-3,4,12,14-tetrahydro-4-hydroxy-3,14-dioxo-1*H*-pyrano[3′,4′:6′,7′]indolizino[1,2-*b*]quinolin-9-yl [1,4′-dipiperidine]-1′-carboxylate hydrochloride trihydrate.

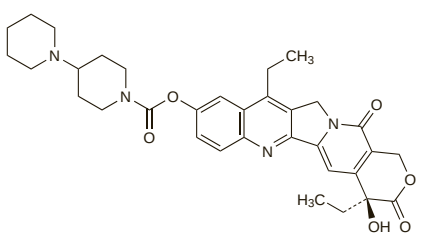
Иринотекана Гидрохлорид

$C_{33}H_{38}N_4O_6,HCl,3H_2O$ = 677.2.

CAS — 97682-44-5 (irinotecan); 136572-09-3 (irinotecan hydrochloride trihydrate).

ATC — L01XX19.

ATC Vet — QL01XX19.



(irinotecan)

Adverse Effects, Treatment, and Precautions

For general discussions, see Antineoplastics, p.635, p.639, and p.641. Neutropenia and diarrhoea may be dose-limiting in patients given irinotecan. The nadir of the white cell count usually occurs about 8 days after a dose, with recovery by about day 22. Anaemia also occurs and, less commonly, thrombocytopenia. Gastrointestinal disturbances are common: acute diarrhoea, occurring within 24 hours of a dose, may be part of a cholinergic syndrome which can also include sweating, hypersalivation, abdominal cramps, lachrymation, and miosis. These symptoms can be controlled with atropine. However a more severe, prolonged diarrhoea may occur, beginning more than 24 hours after a dose, and can be life-threatening; prompt management with high-dose loperamide and fluid replacement is required (see Effects on the Gastrointestinal Tract, below), and irinotecan treatment should be interrupted and any further doses reduced. Other adverse effects include nausea and vomiting, weakness, alopecia, and skin reactions. Hypertension has occurred rarely during or after infusion. There are rare reports of hypersensitivity reactions, interstitial pneumonia, pneumonitis, intestinal perforation, pancreatitis, muscular contraction or cramps, and paraesthesia.

Irinotecan should not be given to patients with inflammatory bowel disease. The risk of diarrhoea may be increased in the elderly and in patients who have had radiotherapy to the abdomen or pelvis. Radiotherapy also increases the risk of myelosuppression. Blood counts should be monitored weekly and liver function tests should be regularly performed.

Severe toxicity resulting in an increased number of deaths has been reported when irinotecan was given with fluorouracil and folinic acid (see under Interactions, below).

Effects on the gastrointestinal tract. *Acute* diarrhoea occurring as part of a cholinergic syndrome with irinotecan is rarely severe. The syndrome is usually treated or prevented with atropine, but pretreatment with hyoscine butylbromide has also been tried.[1,2] In contrast, *delayed* diarrhoea can be dose-limiting or even fatal in some patients. Standard treatment involves fluid and electrolyte replacement and a high-dose loperamide regimen consisting of 4 mg loperamide immediately after the first loose stool, then 2 mg every 2 hours until 12 hours after the last liquid stool. During the night, the patient may take 4 mg every 4 hours. The high-dose therapy should not be given for more than 48 hours and should never be given prophylactically. Specific recommendations[3] state that if the diarrhoea persists for more than 24 hours despite loperamide therapy, patients should also take an oral fluoroquinolone for 7 days. If the diarrhoea persists for more than 48 hours, patients should be hospitalised for parenteral hydration. Other treatments have been tried, including acetorphan, activated charcoal, budesonide, glutamine, and octreotide.[2,4-9] A regimen of thalidomide with irinotecan has been reported to have a striking lack of gastrointestinal adverse effects such as diarrhoea and nausea.[2,10] However, a pharmacokinetic study found no decrease in gastrointestinal toxicity when these 2 drugs were given together, see Thalidomide, under Interactions, below.

Diarrhoea may be caused by direct intestinal damage due to SN-38, the active metabolite of irinotecan; reduction of intestinal SN-38 concentrations using the poorly absorbed aminoglycoside neomycin as prophylaxis was reported to ameliorate diarrhoea in 6 of 7 patients experiencing this adverse effect.[11]

1. Zampa G, Magnolfi E. Premedication for irinotecan. *J Clin Oncol* 2000; **18:** 237.
2. Yang X, *et al.* Novel agents that potentially inhibit irinotecan-induced diarrhea. *Curr Med Chem* 2005; **12:** 1343–58.
3. Rothenberg ML, *et al.* Mortality associated with irinotecan plus bolus fluorouracil/leucovorin: summary findings of an independent panel. *J Clin Oncol* 2001; **19:** 3801–7.
4. Saliba F, *et al.* Pathophysiology and therapy of irinotecan-induced delayed-onset diarrhea in patients with advanced colorectal cancer: a prospective assessment. *J Clin Oncol* 1998; **16:** 2745–51.
5. Lenfers BHM, *et al.* Substantial activity of budesonide in patients with irinotecan (CPT-11) and 5-fluorouracil induced diarrhea and failure of loperamide treatment. *Ann Oncol* 1999; **10:** 1251–3.
6. Savarese D, *et al.* Glutamine for irinotecan diarrhea. *J Clin Oncol* 2000; **18:** 450–1.
7. Ychou M, *et al.* Randomized comparison of prophylactic antidiarrheal treatment versus no prophylactic antidiarrheal treatment in patients receiving CPT-11 (irinotecan) for advanced 5-FU-resistant colorectal cancer: an open-label multicenter phase II study. *Am J Clin Oncol* 2000; **23:** 143–8.
8. Pro B, *et al.* Therapeutic response to octreotide in patients with refractory CPT-11 induced diarrhea. *Invest New Drugs* 2001; **19:** 341–3.
9. Michael M, *et al.* Phase II study of activated charcoal to prevent irinotecan-induced diarrhea. *J Clin Oncol* 2004; **22:** 4410–17.
10. Govindarajan R, *et al.* Effect of thalidomide on gastrointestinal toxic effects of irinotecan. *Lancet* 2000; **356:** 566–7.
11. Kehrer DFS, *et al.* Modulation of irinotecan-induced diarrhea by cotreatment with neomycin in cancer patients. *Clin Cancer Res* 2001; **7:** 1136–41.

Genetic factors. Irinotecan is hydrolysed to SN-38, an active metabolite, which is inactivated by glucuronidation by uridine diphosphate glucuronosyltransferase (UGT) enzymes.[1] Genetic variation in the UGT family may affect irinotecan pharmacodynamics. Although UGT1A1*28 polymorphism appears to be only one of several identified causes of altered SN-38 pharmacokinetics,[1,2] it has been strongly associated with the development of severe neutropenia, and genotyping has been proposed as a method of identifying patients at risk of severe toxicity from irinotecan.[3,4] However, genotyping does not predict for all toxicities, and a significant association between the UGT1A1*28 homozygous genotype and diarrhoea has not been proven. Furthermore, a normal UGT1A1 genotype does not ensure lack of toxicity, although the risk is less; the possibility of underdosing in those with the normal genotype may need to be considered.[5] Despite these limitations, it has been suggested that every patient receiving irinotecan for the first time be tested for UGT1A1 genotype.[5]

Licensed product information in the USA states that reduced initial doses should be considered for patients known to be homozygous for the UGT1A1*28 allele; while heterozygous patients may also be at risk, results of studies have been variable and such patients may tolerate normal initial doses of irinotecan. However, the most appropriate dose reduction in the homozygous population is not known. Some have suggested an initial 20% dose reduction, with escalation to full dosage in subsequent courses in the event of little or no toxicity.[5] A prospective study[6] found that the UGT1A1*28 genotype (homozygous or heterozygous) was significantly associated with haematological toxicity, but only during the first cycle of irinotecan-containing chemotherapy. This called into question the need for a dose reduction in irinotecan for patients with this genotype, particularly since homozygous patients showed a trend to improve clinical response. A study in paediatric patients[7] found that, for low-dose, protracted schedules of irinotecan (doses ranged from 15 to 75 mg/m^2 daily, given either intravenously or orally, for 5 days, for 2 consecutive weeks), UGT1A1 genotyping was not a useful prognostic indicator of severe toxicity.

1. Paoluzzi L, *et al.* Influence of genetic variants in UGT1A1 and UGT1A9 on the in vivo glucuronidation of SN-38. *J Clin Pharmacol* 2004; **44:** 854–60.
2. Ramchandani RP, *et al.* The role of SN-38 exposure, UGT1A1*28 polymorphism, and baseline bilirubin level in predicting severe irinotecan toxicity. *J Clin Pharmacol* 2007; **47:** 78–86.
3. Innocenti F, *et al.* Genetic variants in the UDP-glucuronosyltransferase 1A1 gene predict the risk of severe neutropenia of irinotecan. *J Clin Oncol* 2004; **22:** 1382–8.
4. Hahn KK, *et al.* Pharmacogenetics and irinotecan therapy. *Am J Health-Syst Pharm* 2006; **63:** 2211–17.
5. O'Dwyer PJ, Catalano RB. Uridine diphosphate glucuronosyltransferase (UGT) 1A1 and irinotecan: practical pharmacogenomics arrives in cancer therapy. *J Clin Oncol* 2006; **24:** 4534–8.
6. Toffoli G, *et al.* The role of UGT1A1*28 polymorphism in the pharmacodynamics and pharmacokinetics of irinotecan in patients with metastatic colorectal cancer. *J Clin Oncol* 2006; **24:** 3061–8.
7. Stewart CF, *et al.* UGT1A1 promoter genotype correlates with SN-38 pharmacokinetics, but not severe toxicity in patients receiving low-dose irinotecan. *J Clin Oncol* 2007; **25:** 2594–2600.

Interactions

Irinotecan is partly metabolised by cytochrome P450 CYP3A isoenzymes. Inducers of this system such as carbamazepine, phenobarbital, or phenytoin reduce exposure to irinotecan and its active metabolite SN-38; use with St John's Wort is contra-indicated. Conversely, inhibitors of this system such as ketoconazole increase exposure to irinotecan and SN-38; use with ketoconazole is contra-indicated.

Antidepressants. In a small, crossover study[1] of cancer patients, use of *St John's wort* during irinotecan therapy was found to decrease plasma concentrations of SN-38, the active metabolite of irinotecan. Myelosuppression was also reduced with this combination. The interaction is thought to be due to the induction of the cytochrome P450 isoenzyme CYP3A4 by St John's wort.

1. Mathijssen RHJ, *et al.* Effects of St. John's wort on irinotecan metabolism. *J Natl Cancer Inst* 2002; **94:** 1247–9.

Antineoplastics. Although previously reported to be effective, and not associated with excessive toxicity,[1] a regimen of irinotecan with bolus *fluorouracil* and folinic acid was found to be associated with an excess of early deaths in 2 further studies, which were consequently terminated.[2] Deaths were associated with a variety of events including dehydration (due to diarrhoea, nausea, and vomiting), neutropenia, and sepsis. It has been suggested that use of irinotecan with fluorouracil by continuous infusion might be better tolerated,[3,4] and a small study[5] found that the sequence may be important. Irinotecan followed by an infusion of fluorouracil over 48 hours, was associated with less dose-limiting toxicity, and higher maximum tolerated doses, than fluorouracil infusion followed by irinotecan.

Sorafenib may increase systemic exposure to irinotecan.

1. Saltz LB, *et al.* Irinotecan plus fluorouracil and leucovorin for metastatic colorectal cancer. *N Engl J Med* 2000; **343:** 905–14.
2. Sargent DJ, *et al.* Recommendation for caution with irinotecan, fluorouracil, and leucovorin for colorectal cancer. *N Engl J Med* 2001; **345:** 144–5.