Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

PROLEUKIN 18 x 10^6 IU
Powder for solution for injection or infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

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

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Powder for solution for injection or infusion.
The powder is sterile, white and lyophilized.

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) 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.

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 as a continuous infusion for 5 days, followed by 2-6 days without active substance, an additional 5 days of intravenous Proleukin as a continuous infusion and 3 weeks without active substance. This constitutes one induction cycle. After the 3-week rest 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 every day for 5 days, followed by 2 days rest. For the following 3 weeks 18 x 10^6 IU s.c. 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 rest this 4-week cycle should be repeated.
Maintenance: Maintenance cycles as described above may be given to patients who respond or have disease stabilisation.

If a patient cannot 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.

Elderly: Elderly patients may be more susceptible to the side effects of Proleukin and caution is recommended in the treatment of such patients.

Children: Safety and efficacy of Proleukin in children have not yet been established.

4.3 Contraindications

Proleukin therapy is contra-indicated in the following patients:

1. Patients with hypersensitivity to the active substance or to any of the excipients.
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 < 60 mm 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 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 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.

Warnings

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 and reduced organ perfusion. Severe CLS resulting in death has been reported. Capillary leak syndrome usually begins within hours after initiation of Proleukin treatment. The frequency and severity are lower after subcutaneous administration than with continuous intravenous infusion. In some patients hypotension resolves without therapy. In others, treatment is required with cautious use of intravenous fluids, albumin or, in more refractory cases, low-dose dopamine. If these measures are not successful, the Proleukin therapy should be interrupted.

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 secondary to capillary leakage.

Proleukin may exacerbate pre-existing autoimmune disease, resulting in life threatening complications. 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. A few patients with quiescent Crohn's disease had activation of their disease following treatment with Proleukin, requiring surgical intervention.

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

Pulmonary function should be monitored closely in patients who develop rales or increased respiratory rate, or who complain of dyspnoea. Some patients may require intubation for management of transient respiratory failure. Intubation has only been reported for patients treated with intravenous Proleukin.

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).

Since Proleukin administration results in reversible elevation of hepatic transaminases, serum bilirubin, serum urea and serum creatinine, patients with pre-existing renal or hepatic dysfunction should be closely monitored. 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).

There is a possibility of disturbances in the glucose metabolism in diabetes patients when Proleukin is administered subcutaneously.

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.

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

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).

Baseline electrocardiogram (ECG) (+ stress test if indicated), performance status, vital signs, objective evaluation for coronary vascular disease and, in patients with a history of smoking or respiratory disease, pulmonary function tests with arterial blood gases are recommended as adjuncts to history and physical examination in the pre-treatment evaluation of patients.

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.

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, renal and hepatic function tests. Proleukin may cause renal dysfunction with oliguria, and reversible elevation of hepatic transaminases, serum bilirubin, serum urea and serum creatinine.
- *Chest x-rays*.

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. 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

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

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.

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 causes adverse events that affect the ability to drive and operate machines.

Patients should not drive or operate machines until they have recovered from the undesirable effects.

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. A small number of patients receiving continuous intravenous infusion (3%) died of treatment related adverse reactions. 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.
Blood and lymphatic system disorders (see additional information below the table)*	
Very common:	Anaemia, thrombocytopenia.
Common:	Leucopenia, coagulation disorders including disseminated intravascular coagulation.
Rare:	Agranulocytosis, aplastic anaemia, haemolytic anaemia.
Not known:	Neutropenia, neutropenic fever, eosinophilia (see additional information below the table).
Immune system disorders	
Uncommon:	Hypersensitivity reactions.
Rare:	Anaphylaxis.
Endocrine disorders	
Uncommon:	Hypothyroidism, hyperthyroidism
Metabolism and nutrition disorders	
Very common:	Anorexia.
Common:	Hyperglycaemia, hypocalcaemia, hyperkalaemia, dehydration.
Uncommon:	Hypercalcaemia.
Rare:	Diabetes mellitus, hypoglycaemia.
Psychiatric disorders	
Very common:	Anxiety, confusion.
Common:	Mental status changes including irritability, agitation, depression, hallucinations, insomnia.
Nervous system disorders	
Very common:	Dizziness, headache, somnolence.
Common:	Nervous system disorder, not otherwise specified (including paraesthesia and neuropathy), syncope, speech disorders.
Uncommon:	Convulsions, paralysis, myasthenia, taste loss.
Rare:	Lethargy, coma, central nervous system lesion.
Not known:	Intracranial/cerebral haemorrhage, cerebrovascular accident, leukoencephalopathy (see additional information below the table).
Eye disorders	
Common:	Conjunctivitis.
Rare:	Optic neuropathy.

Cardiac disorders	
Very common:	Tachycardia; chest pain, angina pectoris.
Common:	Arrhythmia, cyanosis.
Uncommon:	Myocardial infarction, cardiovascular disorders including heart failure, myocarditis, transient ECG changes, cardiomyopathy, palpitations, myocardial ischaemia.
Rare:	Ventricular hypokinesia.
Not known:	Cardiac arrest, pericardial effusion, cardiac tamponade.
Vascular disorders	
Very common:	Hypotension.
Common:	Phlebitis, hypertension.
Uncommon:	Thrombosis, haemorrhage.
Rare:	Thrombophlebitis.
Respiratory, thoracic and mediastinal disorders	
Very common:	Dyspnoea, cough.
Common:	Pulmonary oedema, pleural effusions, hypoxia, nasal congestion.
Uncommon:	Haemoptysis, epistaxis.
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.
Uncommon:	Cheilitis, gastritis.
Rare:	Activation of quiescent Crohn’s disease, pancreatitis, intestinal obstruction.
Not known:	Gastrointestinal perforation including necrosis/gangrene.
Hepatobiliary disorders	
Common:	Elevation of hepatic transaminases and alkaline phosphatase, elevation of lactic dehydrogenase, hyperbilirubinaemia.
Rare:	Cholecystitis, liver failure with fatal outcome.
Skin and subcutaneous tissue disorders	
Very common:	Erythema/rash, skin exfoliation, pruritus.
Common:	Sweating, alopecia.
Uncommon:	Vitiligo, Quincke’s oedema.
Rare:	Vesiculobullous rash, Stevens-Johnson syndrome.
Musculoskeletal and connective tissue disorders	
Common:	Myalgia, arthralgia.
Renal and urinary disorders	
Very common:	Oliguria with elevated serum urea and serum creatinine.
Common:	Haematuria.
Uncommon:	Renal failure.
General disorders and administration site conditions	
Very common:	Injection site reaction**, injection site pain**, injection site inflammation**, fever with or without chills, malaise and fatigue, pain, oedematous weight gain, weight loss.
Common:	Oedema, 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.

Capilliary 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, 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 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).

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.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

ATC classification system: 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 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.

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
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. Observed serum levels 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 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. 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 tmax 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.

Elimination
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.

The observed clearance rates in humans after short intravenous infusion (15 minutes) and after 24-hour continuous intravenous infusion approximate renal glomerular filtration clearance and range from 140-300 ml/min.

5.3 Preclinical safety data

Animal studies are insufficient with respect to effects on fertility, embryo/foetal development and peri- and postnatal development. In a study with intravenous application of Proleukin in rats maternal toxicity and an increased embryolethality was seen in all tested dose-groups (0.5- 2mg/kg/day).

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Mannitol (E421)
Sodium laurylsulphate
Sodium dihydrogen phosphate monohydrate (pH adjuster)
Disodium hydrogen phosphate (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

2 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 2°C to 8 °C (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 (2°C to 30°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.

6.5 Nature and contents of container

Proleukin is supplied in 5 ml 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 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.

7 MARKETING AUTHORISATION HOLDER

Novartis Pharmaceuticals UK Ltd

Frimley Business Park
Frimley, Camberley,
Surrey GU16 7SR
United Kingdom

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