SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

PROLEUKIN 18 x 106 IU

Powder for solution for injection or infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

After reconstitution with 1.2ml water for injections, according to the instructions (see section 6.6), each 1ml solution contains 18 x 10^6 IU (1.1mg) aldesleukin.

Each vial of Proleukin powder for solution for injection or infusion contains 22 x 10^6 IU 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.

Proleukin contains less than 23mg sodium per 1ml, and can be considered as 'sodium-free'.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Powder for solution for injection or infusion.

The powder is sterile, white and lyophilised.

4 CLINICAL PARTICULARS

4.1 Therapeutic 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) 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.

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.

4.2 Posology and method of administration

Proleukin should be administered intravenously by continuous infusion or by subcutaneous injection. The following dosage regimen is recommended to treat adult patients with metastatic renal cell carcinoma.

Continuous intravenous infusion

18 x 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-weeks without Proleukin therapy period of the first cycle, a second induction cycle should be given.

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

Subcutaneous injection

18 x 10^6 IU as subcutaneous (s.c.) injection is administered every day for 5 days, followed by 2 days without Proleukin therapy. For the following 3 weeks, 18 x 10^6 IU s.c. is administered on days 1 and 2 of each week followed by 9 x 10^6 IU on days 3-5. On days 6 and 7 no treatment is administered. After 1 week without Proleukin therapy this 4-week cycle should be repeated.

Maintenance: The same cycle as described above may be given to patients who respond or have disease stabilisation.

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.

Renal or hepatic impairment

No formal studies have been conducted to evaluate the pharmacokinetics, safety and tolerability of Proleukin in patients with pre-existing renal or hepatic impairment (see section 4.4).

Elderly patients

No formal clinical trials were conducted to compare the pharmacokinetics, efficacy or safety of Proleukin in geriatric patients to those in younger patients. There were a very small number of patients aged 65 and over in clinical trials of Proleukin. Clinicians should exercise caution in prescribing Proleukin to geriatric patients since decline in renal and hepatic function may occur with increasing age. Hence, elderly patients may be more susceptible to the side effects of Proleukin (see section 5.1 and 5.2).

Paediatric population

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

4.3 Contraindications

Proleukin therapy is contra-indicated in the following patients:

1. Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
2. Patients with a performance status of ECOG ≥ 2[*)].
3. Patients with a simultaneous presence of a performance status of ECOG 1 or greater[*)] and more than one organ with metastatic disease sites and a period of <24 months between initial diagnosis of primary tumour and the date the patient is evaluated for Proleukin 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 <60mm Hg during 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).

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 normal range.
3. Patients with organ allografts.
4. Patients who are likely to require corticosteroids.
5. Patients with pre-existing auto-immune disease.

*) ECOG: see section 4.1.

4.4 Special warnings and precautions for use

Patient screening
See also section 4.3.

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, as listed in section 4.1 and 4.3, present at treatment start: the very low risk group has no risk factor, the low risk group one risk factor, the median group any combination of 2 risk factors, and the high risk group has the simultaneous presence of all 3 risk factors. Response rates and 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.

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.

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. The frequency and severity are lower after subcutaneous administration than with intravenous infusion.

Capillary leak syndrome usually begins within hours after initiation of Proleukin treatment and clinical symptoms (i.e. hypotension, tachycardia, dyspnea, pulmonary oedema) are reported to occur after 2 to 12 hours. Careful monitoring of circulatory and respiratory function is required particularly for patients receiving intravenous Proleukin (see section laboratory and clinical tests).

In some patients hypotension resolves 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.

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.

Because 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 developing 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 patient response to psychotropic medicinal products (see section 4.5).

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 4.5). Close monitoring should be applied to all patients with pre-existing renal or hepatic impairment.

Precautions for use

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 for monitoring the patient's relevant clinical and laboratory parameters. Subcutaneous treatment can be administered in an outpatient setting by qualified health care professionals.

Should serious adverse events occur, dosage should be modified according to section 4.2. 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.

Effusion 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).

Infections

Pre-existing bacterial infections should be treated prior to initiation of Proleukin therapy. Toxicities associated with Proleukin administration may be exacerbated by concurrent bacterial infection.

Administration of Proleukin may be associated with an increased incidence and/or severity of bacterial infection, including septicaemia, bacterial endocarditis, septic thrombophlebitis, peritonitis and pneumonia. This has mainly been reported after intravenous administration. Except for several cases due to *Escherichia coli*, causative organisms have been *Staphylococcus aureus* or *Staphylococcus epidermidis*. During continuous intravenous infusion of Proleukin 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. In patients on subcutaneous treatment injection site reactions are common, sometimes with necrosis. The effects can be reduced by changing the injection site over the body.

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.

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 time of Proleukin administration to reduce fever. Pethidine may be added to control the rigours associated with fever. Anti-emetics and antidiarrhoeals 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 tests: 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 haematologic tests* – including WBC (with differential and platelet counts). Proleukin administration may cause anaemia and thrombocytopenia.
- *Blood chemistry* - including fluid and electrolyte balance, blood glucose, renal and hepatic function tests. Close monitoring should be applied to all patients with pre-existing renal or hepatic impairment.
- *Chest x-rays and ECG* – Pre-treatment evaluation should include chest x-rays and electrocardiogram (ECG, plus stress test if indicated), and arterial blood gases. Abnormalities or other evidence for cardiac ischemia should be followed-up by further testing to exclude significant coronary artery disease.

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

Pulmonary function should be monitored closely in patients who develop rales or increased respiratory rate, or who complain of dyspnoea. Monitoring of pulmonary function during therapy includes pulse oxymetry and arterial blood gas determination.

Proleukin is essentially sodium free, see section 2.

4.5 Interaction with other medicinal products and other forms of interaction

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

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 4.3).

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

Concurrent administration of medicinal products with hepatotoxic, nephrotoxic, myelotoxic, or cardiotoxic effects may increase the toxicity of Proleukin in these systems.

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

Renal or hepatic metabolism or excretion of concomitantly administered medicinal products may be altered by the administration of Proleukin, since Proleukin administration results in reversible elevation of hepatic transaminases, serum bilirubin, serum urea and serum creatinine. Other medicinal products with known nephrotoxic or hepatotoxic potential should be used with caution (see section 4.4).

Proleukin may affect central nervous function. Therefore, interactions could occur following concomitant administration of centrally acting medicinal products. Proleukin may alter patient response to psychotropic medicinal products and therefore patients should be monitored (see section 4.4).

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 recommended not to use contrast media within 2 weeks after treatment with Proleukin.

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

4.6 Fertility, pregnancy and lactation

Women of child-bearing potential and contraception in males and females

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

Pregnancy

There are no adequate data 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 (see also section 5.3).

The potential risk for humans is unknown.

Proleukin should not be used during pregnancy unless the potential benefit to the patient justifies the potential risk to the foetus.

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

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

4.7 Effects on ability to drive and use machines

Proleukin may affect central nervous system function. Hallucination, somnolence, syncope, convulsions may occur during treatment with Proleukin 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.

4.8 Undesirable effects

Frequency and severity of adverse reactions to Proleukin have generally been shown to be dependent on route of administration, dose and 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 metastatic RCC patients who received single-agent Proleukin was 4% (11/255). In patients on subcutaneous treatment less than 1% died of treatment related adverse reactions.

Adverse reactions (Table 1) are ranked under headings of frequency, the most frequent first, using the following convention: 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), not known (cannot be estimated from the available data).

The following adverse drug reactions were reported from clinical studies and from post-marketing experience with Proleukin:

Table 1

Infections and infestations	
Common:	Respiratory tract infection, sepsis.
Blood and lymphatic system disorders	
Very common:	Anaemia, thrombocytopenia.
Common:	Leucopenia, coagulopathy including disseminated intravascular coagulation, eosinophilia.

Uncommon:	Neutropenia.
Rare:	Agranulocytosis, aplastic anaemia, haemolytic anaemia, neutropenic fever.
Immune system disorders	
Uncommon:	Hypersensitivity reactions.
Rare:	Anaphylaxis.
Endocrine disorders	
Very common:	Hypothyroidism.
Common:	Hyperthyroidism.
Metabolism and nutrition disorders	
Very common:	Anorexia.
Common:	Acidosis, hyperglycaemia, hypocalcaemia, hypercalcaemia, hyperkalaemia, dehydration.
Uncommon:	Hypoglycaemia.
Rare:	Diabetes mellitus.
Psychiatric disorders	
Very common:	Anxiety, confusion, depression, insomnia.
Common:	Irritability, agitation, hallucinations.
Nervous system disorders	
Very common:	Dizziness, headache, paraesthesia, somnolence.
Common:	Neuropathy, syncope, speech disorders, taste loss, lethargy.
Uncommon:	Coma, convulsions, paralysis, myasthenia.
Not known:	Intracranial/cerebral haemorrhage, cerebrovascular accident, leukoencephalopathy (see additional information below the table).
Eye disorders	
Common:	Conjunctivitis.
Rare:	Optic nerve disorder including optic neuritis.
Cardiac disorders	
Very common:	Tachycardia, arrhythmia, chest pain.
Common:	Cyanosis, transient ECG changes, myocardial ischaemia, palpitations, cardiovascular disorders including cardiac failure.
Uncommon:	Myocarditis, cardiomyopathy, cardiac arrest, pericardial effusion.
Rare:	Ventricular hypokinesia.
Not known:	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 effusions, hypoxia, haemoptysis, epistaxis, nasal congestion, rhinitis.
Rare:	Pulmonary embolism, adult respiratory distress syndrome.
Gastrointestinal disorders	
Very common:	Nausea with or without vomiting, diarrhea, stomatitis.
Common:	Dysphagia, dyspepsia, constipation, gastrointestinal bleeding including rectal haemorrhage, haematemesis, ascitis, cheilitis, gastritis.
Uncommon:	Pancreatitis, intestinal obstruction, gastrointestinal perforation including necrosis/gangrene.
Rare:	Activation of quiescent Crohn's disease.
Hepatobiliary disorders	
Common:	Elevation of hepatic transaminases, elevation of alkaline phosphatase, elevation of lactic dehydrogenase, hyperbilirubinaemia, hepatomegaly or hepatosplenomegaly.
Rare:	Cholecystitis, liver failure with fatal outcome.
Skin and subcutaneous tissue disorders	
Very common:	Erythema and rash, exfoliative dermatitis, pruritus, sweating.
Common:	Alopecia, urticaria.
Uncommon:	Vitiligo, Quincke's oedema.
Rare:	Vesiculobullous rash, Stevens-Johnson syndrome.
Musculoskeletal and connective tissue disorders	
Common:	Myalgia, arthralgia.
Uncommon:	Myopathy, myositis.
Not known:	Rhabdomyolysis.
Renal and urinary disorders	
Very common:	Oliguria, serum urea increased, serum creatinine increased.
Common:	Haematuria, renal failure, anuria.
General disorders and administration site conditions	
Very common:	Injection site reaction*, injection site pain*, injection site inflammation*, fever with or without chills, malaise asthenia and fatigue, pain, oedema, weight gain, weight loss.
Common:	Mucositis, injection site nodule, hypothermia.
Rare:	Injection site necrosis.

Notes:

* Frequency of injection site reaction, pain and inflammation is less following administration by continuous intravenous infusion.

Leukoencephalopathy

There have been rare reports of leukoencephalopathy associated with Proleukin in the literature, mostly in patients treated for HIV infection. In some cases there were other risk factors like opportunistic infections, co-administration of interferons as well as multiple courses of chemotherapy that might predispose the treated population to such event.

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 4.4). The frequency and severity of capillary leak syndrome are lower after subcutaneous administration than with continuous intravenous infusion.

Severe manifestations of eosinophilia

During treatment most patients experience lymphocytopenia and eosinophilia, with a rebound lymphocytosis within 24 to 48 hours following treatment. These may be related to the mechanism of antitumour 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 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 4.5).

Bacterial infection

Bacterial infection or exacerbation of bacterial infection, including septicaemia, bacterial endocarditis, septic thrombophlebitis, peritonitis, pneumonia, and local catheter site infection have been reported mainly after intravenous administration (see section 4.4).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions

via the national reporting system listed in Appendix V*.

4.9 Overdose

Adverse reactions following the use of Proleukin are dose-related. Therefore patients can 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 result in loss of the therapeutic effects of Proleukin.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: immunostimulants, cytokines and immunomodulators, interleukins, aldesleukin

ATC code: L03A C01

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.

Geriatrics

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 less 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 (see section 4.2 and 5.2).

5.2 Pharmacokinetic properties

The pharmacokinetic parameters of IL-2, following an intravenous or subcutaneous administration of aldesleukin in metastatic renal cell carcinoma and metastatic malignant melanoma patients is as follows:

Absorption and distribution

The pharmacokinetic profile of aldesleukin is characterized by high plasma concentrations after a short intravenous infusion followed by rapid distribution

into the extravascular space. Following subcutaneous administration, peak plasma levels are attained 2 to 6 hours after injection.

Absolute bioavailability of subcutaneous aldesleukin ranges between 31-47%.

Following a continuous intravenous infusion-fixed and continuous intravenous infusion-decrescendo administration of aldesleukin, the mean t_{max} of IL-2 was 11 hours and 4.4 hours, respectively. Compared to the serum levels following the subcutaneous administration, the observed serum levels following the continuous intravenous infusion-fixed and continuous intravenous infusion-decrescendo administration of aldesleukin are 3.20 and 1.95-fold higher.

Observed aldesleukin serum levels following intravenous administration are proportional to the dose of Proleukin.

Biotransformation 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 α phase is 13 minutes and the half-life in the β phase is 85 minutes. The α phase accounts for clearance of 87% of a bolus injection. The mean clearance rate of Proleukin aldesleukin in cancer patients is 155 to 420mL/min. Pharmacokinetic parameters based on a recent study, where Proleukin was administered intravenously to patients with metastatic renal cell carcinoma and metastatic melanoma, (n=4 MRCC, 16 metastatic melanoma) was comparable to results from the previous studies, with a mean clearance of 243.2 to 346.3mL/min and a terminal half-life ($t_{1/2}$) of 100.4 to 123.9 min.

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 3-5 hours. The longer half-life estimate, compared with the intravenous result is likely due to continued absorption of IL-2 from the subcutaneous injection site during the plasma elimination phase.

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 IL-2 receptor- mediated uptake. This active process is induced after chronic dosing. After an aldesleukin-free period between dosing cycles (9-16 days), the clearance of IL-2 is restored to its original value.

Immunogenicity

Fifty-seven of 77 (74%) metastatic renal cell carcinoma (MRCC) patients treated with an every 8-hour Proleukin regimen and 33 of 50 (66%) metastatic melanoma patients treated with a variety of i.v. regimens developed low titers of non-neutralizing anti-aldesleukin 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 wide variety 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 Proluekin administered as a 15 minute i.v. infusion in patients with MRCC or metastatic melanoma. 84.2% of patients developed anti-IL2 antibodies in this study. The formation of anti-IL-

2 antibodies after one cycle of therapy did not result in a decrease in aldesleukin exposure in MRCC or MM. Overall, steady-state concentration (Css) and elimination half-life (t1/2) 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 aldesleukin 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 (CLcr) decreased following repeated doses of IL-2. Decrease in CLcr was not associated with a decrease in IL-2 clearance.

Geriatrics

No formal clinical trials were conducted to compare the pharmacokinetics, efficacy or safety of Proleukin in geriatric patients to those in younger patients; since decline in renal and hepatic function may occur with increasing age, caution is recommended in the treatment of such patients (see section 4.2 and 5.1).

5.3 Preclinical safety data

Animal data on repeated dose toxicity and local tolerance do not add any information to what is already mentioned in other sections of the SPC. Aldesleukin has not been evaluated for effects on fertility, early embryonic development, and prenatal and postnatal development. Embryo-foetal development studies in rats have demonstrated embryolethality in the presence of maternal toxicity. Teratogenicity in rats was not observed.

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.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Mannitol (E421)
Sodium laurilsulfate
Sodium dihydrogen phosphate dihydrate (pH adjuster)
Disodium hydrogen phosphate dihydrate (pH adjuster)

6.2 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 6.6.

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.

6.3 Shelf life

3 years

After reconstitution: 24 hours

Diluted Proleukin should be used within 48 hours after reconstitution, which includes the time taken for infusion.

6.4 Special precautions for storage

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

Store in the original package in order to protect from light.

When reconstituted or reconstituted and diluted according to the directions, chemical and physical in-use stability has been demonstrated for up to 48 hours when stored at refrigerated and room temperatures (2ºC to 30ºC).

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 2ºC to 8ºC, unless reconstitution/ dilution has taken place in controlled and validated aseptic conditions.

6.5 Nature and contents of container

Proleukin is supplied in 5ml single-use clear Type I glass vials with a stopper of synthetic rubber. The product is supplied in carton boxes of 1 or 10 vials.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Reconstitution of Proleukin powder for solution for injection or infusion:

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

Using sterilised injection syringe and injection needle, inject 1.2 ml Water for Injections 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 injected subcutaneously or 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 directions for continuous intravenous infusion:

The total daily dose of reconstituted aldesleukin should be diluted as necessary 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.

7 MARKETING AUTHORISATION HOLDER

Novartis Pharmaceuticals UK Limited
Frimley Business Park
Frimley
Camberley
Surrey
GU167SR

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