NOVARTIS

Proleukin®

Immunostimulants, cytokines and immunomodulators, interleukins, aldesleukin

DESCRIPTION AND COMPOSITION

Each vial of Proleukin powder for solution for infusion contains 22 x 10^6 International Units (IU) aldesleukin.

Pharmaceutical form

One glass vial contains 22 x 10^6 IU sterile freeze-dried, white powder for solution for infusion.

After reconstitution with 1.2 mL water for injection, according to the instructions (see section INSTRUCTIONS FOR USE AND HANDLING), each 1 mL solution contains 18 x 10^6 IU (1.1 mg) aldesleukin.

Active substance

The active substance is aldesleukin.

Aldesleukin is produced by recombinant DNA technology using an *Escherichia coli* strain which contains a genetically engineered modification of the human Interleukin-2 (IL-2) gene.

Excipients

A vial of Proleukin contains, in addition to aldesleukin, mannitol (E421), sodium laurilsulfate, sodium dihydrogen phosphate dihydrate (pH adjuster), disodium hydrogen phosphate dihydrate (pH adjuster).

Pharmaceutical formulations may vary between countries.

INDICATIONS

Treatment of metastatic renal cell carcinoma.

Risk factors associated with decreased response rates and median survival are:

- A performance status of ECOG* 1 or greater
- More than one organ with metastatic disease sites
- A period of <24 months between initial diagnosis of primary tumour and the date the patient is evaluated for Proleukin treatment.

**ECOG (Eastern Cooperative Oncology Group) 0 = normal activity, 1 = symptoms but ambulatory; 2 = in bed less than 50% of time; 3 = in bed more than 50% of time.*

Response rates and median survival decrease with the number of risk factors present. Patients positive for all three risk factors should not be treated with Proleukin.

DOSAGE REGIMEN AND ADMINISTRATION

Proleukin should be administered intravenously by continuous infusion.

Continuous intravenous infusion

18×10^6 IU per m^2 per 24-hours is administered as a continuous infusion for 5 days, followed by 2-6 days without Proleukin therapy, an additional 5 days of intravenous Proleukin as a continuous infusion and 3 weeks without Proleukin therapy. This constitutes one induction cycle. After the 3-week without Proleukin therapy period of the first cycle, a second induction cycle should be given.

Maintenance: Up to four maintenance cycles (18×10^6 IU per m^2 as continuous infusion for 5 days) may be given with 4-week intervals to patients who respond or achieve disease stabilization.

If a patient does not tolerate the recommended dosage regimen, the dose should be reduced or the administration interrupted until the toxicity has moderated. It is not known to what extent dose reduction affects response rates and median survival.

Special populations

Renal impairment

No formal studies have been conducted to evaluate pharmacokinetics; safety and tolerability of Proleukin in patients with pre-existing renal impairment (see section WARNINGS AND PRECAUTIONS).

Patients with pre-existing renal impairment should be closely monitored.

Renal metabolism or excretion of concomitantly administered medicinal products may be altered by the administration of Proleukin.

Hepatic impairment

No formal studies have been conducted to evaluate pharmacokinetics; safety and tolerability of Proleukin in patients with pre-existing hepatic impairment (see section WARNINGS AND PRECAUTIONS).

Proleukin administration results in a reversible elevation of hepatic transaminases, serum bilirubin, serum urea and serum creatinine. Patients with pre-existing renal or hepatic impairment should be closely monitored.

Hepatic metabolism or excretion of concomitantly administered medicinal products may be altered by the administration of Proleukin.

Pediatric patients

The safety and efficacy of Proleukin in children and in adolescents have not yet been established.

Geriatric patients (65 years and above)

No formal clinical trials were conducted to compare the efficacy or safety of Proleukin in geriatric patients to those in younger patients.

However, it is recommended that clinicians exercise caution when prescribing Proleukin to geriatric patients since renal and hepatic function may deteriorate with increasing age.

Method of administration

Proleukin should only be used under the supervision of a qualified physician, experienced in the use of cancer chemotherapeutic agents.

For administration by continuous intravenous infusion it is recommended that patients are admitted to a specialized unit having the facilities of an intensive care unit to monitor the patient's relevant clinical and laboratory parameters.

CONTRAINDICATIONS

Proleukin therapy is contra-indicated in the following patients:

1. Patients with known hypersensitivity to the active substance or to any of the excipients.
2. Patients with an Eastern Cooperative Oncology Group (ECOG)* performance status of 2 or greater.
3. Patients with all three risk factors associated with decreased response rates and median survival. These risk factors are: anECOG* performance status of 1 or greater; more than one organ with metastatic disease; a period of <24 months between initial diagnosis of primary tumour and the date the patient is evaluated for aldesleukin treatment.
4. Patients with a significant history or current evidence of severe cardiac disease. In questionable cases a stress test should be performed.
5. Patients with evidence of active infection requiring antibiotic therapy.
6. Patients with a PaO_2 <60 mm Hg at rest.
7. Patients with pre-existing severe major organ dysfunction.
8. Patients with (Central Nervous System) CNS metastases or seizure disorders, with the exception of patients with successfully treated brain metastases (negative computerized tomography (CT); neurologically stable).

**ECOG performance status 0 = normal activity, 1 = symptoms but ambulatory; 2 = in bed less than 50% of time; 3 = in bed more than 50% of time limited self-care; 4 = completely disabled, no self-care*

In addition, it is recommended to exclude the following patients:

1. Patients with White Blood Count (WBC) <4.000/mm^3; platelets <100.000/mm^3; hematocrit (HCT) < 30%.
2. Patients with serum bilirubin and creatinine outside the normal range.
3. Patients with organ allografts.
4. Patients who are likely to require corticosteroids.
5. Patients with pre-existing auto-immune disease.

WARNINGS AND PRECAUTIONS

Prediction for survival

Clinical studies have shown that patients with metastatic renal cell carcinoma can be divided into 4 distinct risk groups, predictive for survival and to some extent response, following Proleukin therapy. The 4 risk groups are defined by the number of risk factors present at the start of treatment : the very low risk group has no risk factor, the low risk group one risk factor, the intermediate risk group has any combination of 2 risk factors, and the high risk group has all 3 risk factors present at the same time. The response rates and the median survival decrease with the number of risk factors present. Patients who are positive for all three risk factors should not be treated with Proleukin (see section CONTRAINDICATIONS).

Should serious adverse events occur, dosage should be modified according to section DOSAGE AND ADMINISTRATION. It is important to note that adverse reactions, although sometimes serious or in rare cases life threatening, are manageable and usually, although not invariably, resolve within 1 or 2 days of cessation of Proleukin therapy. The decision to resume therapy should be based on the severity and spectrum of the clinical toxicity.

Capillary leak syndrome

Proleukin administration has been associated with capillary leak syndrome (CLS), which is characterized by a loss of vascular tone and extravasation of plasma proteins and fluid into the extravascular space. CLS results in hypotension, tachycardia and reduced organ perfusion. Severe CLS resulting in death has been reported.

Capillary leak syndrome usually begins within hours after initiation of Proleukin treatment and clinical hypotension is reported to occur after 2 to 12 hours. Careful monitoring of circulatory and respiratory function is required particularly for patients receiving intravenous Proleukin (see sub-section Laboratory and clinical monitoring).

In some patients hypotension resolves itself without therapy. In others, treatment is required with cautious use of intravenous fluids. In more refractory cases, low-dose catecholamines are required to maintain blood pressure and organ perfusion. Prolonged use or higher dosages of catecholamines may be associated with cardiac rhythm disturbances.

If intravenous fluids are administered, care must be taken to weigh potential benefits of the expansion of intravascular volume against the risk of pulmonary oedema, ascites, pleural or pericardial effusions secondary to capillary leakage. If these measures are not successful, Proleukin therapy should be interrupted.

Effusions from serosal surfaces

Proleukin may exacerbate effusions from serosal surfaces. Consideration should be given to treating these prior to initiation of Proleukin therapy, particularly when effusions are located in anatomic sites where worsening may lead to impairment of major organ function (e.g. pericardial effusions), see sub-section Laboratory and clinical monitoring.

Autoimmune disease

Proleukin may exacerbate pre-existing autoimmune disease, resulting in life threatening complications. Activation of quiescent Crohn's disease has been reported following treatment with Proleukin.

Since not all patients who develop interleukin-2-associated autoimmune phenomena have a pre-existing history of autoimmune disease, awareness and close monitoring for thyroid abnormalities or other potentially autoimmune phenomena is warranted.

Central nervous system effects

Proleukin administration should be discontinued in patients who develop severe lethargy or somnolence; continued administration may result in coma.

Proleukin may exacerbate disease symptoms in patients with clinically unrecognized or untreated central nervous system (CNS) metastases. All patients should have adequate evaluation and treatment of CNS metastases prior to receiving Proleukin therapy

Patients may experience mental status changes including irritability, confusion, or depression while receiving Proleukin. Although generally reversible when administration of medicinal product is discontinued, these mental status changes may persist for several days. Proleukin may alter the patient response to psychotropic medicinal products (see section INTERACTIONS).

Renal or hepatic impairment

Proleukin administration results in reversible elevation of hepatic transaminases, serum bilirubin, serum urea and serum creatinine.. Renal or hepatic metabolism or excretion of concomitantly administered medicinal products may be altered by the administration of Proleukin. Other medicinal products with known nephrotoxic or hepatotoxic potential should be used with caution (see section INTERACTIONS). Close monitoring should be applied to all patients with pre-existing renal or hepatic impairment (see sub-section Laboratory and clinical monitoring).

Infections

Administration of Proleukin may be associated with an increased incidence and/or severity of bacterial infection, including septicemia, bacterial endocarditis, septic thrombophlebitis, peritonitis and pneumonia.

This has mainly been reported after intravenous administration. For patients receiving intravenous Proleukin infusion, an increased incidence and/or severity of local catheter site infection has been reported. Patients with central lines in place should be treated prophylactically with antibiotics. Except for several cases of urinary tract infection due to *Escherichia coli*, the main causative organisms have been *Staphylococcus aureus* or *Staphylococcus epidermidis*.

Pre-existing bacterial infections should be treated prior to initiation of Proleukin therapy.

Glucose metabolism disorders

There is a possibility of disturbances in the glucose metabolism during treatment with Proleukin. Blood glucose should be monitored; particular attention should be paid to patients with pre-existing diabetes (see sub-section Laboratory and clinical monitoring).

Drug administration

Proleukin administration results in fever and gastrointestinal adverse reactions in most patients treated at the recommended dose. Concomitant therapy with paracetamol can be instituted at the same time as Proleukin administration to reduce fever. Pethidine may be added to control the rigors associated with fever. Anti-emetics and antidiarrheals may be used, as needed, to treat other gastrointestinal adverse reactions. Some patients with pruritic rash benefit from concomitant administration of antihistamines.

Laboratory and clinical monitoring

In addition to those tests normally required for monitoring patients with metastatic renal cell carcinoma, the following tests are recommended for all patients on Proleukin therapy, prior to beginning treatment and then periodically thereafter:

- Standard hematological tests, including white cell blood count (WBC) (with differential and platelet counts). Proleukin administration may lead to anemia and thrombocytopenia.
- Blood chemistry, including fluid and electrolyte balance, blood glucose, renal and hepatic function tests. All patients with pre-existing renal or hepatic dysfunction should be closely monitored.
- Pre-treatment evaluation should include chest x-rays and electrocardiogram (ECG, plus stress test if indicated), and arterial blood gases. Abnormalities or other evidence of cardiac ischemia should be followed -up by further testing to exclude significant coronary artery disease.

Patients receiving intravenous Proleukin circulatory function should be monitored by regular blood pressure and pulse assessment, additionally, other organ functions, including mental status and urine output, should be monitored. More frequent assessments should be performed in patients experiencing a decrease in blood pressure. Hypovolemia should be assessed by monitoring central venous pressure.

Patients who develop rales, increased respiratory rate, or who complain of dyspnea should have their pulmonary function monitored during therapy that includes pulse oxymetry and measuring arterial blood gas.

Driving and using machines

Proleukin may affect central nervous system function. Hallucinations, somnolence, syncope and convulsions may occur during Proleukin treatment (see section ADVERSE DRUG REACTIONS) and may affect the patient's ability to drive and operate machines.

Patients should not drive or operate machines until they have recovered from the adverse drug reactions.

INTERACTIONS

Interactions resulting in effects on other drugs

Observed interactions resulting in concomitant use not recommended

Interactions affecting the use of Proleukin

Antineoplastics

Fatal Tumour Lysis Syndrome has been reported in combination with treatment with cisplatin, vinblastine and dacarbazine. Concomitant use of the active substances mentioned is therefore not recommended.

Hypersensitivity reactions have been reported in patients receiving combination regimens containing sequential high dose Proleukin and antineoplastic agents, specifically, dacarbazine, cis-platin, tamoxifen and interferon-alpha. These reactions consisted of erythema, pruritus, and hypotension and occurred within hours of chemotherapy. These events required medical intervention in some patients.

Severe rhabdomyolysis and myocardial injury, including myocardial infarction, myocarditis and ventricular hypokinesia appear to be increased in patients receiving Proleukin (intravenously) and interferon-alpha concurrently.

There has also been exacerbation or the initial presentation of a number of autoimmune and inflammatory disorders observed following concurrent use of interferon-alpha and Proleukin, including crescentic immunoglobulin A (IgA) glomerulonephritis, oculo-bulbar myasthenia gravis, inflammatory arthritis, thyroiditis, bullous pemphigoid, and Stevens-Johnson syndrome. It is recommended that patients with pre-existing auto-immune disease should not be treated with Proleukin (see section CONTRAINDICATION).

Glucocorticoids

Concomitantly administered glucocorticoids may decrease the activity of Proleukin and should therefore be avoided. However, patients who develop life-threatening signs or symptoms may be treated with dexamethasone until toxicity resolves to an acceptable level.

Contrast media

Use of contrast media after Proleukin administration may result in a recall of the toxicity observed during Proleukin administration. Most events were reported to occur within 2 weeks after the last dose of Proleukin, but some occurred months later. Therefore, it is not recommended to use contrast media within 2 weeks after treatment with Proleukin.

Observed interactions to be considered

Interactions affecting the use of Proleukin

Medicinal products with hepatotoxic, nephrotoxic, myelotoxic, or cardiotoxic effects

Medicinal products with hepatotoxic, nephrotoxic, myelotoxic, or cardiotoxic effects used concomitantly with Proleukin, may increase the toxicity of Proleukin. These products should be used with caution and these systems should be observed and monitored carefully (see section WARNINGS AND PRECAUTIONS).

Centrally-acting medicinal products

Proleukin may affect the central nervous function. Therefore, interactions could occur following concomitant administration of centrally acting medicinal products. Proleukin may alter the patient response to psychotropic medicinal products and therefore patients should be monitored (see section WARNINGS AND PRECAUTIONS).

Antihypertensive agents

Antihypertensive agents, such as beta -blockers, may potentiate the hypotension seen with Proleukin and therefore blood pressure should be monitored.

PREGNANCY, LACTATION, FEMALES AND MALES OF REPRODUCTIVE POTENTIAL

Pregnancy

Risk Summary

There are no adequate data available on the use of aldesleukin in pregnant women.

Experimental animal studies are insufficient to assess the safety with respect to reproduction, development of the embryo or foetus, the course of gestation and peri- and postnatal development. Proleukin has been shown to have embryolethal and maternal toxic effects in rats.

The potential risk for humans is unknown.

Proleukin should not be used during pregnancy unless the potential benefit out-weighs the potential risk to the foetus.

Animal Data

Aldesleukin has not been evaluated for effects on fertility, early embryonic development, and prenatal and postnatal development. Studies in rats have demonstrated embryolethality in the presence of maternal toxicity. Teratogenicity in rats was not observed.

Lactation

Risk Summary

It is not known whether this drug is excreted in human milk.

Since the potential for serious adverse reactions in nursing infants is unknown, mothers should not breast feed their infants during treatment.

Females and males of reproductive potential

Contraception

Both sexually active men and women must use highly effective methods of contraception during treatment.

Infertility

Proleukin has not been evaluated for effects on fertility.

ADVERSE DRUG REACTIONS

Summary of the safety profile

Frequency and severity of adverse reactions to Proleukin have generally been shown to be dependent on the route of administration, the dose and the dose schedule.

Most adverse reactions are self-limited and might reverse within 1 to 2 days of discontinuation of therapy. The rate of treatment-related deaths in the 255 MRCC patients who received single-agent Proleukin was 4% (11/255).

Adverse drug reactions from clinical trials (Table 1) are listed by MedDRA system organ class. Within each system organ class, the adverse drug reactions are ranked by frequency, with the most frequent reactions first. Within each frequency grouping, adverse drug reactions are presented in order of decreasing seriousness. In addition, the corresponding frequency category for each adverse drug reaction is based on the following convention (CIOMS III): very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000), very rare (<1/10,000).

The following adverse drug reactions were reported from clinical trials with Proleukin:

Table 1 Adverse drug reactions from clinical trials

Infections and infestations	
Common:	Respiratory tract infection, sepsis
Blood and lymphatic system disorders (see additional information below the table)	
Very common:	Anaemia, thrombocytopenia
Common:	Leukopenia, coagulopathy,eosinophilia
Uncommon:	Neutropenia
Rare:	Febrile neutropenia
Immune system disorders	
Uncommon:	Hypersensitivity
Endocrine disorders	
Very common:	Hypothyroidism
Common	Hyperthyroidism
Metabolism and nutrition disorders	
Very common:	Decrased appetite
Common:	Acidosis, hyperglycaemia, hypercalcaemia, hypocalcaemia, hyperkalaemia, dehydration
Uncommon:	Hypoglycaemia
Rare:	Diabetes mellitus
Psychiatric disorders	
Very common:	Anxiety, confusional state, depression, insomnia
Common:	Irritability, agitation, hallucination
Nervous system disorders	
Very common:	Dizziness, headache, paraesthesia, somnolence
Common:	Neuropathy, syncope, speech disorders, ageusia, lethargy,
Uncommon:	Coma, convulsion, paralysis, muscular weakness
Eye disorders	
Common:	Conjunctivitis
Uncommon:	Optic nerve disorder, optic neuritis
Cardiac disorders	
Very common:	Tachycardia, arrhythmia

Common:	Cyanosis, transient ECG changes, myocardial ischaemia, palpitations, cardiovascular disorders, cardiac failure,
Uncommon:	Myocarditis, cardiomyopathy, cardiac arrest, pericardial effusion
Rare:	Ventricular hypokinesia
Unknown:	Cardiac arrest, pericardial effusion, cardiac tamponade
Vascular disorders	
Very common:	Hypotension
Common:	Phlebitis, hypertension
Uncommon:	Thrombosis, thrombophlebitis, haemorrhage
Respiratory, thoracic and mediastinal disorders	
Very common:	Dyspnoea, cough
Common:	Pulmonary oedema, pleural effusion, hypoxia, haemoptysis, epistaxis, nasal congestion, rhinitis
Gastrointestinal disorders	
Very common:	Nausea, vomiting, diarrhea, stomatitis
Common:	Dysphagia, dyspepsia, constipation, gastrointestinal haemorrhage, rectal haemorrhage, haematemesis, ascitis, cheilitis, gastritis
Uncommon:	Pancreatitis, intestinal obstruction, gastrointestinal perforationgastrointestinal necrosis, gastrointestinal gangrene
Rare:	Activation of quiescent Crohn's disease
Hepatobiliary disorders	
Common:	Transaminases increased, Blood alkaline phosphatase increased, Blood lactate dehydrogenase increased, hyperbilirubinaemia, hepatomegaly, hepatosplenomegaly
Rare:	Hepatic failure (with fatal outcome)
Skin and subcutaneous tissue disorders	
Very common:	Erythema, rash, dermatitis exfoliative, pruritis, hyperhidrosis
Common:	Urticaria, alopecia
Musculoskeletal and connective tissue disorders	
Common:	Myalgia, arthralgia
Uncommon	Myopathy, myositis
Renal and urinary disorders	
Very common:	Oliguria, blood urea increased and blood creastinine increased
Common:	Haematuria, renal failure, anuria
General disorders and administration site conditions	
Very common:	Injection site reaction, injection site pain, pyrexia with or without chills, malaise, asthenia, fatigue, pain, oedema weight gain
Common:	Mucositis, weight loss
Uncommon	Hypothermia
Rare:	Injection site necrosis

Adverse drug reactions from spontaneous reports and literature cases (frequency not known)

The following adverse drug reactions have been derived from post-marketing experience with Proleukin via spontaneous case reports and literature cases. Because these reactions are

reported voluntarily from a population of uncertain size, it is not possible to reliably estimate their frequency which is therefore categorized as not known. Adverse drug reactions are listed according to system organ classes in MedDRA. Within each system organ class, ADRs are presented in order of decreasing seriousness.

Table 2 Adverse drug reactions from spontaneous reports and literature (frequency not known)

Blood and lymphatic system disorders (see additional information below the table)
Disseminated intravascular coagulation, agranulocytosis, aplastic anaemia, haemolytic anaemia
Immune system disorders
Anaphylactic reaction
Nervous system disorders
Haemorrhage intracranial, cerebral haemorrhage, leukoencephalopathy
Cardiac disorders
Cardiac tamponade
General disorders and administration site conditions
Influenza like illness
Respiratory, thoracic and mediastinal disorders
Adult respiratory distress syndrome, pulmonary embolism
Metabolism and nutrition disorders
Hyponatremia, Hypophosphatemia
Musculoskeletal and connective tissue disorders
Rhabdomyolysis
Gastrointestinal disorders
Activation of quiescent Crohn's disease
Hepatobiliary disorders
Cholecystitis
Skin and subcutaneous tissue disorders
Angioedema, vitiligo, Dermatitis bullous, Steven's-Johnson syndrome

Description of selected ADRs

Capillary leak syndrome

Cardiac arrhythmias (supraventricular and ventricular), angina pectoris, myocardial infarction, respiratory insufficiency requiring intubation, gastrointestinal bleeding or infarction, renal insufficiency, oedema and mental status changes may be associated with capillary leak syndrome (see section WARNINGS AND PRECAUTIONS).

Severe manifestations of eosinophilia

During treatment, most patients experience lymphocytopenia and eosinophilia, with rebound lymphocytosis within 24 to 48 hours following treatment. These may be related to the mechanism of antitumor activity of Proleukin. Severe manifestations of eosinophilia have been reported, involving eosinophilic infiltration of cardiac and pulmonary tissues.

Cerebral vasculitis

Cerebral vasculitis, both isolated and in combination with other manifestations, has been reported. Cutaneous and leukocytoplastic hypersensitivity vasculitis has been reported. Some of these cases are responsive to corticosteroids.

Adverse drug reactions with concurrent interferon alpha treatment

The following undesirable effects have been reported rarely in association with concurrent interferon alpha treatment: crescentic IgA glomerulonephritis, oculo-bulbar myasthenia gravis, inflammatory arthritis, thyroiditis, bullous pemphigoid, rhabdomyolysis and Stevens-Johnson syndrome. Severe rhabdomyolysis and myocardial injury, including myocardial infarction, myocarditis and ventricular hypokinesia appear to be increased in patients receiving Proleukin (intravenously) and interferon-alpha concurrently (see section INTERACTIONS).

Bacterial infection

Bacterial infection or exacerbation of bacterial infection, including septicaemia, bacterial endocarditis, septic thrombophlebitis, peritonitis, pneumonia, and local catheter site infections have been reported mainly after intravenous administration (see section WARNINGS AND PRECAUTIONS).

Leukoencephalopathy

There have been rare reports of leukoencephalopathy associated with interleukin-2 in the literature, mostly in patients treated for HIV infection. The role of interleukin-2 in elucidating this event remains uncertain. However opportunistic infections, co-administration of interferons as well as multiple courses of chemotherapy are other factors that may pre-dispose the treated population to such event.

OVERDOSAGE

Adverse reactions following the use of Proleukin are dose-related. Therefore, patients may be expected to experience these events in an exaggerated fashion when the recommended dose is exceeded.

Adverse reactions generally will reverse when the medicinal product is stopped. Any continuing symptoms should be treated supportively. Life-threatening toxicities may be ameliorated by the intravenous administration of dexamethasone, which may also lead to a loss of therapeutic effect of Proleukin.

CLINICAL PHARMACOLOGY

Mechanism of action (MOA) / Pharmacodynamics (PD)

Proleukin acts as a regulator of the immune response. The biological activities of aldesleukin and native human IL-2, a naturally occurring lymphokine, are comparable. The *in-vivo* administration of Proleukin in animals and humans produces multiple immunological effects in a dose dependent manner. The administration of aldesleukin in murine tumour models has been shown to reduce both tumour growth and spread. The exact mechanism by which aldesleukin-mediated immunostimulation leads to antitumour activity is not yet known.

PHARMACOKINETICS (PK)

Absorption and Distribution

The pharmacokinetic profile of Proleukin is characterized by high plasma concentrations after a short intravenous infusion followed by rapid distribution into the extravascular space. Following subcutaneous administration, peak serum levels are attained 2 to 6 hours after injection.

Biotransformation: Metabolism and elimination

The serum half-life curves of aldesleukin in humans following short intravenous (bolus) administration can be described as bi-exponential. The half-life in the alpha-phase is 13 minutes and the half-life in the β phase is 85 minutes. The alpha-phase accounts for 87% clearance of a bolus injection. The serum levels observed are proportional to the dose of aldesleukin.

The subcutaneous kinetics can be described by a one-compartment model. The IL-2 absorption half-life is 45 minutes, while the elimination half-life is 5.3 hours. The longer half-life estimate, compared with the intravenous result is probably due to continued absorption of IL-2 from the subcutaneous injection site during the plasma elimination phase. Absolute systemic bioavailability following subcutaneous injection was greater than 35%.

The kidney is the major clearance route of recombinant IL-2 (rIL-2) in animals, and most of the injected dose is metabolized in the kidney with no biologically active aldesleukin appearing in the urine. A secondary elimination pathway is receptor-mediated uptake. This active process is induced after chronic dosing. After an aldesleukin-free period between dosing cycles, the clearance of IL-2 is restored to its original value.

The mean clearance rate of Proleukin in cancer patients is 155 to 420 mL/min. Pharmacokinetic parameters based on a recent study was comparable to results from the previous studies, with a mean clearance of 243.2 to 346.3 mL/min and a terminal half-life (t ½) of 100.4 to 123.9 min.

The serum levels observed are proportional to the dose of Proleukin.

Immunogenicity

57 of 77 (74%) metastatic renal cell carcinoma (MRCC) patients treated with Proleukin administered every 8 hours developed low titers of non-neutralizing anti-adesleukin antibodies. Neutralizing antibodies were not detected in this group of patients, but have been detected in 1/106 (<1%) patients treated with i.v. Proleukin using a large number of schedules and doses. The clinical significance of anti-aldesleukin antibodies is unknown.

A recent study examined the influence of anti-IL2 antibodies after one cycle on therapy on the pharmacokinetics of Proleukin administered as a 15 minute i.v. infusion. 84.2% of patients enrolled in this study developed anti-IL2 antibodies. The formation of anti-IL-2 antibodies after one cycle of therapy did not result in a decrease in aldesleukin exposure. Overall, steady-state concentration (C_{SS}) and elimination half-life (t ½) were comparable between Cycle 1 and Cycle 2 in patients with presence of anti-aldesleukin antibodies.

Special populations

Renal impairment

No formal studies have been conducted for patients with pre-existing renal impairment.

Pharmacokinetics of Proleukin IL-2 following intravenous bolus administration of IL-2 was evaluated in a small patient population of 15 cancer patients who were developing renal toxicity. Creatine clearance (CL_{cr}) decreased following repeated doses of IL-2. Decrease in CL_{cr} was not associated with a decrease in IL-2 clearance.

Geriatric patients

There were a very small number of patients aged 65 and over in clinical trials of Proleukin. The response rates were similar in patients 65 years and over as compared to those younger than 65 years of age. The median number of courses and the median number of doses per course were similar between older and younger patients.

However, because no formal clinical trials were conducted to compare the pharmacokinetics efficacy or safety of Proleukin in geriatric patients to those in younger patients it is recommended that clinicians exercise caution when prescribing Proleukin to geriatric patients since renal and hepatic function may decrease with increasing age. Hence, elderly patients may be more susceptible to the side effects of Proleukin and caution is recommended in the treatment of such patients.

CLINICAL STUDIES

The efficacy of Proleukin as single-agent therapy was demonstrated in a series of single and multicenter, historically-controlled studies. Eligible patients generally had an Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) of 0 or 1 and normal organ function, as determined by medical history, laboratory testing, cardiac stress test, pulmonary function tests, and creatinine ≤1.5 mg/dL. Studies excluded patients with brain metastases, active infections, organ allografts and diseases requiring steroid treatment. The studies had very similar evaluation methods, and data was pooled from several studies. Doses were either withheld or reduced in the clinical studies for specific toxicities (see section ADVERSE DRUG REACTIONS). Table 3 below summarizes the efficacy results of these pooled analyses.

Table 3 Response rates to Proleukin as single-agent therapy in clinical trials

Indication	Mode of administration	(N)	Type of response	Number of responding patients (response rate)	Median response duration in months (range)
MRCC	CIV	193	CR	8 (4%)	9.6+ (1.6 to 19.6+)
			PR	20 (10%)	11.4 (4.6-18.6)
			PR+CR	28 (15%)	8.6 (0.9 -31.6+)

Abbreviations: N: number of patients; MRCC: metastatic renal cell carcinoma; i.v.: intravenous; CIV: continuous i.v. infusion; CR: complete response; PR: partial response.

Continuous intravenous infusion

One hundred and ninety three patients with MRCC were treated with single-agent Proleukin by continuous i.v. infusion in two clinical studies. In the pooled results for patients who were considered evaluable for efficacy, objective response was seen in 28 of 193 (15%) patients, 7 (4%) with a complete response and 21 (11%) with a partial response (see Table 3). Responses were observed in both lung and non-lung sites, including liver, bone, skin, lymph node, renal bed occurrences, and soft tissue.

NON-CLINICAL SAFETY DATA

Repeated Dose Toxicity

Repeated doses of aldesleukin in animals by the intravenous or subcutaneous route caused dose-related pharmacological effects such as lymphocytosis, eosinophilia, anemia, extramedullary hematopoiesis, hepato-splenomegaly, and lymphoid hyperplasia, which were fully or partially reversible.

Mutagenicity and Carcinogenicity

Aldesleukin has not been evaluated for mutagenicity or carcinogenicity. The potential for mutagenicity or carcinogenicity is considered low given the similarities in structure and function between aldesleukin and endogenous IL-2.

Reproductive Toxicity

See section PREGNANCY, LACTATION, FEMALES AND MALES OF REPRODUCTIVE POTENTIAL for reproductive toxicity.

Local Tolerance

The intravenous local tolerance of aldesleukin has not been evaluated. Subcutaneous dosing in rats, rabbits, and monkeys caused local toxicity and irritation that included erythema and edema, macroscopic findings at the injection sites (discoloration and subcutaneous hemorrhage, thickening, or edema), and microscopic findings at the injection site that included marked acute inflammation, minimal to moderate hemorrhage, and subcutaneous cellulitis (necrosis and pronounced mixed inflammatory cell infiltration).

INCOMPATIBILITIES

Reconstitution and dilution procedures other than those recommended may result in incomplete delivery of bioactivity and/or formation of biologically inactive protein.

Use of Bacteriostatic Water for Injection or Sodium Chloride Injection 0.9% should be avoided because of increased aggregation.

Proleukin must not be mixed with other medicinal products except those mentioned in section INSTRUCTIONS FOR USE AND HANDLING.

It is recommended that devices or administration sets containing in-line filters are not used for delivery of Proleukin. Bioassays have shown significant loss of aldesleukin when filters are used.

STORAGE

See also folding box.

Store at 2°C to 8°C (in a refrigerator). Do not freeze.

Protect from light. Store in the original packaging.

When reconstituted or reconstituted and diluted according to the directions, chemical and physical in-use stability has been demonstrated for up to 24 hours when stored at refrigerated and room temperatures (4°C to 25°C).

From a microbiological point of view, the reconstituted product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2°C to 8°C, unless reconstitution / dilution has taken place in controlled and validated aseptic conditions.

Proleukin should not be used after the date marked "EXP" on the pack.

Proleukin must be kept out of the reach and sight of children.

INSTRUCTIONS FOR USE AND HANDLING

Reconstitution of Proleukin powder for solution for infusion

Vials (which contain 22 million IU aldesleukin) must be reconstituted with 1.2 mL of Water for Injection. After reconstitution the obtained solution contains 18 million IU aldesleukin per milliliter. The reconstituted solution has a pH of 7.5 (range 7.2 to 7.8).

Using sterilised injection syringe and injection needle, inject 1.2 mL Water for Injection into the vial of Proleukin. Direct the diluent against the side of the vial to avoid excessive foaming. Swirl gently to facilitate complete dissolution of the powder. **Do not shake.** The appropriate dose can then be withdrawn with a sterile injection syringe and diluted for continuous intravenous infusion.

As for all parenteral medicinal products, inspect the reconstituted solution visually for particulate matter and discoloration prior to administration. The solution may be slightly yellow.

The product should be brought to room temperature prior to administration.

Dilution instructions for continuous intravenous infusion:

The total daily dose of reconstituted aldesleukin should be diluted as necessary to up to 500 mL with glucose 50 mg/mL (5%) solution for infusion containing 1 mg/mL (0.1%) human albumin, and infused over a 24-hour period.

Order of addition: human albumin should be added and mixed with the glucose solution prior to the addition of the reconstituted aldesleukin. Human albumin is added to protect against loss of bioactivity.

For single use only. Any unused solution, the vial, and the syringe used for the reconstituted solution should be adequately disposed of, in accordance with local requirements for the handling of biohazardous waste.

Manufacturer:

See folding box.

International Package Leaflet

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Novartis Pharma AG, Basel, Switzerland