NEW ZEALAND DATA SHEET

1. NAME OF THE MEDICINAL PRODUCT

PROLEUKIN® 18 x 10^6 IU, powder for solution for injection or infusion
Aldesleukin powder for injection 18 million International Units (1.1mg)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial of Proleukin® powder for solution for injection or infusion contains 22 x 10^6 International Units (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.

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

3. PHARMACEUTICAL FORM

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

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

Proleukin is indicated for:

- The treatment of metastatic melanoma (MM).
- The treatment of metastatic renal cell carcinoma (MRCC).

Risk factors associated with decreased response rates and median survival have been identified and should be taken into consideration when selecting appropriate patients for therapy (see Contraindications).

4.2 Posology and method of administration

Posology

For MRCC, Proleukin should be administered by high dose intravenous (i.v.) bolus infusion, by continuous i.v. infusion or by subcutaneous injection.

For MM, Proleukin should be administered by high dose i.v. bolus infusion or by continuous i.v. infusion.

High dose bolus infusion

0.6 x 10^6 IU/kg (0.037 mg//kg) is administered every 8 hours by a 15-minute intravenous infusion for a maximum of 14 doses. Following 5 to 9 days without Proleukin therapy, the schedule is repeated for another 14 doses, for a maximum of 28 doses per course, as tolerated. During clinical trials, doses were frequently withheld for toxicity Metastatic RCC patients treated with this schedule received a median of 20 of the 28 doses during the first course of therapy. Metastatic melanoma patients received a median of 18 of the 28 doses during the first course of therapy.

Maintenance: Patients should be evaluated for response approximately 4 weeks after completion of a course of therapy and again immediately prior to the scheduled start of the next treatment course. Additional courses of treatment should be given to patients only if there is evidence of tumor regression following the last course and retreatment is not contraindicated (see Contraindications and

Warnings and precautions). Each treatment course should be separated by a period without Proleukin therapy of at least 7 weeks.

Continuous intravenous infusion

18 x 10^6 IU per m^2 per 24-hours is administered as a continuous i.v. infusion for 5 days, followed by 2 to 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 to 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 maintenance cycles as described above may be given to patients who respond or have 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.

Renal impairment

No formal studies have been conducted to evaluate the pharmacokinetics; safety and tolerability of Proleukin in patients with pre-existing renal impairment (see 6 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 the pharmacokinetics; safety and tolerability of Proleukin in patients with pre-existing hepatic impairment (see section 6 Warnings and precautions).

Proleukin administration results in 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.

Special populations

Paediatric patients (below 18 years)

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

Geriatrics (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 in prescribing Proleukin to geriatric patients since decline in renal and hepatic function may occur 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 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.

4.3 Contraindications

Proleukin therapy is contraindicated in the following patients:

- Patients with known hypersensitivity to the active substance or to any of the excipients.
- Patients with an Eastern Cooperative Oncology Group (ECOG)* performance status of 2 or greater.
- Patients with all three risk factors associated with decreased response rates and median survival. These risk factors are: an ECOG* performance status of 1 or greater; more than one organ with metastatic disease; a period of <24 months between initial diagnosis of primary tumor and the date the patient is evaluated for aldesleukin treatment.
- Patients with a significant history or current evidence of severe cardiac disease. In questionable cases a stress test should be performed.
- Patients with evidence of active infection requiring antibiotic therapy.
- Patients with a PaO_2 <60 mm Hg during rest.
- Patients with pre-existing severe major organ dysfunction.
- 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:

- Patients with White Blood Count (WBC) <4,000/mm^3; platelets <100,000/mm^3; hematocrit (HCT) <30%.
- Patients with serum bilirubin and creatinine outside normal range.
- Patients with organ allografts.
- Patients who are likely to require corticosteroids.
- Patients with pre-existing auto-immune disease.
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4.4 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 treatment start: the very low risk group has no risk factor, the low risk group one risk factor, the intermediate risk 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 (see Contraindications).

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 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 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 edema, 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 following laboratory and clinical tests.

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 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 Interactions). Close monitoring should be applied to all patients with pre-existing renal or hepatic impairment (see 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 patient 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*, main causative organisms have been *Staphylococcus aureus* or *Staphylococcus epidermidis*.

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.

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 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 time of Proleukin administration to reduce fever. Pethidine may be added to control the rigors associated with fever. Anti-emetics and antidiarrheal 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 or metastatic melanoma, the following tests are recommended for all patients on Proleukin therapy, prior to beginning treatment and then periodically thereafter:

- Standard hematologic 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. Close monitoring should be applied to all patients with pre-existing renal or hepatic dysfunction.
- 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 high dose intravenous Proleukin a Thallium stress tests should be performed to document unimpaired wall motion. Adequate pulmonary function should be documented (FEV1 >2 liters or 75% of predicted for height and age) prior to initiating therapy.
- 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 venous pressure.
- Patients who develop rales, increased respiratory rate, or who complain of dyspnea should have monitoring of pulmonary function during therapy that includes pulse oxymetry and arterial blood gas determination.

4.5 Interaction with other medicinal products and other forms of interaction

Interactions resulting in effects on other drugs

Observed interactions resulting in a concomitant use not recommended

Interactions affecting the use of Proleukin.

Antineoplastics

Fatal Tumor Lysis Syndrome has been reported in combination with treatment with cis-platinum, vinblastine and dacarbazine. Concomitant use of the mentioned active substances 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-platinum, 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.

Glucocorticoids

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.

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 recommended not 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

The concurrent used of medicinal products with hepatotoxic, nephrotoxic, myelotoxic, or cardiotoxic effects 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 Warnings and precautions).

Centrally acting medicinal products

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 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.

4.6 Pregnancy, lactation and females and males of reproductive potential

Pregnancy

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

Experimental animal studies are insufficient to assess the safety with respect to reproduction, development of the embryo or fetus, the course of gestation and peri and postnatal development. Proleukin has been shown to have embryo-lethal and maternal toxic effects in rats (see also Non-clinical safety data).

The potential risk for humans is unknown.

Proleukin should be used during pregnancy only if the expected benefit out-weights the potential risk to the fetus.

Lactation

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.

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 (see Non-clinical safety data).

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Summary of the safety profile

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. The rate of drug-related deaths in the 270 metastatic melanoma patients who received single-agent Proleukin was 2% (6/270).

Tabulated summary of Adverse drug reactions from clinical trials: Adverse reactions (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 studies 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:	Anemia, thrombocytopenia.
Common:	Leucopenia, coagulopathy, eosinophilia.
Uncommon:	Neutropenia.
rare:	Neutropenic fever.
Immune system disorders	
Uncommon:	Hypersensitivity reactions.

Endocrine disorders	
Very common:	Hypothyroidism.
Common:	Hyperthyroidism.
Metabolism and nutrition disorders	
Very common:	Anorexia.
Common:	Acidosis, hyperglycemia, hypercalcemia. hypocalcemia, hyperkalemia, dehydration.
Uncommon:	Hypoglycemia.
Rare:	Diabetes mellitus.
Psychiatric disorders	
Very common:	Anxiety, confusion, depression, insomnia.
Common:	Irritability, agitation, hallucinations.
Nervous system disorders	
Very common:	Dizziness, headache, paresthesia, somnolence.
Common:	Neuropathy), syncope, speech disorders, taste loss, lethargy.
Uncommon:	Coma, convulsions, paralysis, myasthenia.
Eye disorders	
Common:	Conjunctivitis.
Uncommon:	Optic nerve disorder including optic neuritis.
Cardiac disorders	
Very common:	Tachycardia, arrhythmia.
Common:	Cyanosis, transient ECG changes, myocardial ischemia, palpitations, cardiovascular disorders including cardiac failure.
Uncommon:	Myocarditis, cardiomyopathy, cardiac arrest, pericardial effusion.
Rare:	Ventricular hypokinesia.
Vascular disorders	
Very common:	Hypotension.
Common:	Phlebitis, hypertension.
Uncommon:	Thrombosis, thrombophlebitis, hemorrhage.
Respiratory, thoracic and mediastinal disorders	
Very common:	Dyspnea, cough.
Common:	Pulmonary edema, pleural effusions, hypoxia, Hemoptysis, epistaxis, nasal congestion, rhinitis.
Gastrointestinal disorders	
Very common:	Nausea with or without vomiting, diarrhea, stomatitis.
Common:	Dysphagia, dyspepsia, constipation, gastrointestinal bleeding including rectal hemorrhage, hematemesis, ascitis, cheilitis, gastritis.
Uncommon:	Pancreatitis, intestinal obstruction, Gastrointestinal perforation including necrosis/gangrene.
Rare:	Activation of quietscent Crohn's disease.
Hepatobiliary disorders	
Common:	Elevation of hepatic transaminases, elevation of alkaline phosphatase, elevation of lactic dehydrogenase, hyperbilirubinaemia, hepatomegaly or hepatosplenomegaly.
Rare:	Liver failure (with fatal outcome).

Skin and subcutaneous tissue disorders	
Very common:	Erythema and rash, exfoliative dermatitis, pruritus, sweating.
Common:	Urticaria, alopecia.
Musculoskeletal and connective tissue disorders	
Common:	Myalgia, arthralgia.
Uncommon:	Myopathy, myositis.
Renal and urinary disorders	
Very common:	Oliguria, serum urea increased and serum creatinine increased.
Common:	Haematuria, renal failure, anuria.
General disorders and administration site conditions	
Very common:	Injection site reaction, injection site pain, fever with or without chills, malaise, asthenia and fatigue, pain, edema, weight gain.
Common:	Mucositis, weight loss.
Uncommon:	Hypothermia.
Rare:	Injection site necrosis.

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

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 anemia, haemolytic anemia.
Immune system disorders
Anaphylaxis.
Nervous system disorders
Intracranial/ cerebral hemorrhage, 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
Quincke's edema, vitiligo, vesiculobullous rash, 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 Warnings and precautions). The frequency and severity of capillary leak syndrome are lower after subcutaneous administration than with 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 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.

Bacterial infection

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

Leukoencephalopathy

There have been rare reports of leukoencephalopathy associated with interleukin-2 in the literature, mostly in patients treated for off-label use indication. 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.

4.9 Overdosage

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

ATC classification system: immunostimulants, cytokines and immunomodulators, interleukins, aldesleukin, ATC code: L03A C01

Mechanism of action (MOA)

Proleukin acts as a regulator of the immune response. The biological activities of aldesleukin and native human interleukin-2 (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 tumor models has been shown to reduce tumor growth. The exact mechanism by which aldesleukin-mediated immunostimulation leads to antitumor activity is not yet known.

Clinical studies

The efficacy of Proleukin as single-agent therapy was demonstrated in a series of single and multicenter, historically controlled studies that enrolled patients with metastatic renal cell carcinoma or metastatic melanoma. Eligible patients generally had an Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) of 0 or 1 and normal organ function, as determined by 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 within each disease indication and method of Proleukin administration. Doses were either withheld or reduced in the clinical studies for specific toxicities (See Section 7 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	HDB	255	CR	17 (7%)	80+ (7 to 131+)
			PR	20 (8%)	20 (3 to 126+)
			PR+CR	37 (15%)	54 (3 to 131+)
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+)
MRCC	SC	103	CR	4 (4%)	65
			PR	10 10%)	-
			PR+CR	14 (14%)	11
MM	HDB	270	CR	17 (6%)	59+ (3 to 122+)
			PR	26 (10%)	6 (1 to 111+)
			PR+CR	43 (16%)	9 (1 to 122+)
MM	CIV	359	CR	8 (2%)	-
			PR	53 (15%)	-
			PR+CR	61 (17%)	-

Abbreviations: N, number of patients; MRCC, metastatic renal cell carcinoma; MM, metastatic melanoma; i.v., intravenous; HDB, high-dose i.v. bolus; CIV, continuous i.v. infusion; SC, subcutaneous injection; CR, complete response; PR, partial response.

Metastatic Renal Cell Cancer

High dose bolus

Two hundred fifty-five patients with MRCC were treated with single-agent Proleukin by high-dose bolus i.v. infusion in 7 clinical studies conducted at 21 institutions. MRCC patients received a median of 20 of 28 scheduled doses of Proleukin during the first course of therapy. In the pooled results for these patients, objective response was seen in 37 (15%) patients, with 17 (7%) complete (CR) and 20 (8%) partial responders (PR) (See Table 3). The 95% confidence interval for objective response was 11% to 20%. The onset of tumor regression was observed as early as 4 weeks after completion of the first course of treatment, and in some cases, tumor regression continued for up to 12 months after the start of treatment. Responses were observed in both lung and non-lung sites (e.g., liver, lymph node,

renal bed occurrences, soft tissue). Responses were also observed in patients with individual bulky lesions and high tumor burden.

Continuous intravenous infusion

One hundred 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.

Subcutaneous injection

One hundred three patients with MRCC were treated with single-agent Proleukin by subcutaneous injection. In the pooled results for these patients, objective response was seen in 14 (14%) patients, 4 (4%) with a complete response and 10 (10%) with a partial response. The median progression-free survival (PFS) for all responding patients was 11 months. For the CR patients, the median PFS is 65 months. Responses were observed primarily in lung. At the time of the five-year follow-up, four of 14 (29%) responding patients were still alive: three of the CR patients (26+, 55+, 87+ months) and one of the PR patients (31+ months).

Metastatic Melanoma
High dose bolus

Two hundred seventy patients with metastatic melanoma were treated with single-agent Proleukin in 8 clinical studies conducted at 22 institutions. Metastatic melanoma patients received a median of 18 of 28 scheduled doses of Proleukin during the first course of therapy. In the pooled results for these patients, objective response was seen in 43 (16%) patients, with 17 (6%) complete and 26 (10%) partial responders (See Table 3). The 95% confidence interval for objective response was 12% to 21%. Responses in metastatic melanoma patients were observed in both visceral and non-visceral sites (e.g., lung, liver, lymph node, soft tissue, adrenal, and subcutaneous). Responses were also observed in patients with individual bulky lesions and large cumulative tumor burden.

Continuous infusion

Three hundred fifty-nine patients with metastatic melanoma were treated with single-agent Proleukin by continuous i.v. infusion in 6 clinical studies. In the pooled results for these patients, objective response was seen in 61 (17%) patients, 8 (2%) with a complete response and 53 (15%) with a partial response.

5.2 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 beta phase is 85 minutes. The alpha-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 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, 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 346.3 mL/min and a terminal half-life ($t_{1/2}$) of 100.4 to 123.9 min.

Observed serum levels are proportional to the dose of Proleukin.

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 (MM) patients treated with a variety of i.v. regimens 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 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 once cycle on therapy on the pharmacokinetics of Proleukin 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 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 (CLcr) decreased following repeated doses of IL-2. Decrease in CLcr was not associated with a decrease in IL-2 clearance.
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.

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 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 and caution is recommended in the treatment of such patients.

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

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.

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).

6. PHARMACEUTICAL PARTICULARS

6.1 List of 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)

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 Pharmaceutical information – 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.

6.3 Shelf life

36 months

After reconstitution: immediately (within 24 hours)

6.4 Special precautions for storage

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

Protect from light. Store in the Original Package.

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.

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

6.5 Nature and content 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 a carton box of 1 vial.

Not all pack sizes may be marketed.

6.6 Instructions for use and handling and disposal

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 milliliter. The reconstituted solution has a pH of 7.5 (range 7.2 to 7.8).

Using sterilized 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 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.

Dilution directions for high dose bolus intravenous infusion:

The dose of Proleukin, reconstituted with sterile water for injection, USP (without preservative) should be diluted aseptically in 50 mL of 5% Dextrose Injection, USP (D5W) and infused over a 15-minute period.

Reconstitution or dilution with bacteriostatic water for injection, USP, or 0.9% Sodium Chloride Injection, USP should be avoided because of increased aggregation. Proleukin should not be co-administered with other drugs in the same container.

7. SPONSOR

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8. MEDICINE CLASSIFICATION

Prescription Medicine

9. DATE OF FIRST APPROVAL

Provisional consent
Approval date: 29/1/2015
Expiry date: 29/1/2019

10. DATE OF PREPARATION

4 July 2018