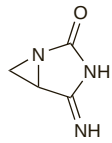
Imexon *(rINN)*

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.