1. NAME OF THE MEDICINAL PRODUCT

PROLEUKIN 18 x 10⁶ IU
Powder for solution for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

After reconstitution with 1.2 ml water for injection, according to the instructions (see section 6.6), each 1 ml solution contains 18 x 10⁶ IU (1.1 mg) aldesleukin.

Each vial of Proleukin powder for solution for infusion contains 22 x 10⁶ 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 excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder for solution for 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. The following dosage regimen is recommended to treat adult patients with metastatic renal cell carcinoma.

18 x 10⁶ IU per m² 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.

Up to four maintenance cycles (18 x 10⁶ IU per m² as continuous infusion for 5 days) may be given with 4-week intervals to patients who respond or have disease stabilization.

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
cautions are 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 PaO2 < 60 mm Hg during rest.
7. Patients with pre-existing severe 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/mm³; platelets < 100.000/mm³;
   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 special 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**

It is recommended to exclude the following patients from treatment with Proleukin:
1. Patients with White Blood Count (WBC) < 4,000/mm³; platelets < 100,000/mm³; hematocrit (HCT) < 30%.
2. Patients with serum bilirubin and creatinine outside normal range.
3. Patients who are likely to require corticosteroids.
4. Patients with pre-existing auto-immune disease.

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. 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.

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 sepsis, 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.

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 cis-platinum, 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.

Concomitantly administered glucocorticoids may decrease the activity of Proleukin. 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.

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 (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.

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.

### 4.6 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 dose and schedule. For information on the toxicity of subcutaneous use review the Summary of Product Characteristics (SPC) of Proleukin powder for solution for injection.

Most adverse reactions are self-limited and might reverse within 1 to 2 days of discontinuation of therapy. A small number of patients (3%) died of treatment related adverse reactions.

Explanatory table of frequency of undesirable effects

| Very common | > 1/10 |
| Common | > 1/100 but < 1/10 |
| Uncommon | > 1/1,000 but < 1/100 |
| Rare | > 1/10,000 but < 1/1,000 |
| Very rare | < 1/10,000 |

<table>
<thead>
<tr>
<th>System</th>
<th>Very common</th>
<th>Common</th>
<th>Uncommon</th>
<th>Rare</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiovascular</td>
<td>mild to severe hypotension, mild to severe tachycardia</td>
<td>mild to severe arrhythmia, hypertension, phlebitis</td>
<td>angina pectoris, thrombosis, palpitations, transient ECG changes, cardiovascular disorders including myocardial infarction, myocarditis,</td>
<td>ventricular hypokinesia, pulmonary embolism</td>
</tr>
<tr>
<td>System</td>
<td>Adverse Reaction</td>
<td>Description</td>
<td>Description</td>
<td></td>
</tr>
<tr>
<td>------------------------</td>
<td>----------------------------------------------------------------------------------</td>
<td>------------------------------------------------------------------------------------------------------</td>
<td>------------------------------</td>
<td></td>
</tr>
<tr>
<td>Kidneys</td>
<td>mild to severe oliguria with elevated serum urea and serum creatinine</td>
<td>haematuria</td>
<td>renal failure</td>
<td></td>
</tr>
<tr>
<td>Respiratory tract</td>
<td>mild to severe dyspnoea, cough</td>
<td>mild to severe pulmonary oedema, mild to severe cyanosis, hypoxia, respiratory tract infection, mild to severe pleural effusions</td>
<td>haemoptysis</td>
<td>adult respiratory distress syndrome</td>
</tr>
<tr>
<td>Liver</td>
<td>N/A</td>
<td>mild to severe hyperbilirubinemia, mild to severe elevation of hepatic transaminases and alkaline phosphatase</td>
<td>mild to severe elevation of hepatic transaminases and alkaline phosphatase</td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal tract</td>
<td>mild to severe nausea with or without vomiting, mild to moderate diarrhoea, mild to severe anorexia</td>
<td>dysphagia, dyspepsia, constipation, gastrointestinal bleeding (including rectal hemorrhage), haematemesis</td>
<td>gastritis, cholecystitis, activation of quiescent Crohn’s disease</td>
<td></td>
</tr>
<tr>
<td>Blood*</td>
<td>mild to severe anaemia, mild to severe thrombocytopenia</td>
<td>mild to moderate leucopenia, moderate coagulation disorders</td>
<td>epistaxis, haemorrhage</td>
<td></td>
</tr>
<tr>
<td>Nervous system</td>
<td>moderate to severe anxiety, mild to severe confusion, mild to severe dizziness, mild to severe somnolence</td>
<td>mental status changes including irritability, moderate to severe agitation, paraesthesia, syncope, depression, hallucinations, speech disorders</td>
<td>mild to severe central or peripheral motor neurological disorders, paralysis</td>
<td></td>
</tr>
<tr>
<td>Abnormal laboratory findings</td>
<td>hyperglycaemia, hypocalcaemia, hyperkalaemia</td>
<td>hypo- or hyperthyroidism</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Skin and mucous membranes</td>
<td>mild to severe erythema/rash, mild to severe pruritus, mild to severe skin exfoliation</td>
<td>mild to moderate conjunctivitis, mild to moderate mucositis, alopecia, nasal congestion</td>
<td>mild to severe vitiligo</td>
<td></td>
</tr>
<tr>
<td>Other adverse reactions</td>
<td>mild to moderate weight gain with</td>
<td>moderate to severe pain, moderate to</td>
<td>hypersensitivity reactions,</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>oedema, mild to severe fever with or without chills, mild to severe malaise and fatigue, mild to severe headache</td>
<td>severe arthralgia, myalgia, ascitis</td>
<td>anaphylaxis, diabetes mellitus</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Note: During treatment most patients experience lymphocytopenia and eosinophilia, with a rebound lymphocytosis within 24-48 hours following treatment. These are not considered adverse reactions and may be related to the mechanism of antitumour activity of Proleukin.

**Additional information**
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.

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

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 or exacerbation of bacterial infection, including septicaemia, bacterial endocarditis, septic thrombophlebitis, peritonitis, pneumonia, and local catheter site infection has been reported (see section 4.4).

Liver failure with fatal outcome, haemolytic anaemia, agranulocytosis, aplastic anaemia, serious coagulation disorders (including Disseminated Intravascular Coagulation), optic neuropathy, Stevens-Johnson syndrome have been reported rarely after subcutaneous administration.

**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

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 $\alpha$ 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 bioavailability ranges between 35-47%.

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 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 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 dodecyl sulphate  
Sodium dihydrogen phosphate (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 to 8 °C (in a refrigerator). Do not freeze.

When 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 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 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 Instructions for use and handling and disposal

Reconstitution of Proleukin powder for solution for infusion:
Vials 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 diluted for
administration.

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:
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

8. MARKETING AUTHORISATION NUMBER(S)

9. DATE OF FIRST AUTHORISATION/RENEWAL OF AUTHORISATION

10. DATE OF REVISION OF THE TEXT