ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

▼ This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

Provenge 50 x 10^6 $CD54^+$ cells/250mL dispersion for infusion.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

2.1 General description

Autologous peripheral blood mononuclear cells activated with PAP-GM-CSF (Sipuleucel-T).

2.2 Qualitative and quantitative composition

One bag contains autologous peripheral blood mononuclear cells activated with PAP-GM-CSF (prostatic acid phosphatase-granulocyte macrophage-colony stimulating factor), including a minimum of 50 x 10^6 autologous $CD54^+$ cells.

The cellular composition and the cell number per dose of Provenge will vary according to the patient's leukapheresis. In addition to antigen presenting cells (APCs), the final product thus contains T cells, B cells, natural killer (NK) cells, and other cells.

Excipients with known effect
This medicinal product contains approximately 800 mg of sodium and 45 mg of potassium per infusion.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Dispersion for infusion.
The dispersion is slightly cloudy, with a cream-to-pink colour.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Provenge is indicated for treatment of asymptomatic or minimally symptomatic metastatic (non-visceral) castrate resistant prostate cancer in male adults in whom chemotherapy is not yet clinically indicated.

4.2 Posology and method of administration

Provenge must be administered under the supervision of a physician experienced in the medical treatment of prostate cancer and in an environment where availability of resuscitation equipment must be ensured.

Posology
One dose of Provenge contains a minimum of 50 x 10^6 autologous $CD54^+$ cells activated with PAP-GM-CSF, suspended in 250 mL of Lactated Ringer's Injection, in a sealed, patient-specific polyolefin bag.

The recommended course of treatment is 3 doses at approximately 2-week intervals. Each dose of Provenge is preceded by a standard leukapheresis procedure approximately 3 days prior to the scheduled infusion date. Prior to the first leukapheresis procedure, a complete blood count (CBC) test should be performed and be within ranges acceptable for the local facility. Additional CBC tests may be performed in accordance with local requirements.

If, for any reason, the patient is unable to receive a scheduled infusion of Provenge, the patient will need to undergo an additional leukapheresis procedure if the course of treatment is to be continued. Patients should be advised of this possibility prior to initiating treatment. In controlled clinical trials, 25.4% of patients treated with Provenge required more than 3 leukapheresis procedures in order to receive 3 infusions. In post-marketing experience of greater than 5,000 patients treated, this incidence is approximately 19% (see section 4.4). In controlled clinical trials, the dosing interval range was 1 – 15 weeks (see section 5.1).

Premedication
Acute infusion reactions such as chills, fatigue, fever, nausea, and joint ache were frequently observed in clinical studies. To mitigate such reactions, premedication, consisting of paracetamol and an antihistamine was administered in clinical studies prior to infusion.

To minimize potential acute infusion reactions such as chills and/or fever, it is recommended that patients be pre-medicated orally with paracetamol and an antihistamine approximately 30 minutes prior to administration of Provenge. The doses of paracetamol and antihistamine given should be in accordance with local practice.

In case of using premedication, the status of the patient and possible contraindications/interactions should be taken into account.

Dose adjustments
In the event of an acute infusion reaction, the infusion may be interrupted or slowed, depending on the severity of the reaction. Appropriate medical therapy, which could include paracetamol, intravenous H1 and/or H2 blockers, and low dose intravenous pethidine, should be administered as needed.

In controlled clinical trials, 23.8% of patients treated with Provenge required opioids (a single dose of pethidine) on the day of infusion for infusion reactions (see sections 4.4 and 4.8).

If the infusion of Provenge must be interrupted, it should not be resumed if the infusion bag has been held at room temperature (25°C) for more than 3 hours (see section 6.3).

Special populations

Older people
No dose adjustment is required in the elderly population.

Patients with hepatic impairment
Provenge has not been investigated in patients with hepatic impairment. No specific dose recommendation can be provided in these patients.

Patients with renal impairment and/or hyperkalaemia and/or on a controlled potassium diet
Provenge has not been investigated in patients with renal impairment. The potassium content per infusion should be taken into account if administered to patients with renal impairment and/or those on a controlled potassium diet. Hyperkalaemia should be corrected prior to Provenge administration (see section 4.4).

Paediatric population

There is no relevant use of Provenge in the paediatric population in children and adolescents less than 18 years of age in the indication of asymptomatic or minimally symptomatic metastatic (non-visceral) castrate resistant prostate cancer in male adults in whom chemotherapy is not yet clinically indicated.

Method of administration
Provenge is solely intended for autologous use via intravenous infusion.

Provenge should be infused intravenously over a period of approximately 60 minutes. The entire volume of the bag should be infused. A cell filter should not be used. Vital signs should be taken at least 30 minutes prior to and 30 minutes following each infusion. Patients should be observed for at least 30 minutes following each infusion. For patients with cardiovascular disease or those at risk for cardiac ischaemia, physicians should consider observing patients for at least 60 minutes following each infusion with vital signs taken at 30 minutes and 60 minutes following the infusion.

If the infusion of Provenge must be interrupted, it should not be resumed if the infusion bag has been held at room temperature (25°C) for more than 3 hours.

Precautions to be taken before handling or administering the medicinal product
Provenge is not tested for transmissible infectious diseases and hence may carry the risk of transmitting infectious diseases to healthcare professionals handling the product. Appropriate precautions should be employed when handling Provenge (see section 4.4).

It must be ensured that the APPROVED Final Product Disposition Notification form has been received from the marketing authorisation holder and the product has not expired (see section 6.6).

Before infusion, it must be confirmed that the patient's identity matches the essential unique patient information on the Provenge bag and on the Final Product Disposition Notification form.

The bag should be removed from the insulated polyurethane container and inspected for leaks, external damage, foreign particulate matter, or clumps/clots.

Contents of the bag will be slightly cloudy, with a cream to pink colour. Gently mix and re-suspend the contents of the bag, inspecting for particles, clumps or clots. Small clumps of cellular material should disperse with gentle manual mixing.

Do not administer if the bag leaks during handling or if particles or clumps remain in the bag.

For full instructions on the preparation and handling of Provenge, see section 6.6.

4.3 Contraindications

Hypersensitivity to the active substances or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

General
Provenge is intended solely for autologous use and should under no circumstances be administered to other patients. Prior to infusion, it must be confirmed that the patient's identity matches the essential unique patient information on the Provenge bag and on the Final Product Disposition Notification form (see sections 4.2 and 6.6).

Acute infusion reactions
Acute infusion reactions have been observed in patients treated with Provenge. Acute infusion reactions (reported within 1 day of infusion) included, but were not limited to, fever, chills, respiratory events (dyspnoea, hypoxia, and bronchospasm), nausea, vomiting, fatigue, hypertension, and tachycardia. In the event of an acute infusion reaction, the infusion rate may be decreased, or the

infusion stopped, depending on the severity of the reaction. Appropriate medical therapy should be administered as needed.

In controlled clinical trials, 23.8% of patients treated with Provenge required opioids (a single dose of pethidine) on the day of infusion for infusion reactions (see sections 4.2 and 4.8).

Patients with cardiac or pulmonary conditions should be closely monitored (see section 4.8).

Infection
Patients with positive serology tests for human immunodeficiency virus [HIV] 1 and 2, human T cell lymphotropic virus [HTLV] 1, and hepatitis B and C were excluded from controlled clinical trials. No data are available for these patients.

Provenge should be delayed in patients with active systemic infection until resolution. Serious infections including sepsis have been observed in patients treated with Provenge. Some serious infections and sepsis were related to the use of central venous catheters (CVCs). To reduce the risk of catheter-related infections, CVCs should be considered only for patients with poor peripheral venous access. These patients should be closely monitored for signs and symptoms of infection.

Embolic and thrombotic events
Provenge should be used with caution in patients with a history of embolic and thrombotic disorders.

Cerebrovascular disease
In controlled clinical trials, cerebrovascular events (hemorrhagic and ischaemic strokes) were observed in 3.5% of patients in the Provenge group compared with 2.6% of patients in the control group. The clinical significance is uncertain.

Cardiovascular disorders
In controlled clinical trials, myocardial infarctions were observed in 0.8% of patients in the Provenge group compared with 0.3% of patients in the control group. The clinical significance is uncertain.

Immunocompromised patients
Provenge should be used with caution in immunocompromised patients in general including patients taking systemic immunosuppressive therapy, after careful consideration of the potential risk-benefit on an individiual basis. No data are available for these patients.

Microbiological testing
Provenge is released for infusion based on the microbial and sterility results from several tests: microbial contamination determination by Gram stain, endotoxin content, and in-process sterility with a 2-day incubation to determine absence of microbial growth. The final (7-day incubation) sterility test results will not be available at the time of infusion. If the sterility results become positive for microbial contamination after Provenge has been approved for infusion, the marketing authorisation holder will notify the treating physician and may request additional information from the physician in order to determine the source of contamination. The physician should monitor and/or treat the patient as appropriate.

Handling precautions for control of infectious disease
Provenge is prepared from human blood of the specific patient and is not tested for transmissible infectious agents. Patient leukapheresis material is tested for transmissible infectious agents in line with applicable member state requirements. However, as Provenge is an autologous product, a positive test does not preclude the manufacture of the product. Therefore, patient leukapheresis material and Provenge may carry the risk of transmitting infectious viruses (HIV 1 and 2, hepatitis B and C) to healthcare professionals handling the product. Accordingly, healthcare professionals should employ appropriate precautions when handling leukapheresis material or Provenge.

Additionally, there is the small possibility/risk of transmitting infectious viruses to a patient if he is not the intended recipient of the product. Hence it is important that the procedures for handling and

administering the product are precisely followed (see section 6.6). It is strongly recommended that upon completion of each Provenge infusion, the patient specific label on the infusion bag, which contains the patient name, product name, and chain of identity (COI) product lot number, is removed and adhered to the patient file in order to maintain a link between the patient and the lot of the product.

Cases in which Provenge cannot be infused
In some cases, the patient may be unable to receive a scheduled infusion of Provenge. This may be due to release criteria not being met during manufacturing, the expiration time being exceeded, or the patient being unable to meet the scheduled infusion time. In such cases, the patient may need to undergo an additional leukapheresis procedure if the treatment is to be continued. It is recommended that the minimum interval between leukapheresis procedures should not be less than 2 weeks. In controlled clinical trials, 25.4% of patients treated with Provenge required more than 3 leukapheresis procedures in order to receive 3 infusions. In post-marketing experience of greater than 5,000 patients treated, this incidence is approximately 19% (see section 4.2).

Immunisations
The risks and benefits of vaccinating patients during the course of treatment with Provenge have not been studied. Therefore, vaccinations with live attenuated or inactivated vaccines whilst receiving Provenge should be carefully considered.

Educational materials
All physicians who intend to prescribe Provenge must review the educational materials and sign the training verification form. Physicians must provide the educational materials to the patient as well as the package leaflet and the Patient Alert Card.

Sodium and potassium content
This medicinal product contains approximately 800 mg sodium per infusion. To be taken into consideration by patients on a controlled sodium diet. The product also contains approximately 45 mg potassium per infusion. To be taken into consideration by patients with reduced kidney function or patients on a controlled potassium diet.

Patients with renal impairment and/or hyperkalaemia
The content of sodium and potassium per infusion should be taken into account if administered in patients with cardiovascular diseases and/or renal impairment. Hyperkalaemia should be corrected prior to Provenge administration (see section 4.2).

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed with Provenge.

Provenge is designed to stimulate the immune system. Immunocompromised patients and patients taking systemic immunosuppressive therapy were excluded from controlled clinical trials. Concurrent use of immunosuppressive agents (such as systemic corticosteroids) may alter its efficacy and/or safety. Therefore, concurrent use of immunosuppressive agents (such as systemic corticosteroids) should be avoided during Provenge treatment. Patients should be carefully evaluated to determine whether it is medically appropriate to discontinue immunosuppressive agents prior to treatment with Provenge (see section 4.4).

4.6 Fertility, pregnancy and lactation

Pregnancy
Provenge is not intended for use in women.

Breast-feeding
Provenge is not intended for use in women.

Fertility
Effect on male fertility is not known.

Conventional reproductive and development toxicity studies are not considered relevant given the nature and the intended clinical use of this autologous cell therapy product.

4.7 Effects on ability to drive and use machines

Provenge has moderate influence on the ability to drive and use machines, as it may cause fatigue, dizziness, syncope, chills, and headache. Patients should be advised not to drive or use machines if they experience these symptoms following their infusion.

4.8 Undesirable effects

Summary of safety profile
The safety evaluation of Provenge is based on data from 601 prostate cancer patients in four randomized, controlled clinical trials (3 studies in metastatic castrate resistant prostate cancer and 1 study in androgen dependent prostate cancer) and post-marketing surveillance.

Serious adverse reactions include acute infusion reactions, catheter sepsis, staphylococcal bacteraemia, myocardial infarction, and cerebrovascular events.

The most commonly reported adverse reactions are chills, fatigue, pyrexia, nausea, arthralgia, headache, and vomiting.

In the pivotal randomised controlled study (D9902B, IMPACT, see section 5.1) Provenge was discontinued in 1.5% of patients due to adverse reactions. Some patients developed infection, including sepsis. Infections due to contaminated product also occurred in some patients. A small number of these patients discontinued treatment as a result.

Tabulated list of adverse reactions
The following list of adverse reactions is based on experience from clinical trials and on post-marketing experience and are displayed by system organ class and frequency of occurrence: 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), and not known (cannot be estimated from the available data). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Table 1 Adverse reactions from clinical studies and post-marketing reports

System organ class	Frequency	Adverse reactions
Infections and infestations	Common	Bacteraemia
	Uncommon	Catheter sepsis Catheter related infection Catheter site infection Sepsis
Blood and lymphatic system disorders	Very common	Anaemia*
	Common	Thrombocytopenia*
	Uncommon	Eosinophilia
Nervous system disorders	Very common	Dizziness Paraesthesia* Paraesthesia oral* Headache
	Common	Cerebrovascular accident Transient ischaemic attack Tremor Hypoaesthesia Spinal cord compression Syncope
	Uncommon	Cerebral infarction
Cardiac disorders	Common	Atrial fibrillation
	Uncommon	Myocardial infarction Myocardial ischaemia
Vascular disorders	Common	Hypertension Hypotension
Respiratory, thoracic, and mediastinal disorders	Common	Hypoxia Wheezing Dyspnoea
	Uncommon	Bronchospasm
Gastrointestinal disorders	Very common	Vomiting Nausea
	Common	Abdominal pain
Skin and subcutaneous tissue disorders	Common	Rash Hyperhidrosis Pruritus Urticaria
Musculoskeletal and connective tissue disorders	Very common	Arthralgia Myalgia
	Common	Muscle spasms*
Renal and urinary disorders	Common	Haematuria
General disorders and administration site conditions	Very common	Chills Fatigue Pyrexia Pain Asthenia
	Common	Influenza-like illness Chest discomfort
	Uncommon	Infusion site reaction
Injury, poisoning and procedural complications	Very common	Citrate toxicity*

* Primarily associated with the leukapheresis procedure

Description of selected adverse reactions

Acute infusion reactions
In controlled clinical trials, 71.2% of patients in the Provenge group developed an acute infusion reaction. The most common reactions (≥ 20%) were chills, fever, and fatigue. In 95.1% of patients reporting acute infusion reactions, the events were mild or moderate. Fevers and chills generally resolved within 2 days (71.9% and 89.0%, respectively).

In controlled clinical trials, severe (Grade 3) acute infusion reactions were reported in 3.5% of patients in the Provenge group. Reactions included chills, fever, fatigue, asthenia, dyspnoea, hypoxia, bronchospasm, dizziness, headache, hypertension, muscle ache, nausea, and vomiting. The incidence of severe reactions was greater following the second infusion (2.1% vs. 0.8% following the first infusion), and decreased to 1.3% following the third infusion. Some (1.2%) patients in the Provenge group were hospitalized within 1 day of infusion for management of acute infusion reactions. No Grade 4 or 5 acute infusion reactions were reported in patients in the Provenge group.

In controlled clinical trials, 23.8% of patients in the Provenge group required opioids (a single dose of pethidine) on the day of infusion for infusion reactions compared with 2.4% of patients in control group (see sections 4.2 and 4.4).

In the post-marketing setting, serious acute infusion reactions involving hypotension and syncope have been reported. Some have resulted in hospitalization.

Patients should be informed of the possibility of late onset reactions and instructed to contact their physician if symptoms of dyspnoea, bronchospasm, dizziness, rash, or pyrexia occur.

Infection
In controlled clinical trials, infection occurred in 27.5% of subjects in the Provenge group and 27.7% of subjects in the control group. Serious infections occurred in 4.7% of subjects in the Provenge group and 4.0% of subjects in the control group. The most frequently occurring serious infections in the Provenge group were catheter sepsis (0.7%), staphylococcal bacteraemia (0.7%), sepsis (0.7%), staphylococcal sepsis (0.5%), and pneumonia (0.5%).

Reports of serious infection have been received in post-marketing surveillance including device-related infection, device-related sepsis, pneumonia, sepsis, bacteraemia, and urinary tract infection.

Adverse reactions associated with leukapheresis
Each dose of Provenge requires a standard leukapheresis procedure approximately 3 days prior to the infusion. Citrate is generally the preferred anticoagulant used during leukapheresis and can result in hypocalcaemia. Adverse reactions that were reported most commonly ≤ 1 day following a leukapheresis procedure in controlled clinical trials included citrate toxicity (14.6%), oral paraesthesia (12.0%), and paraesthesia (11.1%). Additional adverse reactions that were seen commonly ≤ 1 day following a leukapheresis procedure in controlled clinical trials included fatigue (5.5%), muscle spasm (4.0%), chills (3.0%), dizziness (2.8%), and anaemia (2.8%). Additionally, there have been reports of thrombocytopenia received in spontaneous post-marketing reporting that have been temporally associated with leukapheresis.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

Each Provenge infusion comprises the maximum number of cells that can be manufactured from a single leukapheresis procedure. The number of cells in Provenge does not exceed the number of cells

from the leukapheresis. There are no known instances of overdose from either a single infusion or a full course of therapy with Provenge.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Immunostimulants, other immunostimulants, ATC code: L03AX17.

Mechanism of action
Provenge is an autologous cellular immunotherapy designed to induce an immune response targeted against prostatic acid phosphatase (PAP), an antigen expressed in most prostate cancers. Peripheral blood mononuclear cells collected from the patients are cultured with PAP-GM-CSF, a fusion protein consisting of PAP linked to granulocyte-macrophage colony-stimulating factor (GM-CSF) an immune cell activator. During *ex vivo* culture with PAP-GM-CSF, activated APCs (antigen presenting cells) take up and process the recombinant target antigen into peptides that are then presented to T cells. Product characterization shows that PAP and PAP-GM-CSF fusion protein-specific T cells are generated during treatment and are detected in the peripheral blood of patients after treatment with Provenge.

Pharmacodynamic effects
As part of lot release, each product is assessed for activation of antigen presenting cells (APCs) by virtue of increased surface CD54 expression after culture with PAP-GM-CSF. CD54 is an adhesion and costimulatory molecule essential in the formation of the immunological synapse between an APC and a T cell. The degree of CD54 upregulation correlates with overall survival in the randomised controlled clinical trials carried out with Provenge in metastatic castrate resistant prostate cancer. In clinical study D9902B (IMPACT), 237 out of the 512 patients randomized were evaluated for the development of humoral or cellular immune responses (T cell proliferation and gamma-interferon (γIFN) ELISPOT) to the target antigens at baseline, and at Weeks 6, 14, and 26. Antibody (IgM and IgG) responses against both PAP-GM-CSF and the PAP antigens were observed in the Provenge group through the follow up period. T cell proliferative and γIFN ELISPOT responses to PAP and PAP-GM-CSF were observed in cells collected from peripheral blood of patients through the follow-up period in the Provenge treatment group but not in controls. There was a correlation between cellular or antibody responses to PAP or PAP-GM-CSF in the Provenge group and improved survival. Neutralising antibody responses to GM-CSF were transient.

Clinical efficacy and safety
The efficacy and safety of Provenge in patients with asymptomatic or minimally symptomatic metastatic castrate resistant prostate cancer were studied in three similar Phase III, randomised, double-blind, controlled, multicentre trials: D9902B (IMPACT), D9901, and D9902A. The patients enrolled in these trials had failed surgical or medical castration (e.g. luteinising hormone-releasing hormone [LHRH] agonist or gonadotropin-releasing hormone [GnRh] antagonist) therapies and had metastatic disease in the soft tissue and/or bone. Patients did not require opioid analgesics for pain management and the majority had not received prior chemotherapy.

Following randomization, patients from both treatment groups underwent a series of 3 leukapheresis procedures (at approximately 2 week intervals, range 1 to 15 weeks). Each leukapheresis was followed approximately 3 days later by infusion of Provenge or control. The control was non-activated autologous peripheral blood mononuclear cells. Following disease progression, patients were treated at the physician's discretion with other anti-cancer interventions. Patients in the control group could enrol in an open-label protocol and receive an investigational autologous cellular therapy manufactured from cells cryopreserved at the time the control product was prepared.

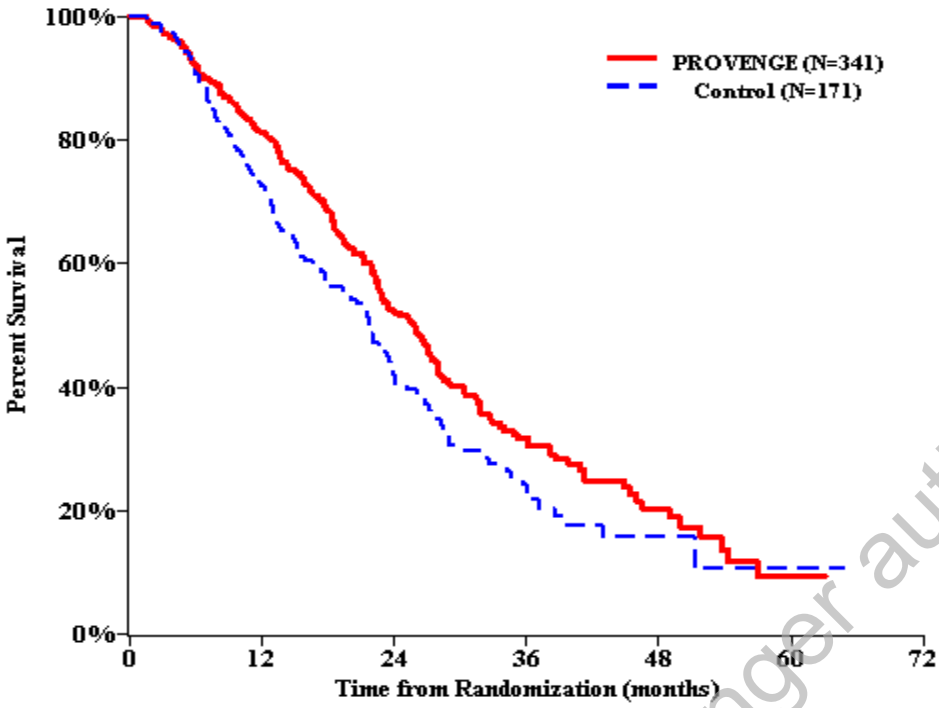
IMPACT study
The IMPACT study was a randomised, double-blind, controlled, multicentre trial in patients with asymptomatic or minimally symptomatic metastatic castrate resistant prostate cancer. Eligible

patients had metastatic disease in the soft tissue and/or bone with current or historical evidence of disease progression concomitant with surgical or medical castration, as evidenced by progression of serum prostate specific antigen (PSA) and/or bone or soft tissue disease, and an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1. Exclusion criteria included visceral (liver, lung, or brain) metastases, malignant pleural effusions or malignant ascites, pathologic long bone fractures, imminent pathologic long-bone fractures (cortical erosion on radiography >50%), spinal cord compression, moderate to severe prostate cancer-related pain and use of narcotics for cancer-related pain, and treatment with chemotherapy at least 3 months prior to randomisation. The primary endpoint was overall survival. Secondary endpoints included time to objective disease progression, time to clinical progression, and PSA doubling time (PSADT).

A total of 512 patients were randomised in a 2:1 ratio to receive Provenge (n=341) or control (n=171). The median age was 71, 90% of the patients were Caucasian, and all had a life expectancy of at least 6 months. Thirty-five percent of patients had undergone radical prostatectomy, 54% had received local radiotherapy, and 82% had received combined androgen blockade. All patients had baseline testosterone levels < 50 ng/mL. Forty-eight percent of patients were receiving bisphosphonates and 18% had received prior chemotherapy, including docetaxel. Eighty-two percent of patients had an ECOG performance status of 0; 75% had a Gleason sum ≤ 7; 44% had bone and soft tissue disease; 48% had bone-only disease; 7% had soft tissue-only disease; and 43% had greater than ten bony metastases.

A statistically significant improvement in overall survival was seen in patients treated with Provenge, with a 22.5% reduction in the risk of death compared with control (see Table 2 and Figure 1). Of the control arm patients, 64% crossed over to receive an investigational autologous cellular immunotherapy manufactured from cells cryopreserved at the time the control was manufactured; patients were not randomised to subsequent autologous cellular immunotherapy.

Figure 1 Kaplan-Meier overall survival curve, IMPACT study



A retrospective subgroup analysis has suggested a greater Provenge treatment effect in patients with a baseline PSA < 22.1 ng/mL [HR= 0.521 (95% CI: 0.309, 0.879)]. Intermediate results were observed in patients with baseline PSA > 22.1 to 50.1 ng/mL [HR=0.685 (95% CI: 0.431, 1.088)] and patients with baseline PSA > 50.1 to 134.1 ng/mL [HR=0.819 (95% CI: 0.532, 1.262)]. A smaller treatment effect was observed in those with baseline PSA > 134.1 ng/mL [HR=0.853 (95% CI: 0.554, 1.315)].

Analyses of time to objective disease progression, time to clinical progression, or PSA doubling time (PSADT) did not meet statistical significance.

Supportive studies

Study D9901 was a randomised, double-blind, controlled, multicentre trial in patients with metastatic castrate resistant prostate cancer and no cancer-related pain. The primary endpoint was time to disease progression, which did not reach statistical significance. Overall survival was not a study endpoint but a pre-specified analysis. Patients treated with Provenge had a statistically significant survival advantage compared with control.

A third study, D9902A, similar in design to study D9901, was terminated prior to completion of planned accrual based on the time to disease progression results in study D9901. The primary endpoint was time to disease progression and the secondary endpoint was overall survival. Neither endpoint met statistical significance.

Summary of study results

Table 2 presents overall survival results observed in IMPACT, study D9901, and study D9902A.

Table 2 Summary of overall survival (all patients as randomized)

	IMPACT		D9901		D9902A	
	Provenge (N=341)	Control (N=171)	Provenge (N=82)	Control (N=45)	Provenge (N=65)	Control (N=33)
Overall survival						
Median, months (95% CI)	25.8 (22.8, 27.7)	21.7 (17.7, 23.8)	25.9 (20.0, 32.4)	21.4 (12.3, 25.8)	19.0 (13.6, 31.9)	15.7 (12.8, 25.4)
Hazard ratio (95% CI)	0.775[a] (0.614, 0.979)		0.586[b] (0.388, 0.884)		0.786[b] (0.484, 1.278)	
p-value	0.032[a]		0.010[c]		0.331[c]	
36-month survival (%)	32%	23%	34%	11%	32%	21%

[a] Hazard ratio and p-value based on the Cox Model adjusted for PSA (ln) and LDH (ln) and stratified by bisphosphonate use, number of bone metastases, and primary Gleason grade.
[b] Hazard ratio based on the unadjusted Cox Model.
[c] p-value based on a log-rank test.
Abbreviations: CI = confidence interval.

Paediatric population
The European Medicines Agency has waived the obligation to submit the results of studies with Provenge in all subsets of the paediatric population in the treatment of prostate cancer (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

Provenge is an autologous cellular therapy. The nature of Provenge is such that conventional studies on pharmacokinetics, absorption, distribution, metabolism, and elimination are not applicable.

5.3 Preclinical safety data

Conventional toxicology, carcinogenicity, mutagenicity, and reproductive toxicity studies have not been performed.

6. QUALITY PARTICULARS

6.1 List of excipients

Sodium chloride
Sodium lactate
Potassium chloride
Calcium chloride

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

In the insulated container
18 hours.

After removal from the insulated container
The medicinal product should be used immediately. If not used immediately, in-use storage times and conditions should not exceed 3 hours at room temperature (25°C).

6.4 Special precautions for storage

Store the bag in the insulated container to maintain the correct storage temperature (2°C–8°C) until infusion.
Do not refrigerate or freeze the container.

6.5 Nature and contents of container and special equipment for use, administration or implantation

250 mL dispersion in a bag (breathable polyolefin tri-laminate with 3 sample ports (2 spike ports and 1 port with sealed tubing)).

6.6 Special precautions for disposal and other handling

Provenge is intended solely for autologous use. The identity of the patient must be matched with the essential unique patient information on the infusion bag and the Final Product Disposition Notification form prior to infusion.

Provenge is not tested for transmissible infectious agents. Patient leukapheresis material is tested for transmissible infectious agents in line with applicable member state requirements. However, as it is an autologous product, a positive test does not preclude the manufacture of the product. Therefore patient leukapheresis material and Provenge may carry the risk of transmitting infectious diseases to healthcare professionals handling the product. Accordingly, healthcare professionals should employ appropriate precautions when handling leukapheresis material or Provenge (see section 4.4).

Handling instructions

Before handling or administering Provenge

- Provenge is shipped directly to the medical facility where the infusion will be administered. The infusion bag is placed inside an insulated polyurethane container and packed in a shipping box. The insulated container and the gel packs within are designed to maintain the appropriate transportation and storage temperature of Provenge until infusion. Do not irradiate.
- The outer shipping box should be opened to verify the product and patient-specific labels located on the top of the insulated container. Do not remove this insulated container from the shipping box, or open the lid of the insulated container, until the patient is ready for infusion.

Preparing the infusion
Take care to ensure aseptic handling when preparing the infusion.

What to check prior to infusion

- It must be ensured that the Final Product Disposition Notification form containing the patient identifiers, expiration date and time, and the disposition status (approved for infusion or rejected), has been received from the marketing authorisation holder.
- It must be ensured that the patient's identity matches the essential unique patient information on the Provenge bag and on the Final Product Disposition form.
- Once the patient is prepared for infusion and the APPROVED Final Product Disposition Notification form has been received, the Provenge bag should be removed from the insulated container and inspected for leaks, external damage, foreign particulate matter, or clumps/clots.
- Contents of the bag will be slightly cloudy, with a cream to pink colour. Gently mix and re-suspend the contents of the bag, inspecting for clumps and clots. Small clumps of cellular material should disperse with gentle manual mixing.
- If the Provenge bag leaks, is damaged, or if particles or clumps remain in the bag after gentle manual mixing, the product **must not be used.**

Administration

- Infusion must begin prior to the expiration date and time indicated on the Final Product Disposition Notification form and bag label. **Do not initiate infusion of expired Provenge**.
- Only one of the 2 spike ports should be used and should not be opened prior to administration in order to avoid contamination.
- Provenge is infused over a period of approximately 60 minutes through a large bore needle appropriate for transfusion of red blood cells. This peripheral delivery system is commonly used in clinical practice for the transfusion of blood components. **Do not use a cell filter for infusion.** The entire volume of the infusion bag should be used.
- If the infusion of Provenge must be interrupted, it should not be resumed if the infusion bag has been held at room temperature (25°C) for more than 3 hours.

After the infusion

- Upon completion of the infusion, the patient specific label on the infusion bag should be removed and adhered to the patient file.
- Any unused product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Dendreon UK Limited
41 Chalton Street
London, NW1 1JD
United Kingdom

Tel: (0)20 7554 2222
Fax: (0)20 7554 2201
dendreonuk@dendreon.com

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/13/867/001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

ANNEX II

A. MANUFACTURER OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer of the biological active substance

PharmaCell
Oxfordlaan 70
NL-6229 EV, Maastricht
The Netherlands

Name and address of the manufacturer responsible for batch release

PharmaCell
Oxfordlaan 70
NL-6229 EV, Maastricht
The Netherlands

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports**

The marketing authorisation holder shall submit the first periodic safety update report for this product within six months following authorisation. Subsequently, the marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time.

- **Additional risk minimisation measures**

Prior to launch of Provenge in each Member State, the Marketing Authorisation Holder (MAH) shall agree the content and format of the educational materials with the National Competent Authority. The MAH shall also agree with the National Competent Authority any requirements for prior audit of apheresis centres and training courses for healthcare professionals in the use of Provenge.

The MAH shall ensure that all healthcare professionals who are expected to prescribe or use Provenge are provided with the following items:

1. Summary of Product Characteristics (SmPC)
2. Educational material for Healthcare professionals
3. Provenge treatment checklists
4. Apheresis catheter care sheets
5. Educational materials for patients
6. Patient Alert card to record the scheduled leukapheresis and infusion dates

The educational material for healthcare professionals will include the following key elements:

- Training completion form as agreed with the national competent authority
- Selection of patients for treatment with Provenge
- Specific handling and administration requirements for Provenge
- Chain of identity requirements
- The need to provide patients with the educational material and explain the use of the patient alert card
- The existence of the EU Registry of patients treated for metastatic castrate resistant prostate cancer and how to enter patients in it.

Educational material for patients and/or carers to explain:

- The leukapheresis process
- The Provenge treatment process

- **Obligation to conduct post-authorisation measures**

The MAH shall complete, within the stated timeframe, the below measures:

Description	**Due dates**
To establish and keep an observational EU-based registry of men with mCRPC to evaluate overall survival, the risk of ischemic stroke or myocardial infarction following treatment with Provenge and other identified and potential risks (observational study P13-1)	Submission of study protocol with first PSUR Interim data submitted in each PSUR Final study report by 31 December 2018
To provide data from the observational US-based registry (PROCEED, Study P10-3)	Interim data submitted in each PSUR Final study report by 30 September 2016
To submit the results from study P-11, a randomised, double-blind trial evaluating Provenge versus placebo in patients with non-metastatic prostate cancer who experience PSA elevation following radical prostatectomy	Final study report by 31 December 2020
To conduct study P12-1 to evaluate characteristics predictive of a positive imaging study for distant metastases in patients with castrate-resistant prostate cancer. The study should provide a summary of baseline patient characteristics including PSA and	Submission of study protocol within 1 month of authorisation Update on study outcome annually Final study report by 31 December 2019

PSA doubling time, the number of patients who develop metastatic disease, subsequent therapies received after diagnosis of metastatic disease, and efficacy parameters following subsequent therapies, including PSA progression, PSA progression-free survival, time to next line therapy, and overall survival.	

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

INSULATED POLYURETHANE CONTAINER

1. NAME OF THE MEDICINAL PRODUCT

PROVENGE 50 x 10^6 $CD54^+$ cells/250 mL dispersion for infusion.

Autologous peripheral blood mononuclear cells activated with PAP-GM-CSF (Sipuleucel-T).

2. STATEMENT OF ACTIVE SUBSTANCE(S)

One bag contains autologous peripheral blood mononuclear cells activated with PAP-GM-SF (prostatic acid phosphatase-granulocyte macrophage-colony stimulating factor), including a minimum of 50 x 10^6 autologous $CD54^+$ cells.

3. LIST OF EXCIPIENTS

Sodium chloride
Sodium lactate
Potassium chloride
Calcium chloride.
See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Dispersion for infusion.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Gently mix and re-suspend the contents of the bag.
Read the package leaflet before use.
For intravenous infusion

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

For autologous use only.

Do not remove the top insulated lid and do not open the insulated box until both of the following have occurred:

- The disposition form verifying the product has been APPROVED has been provided
- The patient has arrived at the site and is ready for infusion

Do not initiate infusion if expired, after 3 hours at room temperature (25°C), or if particles/clumps are visible despite gentle manual mixing

8. EXPIRY DATE

Exp. Date {DD month YYYY}, Exp. Time {hh:mm}, Time Zone

9. SPECIAL STORAGE CONDITIONS

Store the bag in the insulated container to maintain the correct storage temperature (2°C–8°C) until infusion.
Do not refrigerate or freeze the container.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Dispose of in accordance with local requirements.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Dendreon UK Ltd.
41 Chalton Street
London, NW1 1JD
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/13/867/001

13. BATCH NUMBER, DONATION AND PRODUCT CODES

Lot /COI {lot number/chain of identity}
First Name, Middle Initial, Last Name {patient name}
DOB {patient date of birth}

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

INFUSION BAG

1. NAME OF THE MEDICINAL PRODUCT

PROVENGE 50 x 10^6 $CD54^+$ cells/250 mL dispersion for infusion.

Autologous peripheral blood mononuclear cells activated with PAP-GM-CSF (Sipuleucel-T).

2. STATEMENT OF ACTIVE SUBSTANCE(S)

One bag contains autologous peripheral blood mononuclear cells activated with PAP-GM-CSF (prostatic acid phosphatase-granulocyte macrophage-colony stimulating factor), including a minimum of 50 x 10^6 autologous $CD54^+$ cells

3. LIST OF EXCIPIENTS

Sodium chloride
Sodium lactate
Potassium chloride
Calcium chloride.
See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Dispersion for infusion.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Gently mix and re-suspend the contents of the bag.
Read the package leaflet before use.
For intravenous infusion.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

For autologous use only.
Do not initiate infusion if expired, after 3 hours at room temperature (25°C), or if particles/clumps are visible despite gentle manual mixing.

8. EXPIRY DATE

Exp. Date {DD month YYYY}, Exp. Time {hh:mm}, Time Zone

9. SPECIAL STORAGE CONDITIONS

Store the bag in the insulated container to maintain the correct storage temperature (2°C–8°C) until infusion.
Do not refrigerate or freeze the container.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Dispose of in accordance with local requirements.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Dendreon UK Ltd.
41 Chalton Street
London, NW1 1JD
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

13. BATCH NUMBER, DONATION AND PRODUCT CODES

Lot/COI {lot number/chain of identity}
First Name, Middle Initial, Last Name {patient name}
DOB {patient date of birth}

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

Provenge 50 x 10^6 $CD54^+$ cells/250 mL dispersion for infusion

Autologous peripheral blood mononuclear cells activated with PAP-GM-CSF (Sipuleucel-T)

▼ This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before you are given this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or nurse.
- If you get any side effects, talk to your doctor or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Provenge is and what it is used for

Provenge is used to control your prostate cancer. It consists of immune cells (part of your body's natural defense system) taken from your own blood (also called autologous immune cells). These immune cells are then mixed with an antigen (a protein, which is able to stimulate your immune system) at a specific manufacturing facility. When given as a drip (infusion) into your vein, Provenge works by teaching your immune cells to recognise and attack prostate cancer cells.

Provenge is used as treatment for prostate cancer that has spread outside of the prostate but not to the liver, lung or brain, and no longer responds to medicines that lower the levels of the male hormone testosterone in patients who are not considered appropriate for treatment with chemotherapy.

2. What you need to know before you are given Provenge

Do not use Provenge
If you are allergic (hypersensitive) to the active substances or any of the ingredients of this medicine (listed in section 6).

Warnings and precautions
Tell your doctor if you have any of the conditions listed below as you will have to be closely monitored during and after your infusion:

- An infection which affects your whole body (e.g., sepsis, seen as high temperature, increased heart rate or breathing)
- A history of stroke
- A heart condition including blocked blood vessels which could lead to a heart attack
- You are immunocompromised (your immune system's ability to fight infections is reduced) or taking any immunosuppressant medicines (such as those used to treat or prevent organ

rejection and certain medicines used to treat rheumatoid arthritis, multiple sclerosis, Crohn's disease, and ulcerative colitis)
- You are on a controlled sodium/potassium diet or you have reduced kidney function.

Your doctor may decide that Provenge is not suitable for you due to one or more of these conditions.

On the **first day of the infusion**, Provenge may cause infusion-related reactions such as:
- high temperature, chills, breathing difficulties
- feeling or being sick (nausea and vomiting)
- tiredness
- increased heart rate, high blood pressure, low blood pressure, fainting.

To reduce these reactions your doctor may suggest that you take paracetamol and an antihistamine medicine about 30 minutes before your treatment with Provenge.

If you have **severe reactions during** the infusion your doctor may either slow down the infusion or stop it. You may also be given other medicines if needed. Tell the doctor or nurse if you do not feel well during the infusion.

Provenge is manufactured specifically for you using your own blood and must not be used in anyone else.

Provenge undergoes several tests before use to show that it is sterile. As it has to be given to you shortly after it has been manufactured, the final sterility results may not always be available before you are given your infusion of Provenge. If the final results show that your medicine was not sterile, your doctor will be notified and you will be monitored closely for any signs of infection and will be treated accordingly.

When Provenge cannot be given
In some cases, you may be unable to receive a scheduled infusion of Provenge. This may be due to a number of reasons, for example, if there is:
- a problem at the time your blood cells are taken for the manufacturing of Provenge.
- not enough of the right type of cells to manufacture the medicine.
- contamination of the product.
- a delay in Provenge reaching the clinic where you will be given your treatment.
- damage to the product when it arrives at the clinic; for example, the bag containing the product has leaked, or the cells have formed clumps that cannot be dispersed.

In such cases, if your doctor decides that the course of treatment should be continued, he or she will arrange for another collection of your blood cells (leukapheresis) and the manufacturing process will be repeated (see information on leukapheresis in section 3). In clinical studies, about one quarter of the patients required more than 3 leukapheresis procedures in order to receive 3 infusions of Provenge.

Children and adolescents
Provenge is for use in adult men only. It should not be given to children or adolescents under the age of 18 years.

Other medicines and Provenge
Tell your doctor or nurse if you are taking, have recently taken, or might take any other medicines. This includes medicines obtained without a prescription and herbal medicines.

Provenge is designed to stimulate your immune system, and therefore it may not be appropriate to be treated with Provenge if you are currently taking other treatments that could affect the ability of your immune system to respond to Provenge e.g., immunosuppressant medicines such as those used to treat

or prevent organ rejection and certain medicines used to treat rheumatoid arthritis, multiple sclerosis, Crohn's disease, and ulcerative colitis.

If you need a vaccination whilst receiving Provenge, you should first discuss this with your doctor.

Pregnancy, breast-feeding and fertility
Provenge is for use in men only. The effects of Provenge on male fertility are not known at this time.

Driving and using machines
You may feel tired, faint, or dizzy or have a headache or chills after receiving your Provenge infusion. If this happens, do not drive or use any tools or machines until you feel better.

Provenge contains sodium and potassium
This medicine contains:

- approximately 800 mg sodium per infusion. To be taken into consideration by patients with heart conditions or those on a controlled sodium diet.
- approximately 45 mg potassium per infusion. To be taken into consideration by patients with reduced kidney function or on a controlled potassium diet.

3. How Provenge is given to you

Provenge can only be administered by a doctor or nurse who has been trained in using this medicine. Practical information for handling and administration of Provenge for the doctor or nurse can be found at the end of this leaflet.

As Provenge is made from your own blood cells, your cells will be collected approximately 3 days before each scheduled infusion. This procedure will take 3 to 4 hours (see section "Steps before Provenge treatment" below). Your blood will be tested before it is collected (see section "Tests" below).

Steps before Provenge treatment

1. The first step in your Provenge treatment is to collect your blood cells in order to manufacture your personal infusion of Provenge. This involves a procedure called **leukapheresis,** which consists of extracting white blood cells from your blood, usually from the veins in your arms. A machine is used to take blood from one arm, extract the white blood cells and return the rest of the blood to you, usually in the other arm. This procedure usually takes 3-4 hours. You will have to have this procedure on at least 3 occasions approximately 3 days before each of your 3 Provenge infusion treatments.
2. The second step is to send your collected cells to a special manufacturing centre where they are mixed with an antigen to make them ready for your infusion.

Tests
Before, or on the day, your blood cells are collected, a blood sample will be taken from you for a complete blood count (CBC) test. This test will determine whether you have enough blood cells to allow the leukapheresis procedure to be safely carried out. In addition, your blood will be tested for specific viruses (for example HIV-1, HIV-2, hepatitis B and hepatitis C). This testing is a legal requirement and is to ensure that your blood cells can be safely handled by the healthcare professionals involved in your treatment. You may need to have further CBC tests during your treatment in line with local or country-wide practices. If you need more information on the testing of your blood please ask your doctor or nurse.

How Provenge is given and duration of treatment
Your doctor may suggest you take paracetamol and an antihistamine medicine about 30 minutes before your infusion to reduce the possible reactions to Provenge.

Your Provenge treatment will be given by a drip (infusion) into one of your veins (intravenous use).

You will receive a total of 3 infusions of Provenge at approximately 2 week intervals.

The first infusion of Provenge will be given approximately 3 days after the cell collection and will last approximately 1 hour (see also section 2 "Warnings and precautions"). You will be monitored before and during the infusion. If your infusion of Provenge has to be interrupted for any reason, your doctor will not be able to restart the infusion if the medicine has been at room temperature for more than 3 hours.

Once the infusion is complete you will be observed and monitored for at least 30–60 minutes, after which, you may go home.

Your treatment will involve at least 6 visits to the cell collection site and/or clinic. You may need one or more additional visits in order to have your blood tested before your leukapheresis procedure (depending on the usual pratice in the clinic where you are having your treatment), or your blood may be tested during your leukapheresis visits:
Visit 1 – Blood cell collection (leukapheresis)
Visit 2 – Provenge infusion
Visit 3 – Blood cell collection (leukapheresis)
Visit 4 – Provenge infusion
Visit 5 – Blood cell collection (leukapheresis)
Visit 6 – Provenge infusion

Your doctor will give you a schedule for your cell collection and infusion appointments. This will be added to your Patient Alert Card that you should bring to each appointment.

Missed treatment
It is very important that you arrive on time for your appointments. If you miss an appointment and you cannot be given your Provenge infusion, it will no longer be usable. Your doctor will work with you to schedule new appointments for cell collection and infusion.

If you have any further questions on the use of this medicine, ask your doctor or nurse.

4. Possible side effects of Provenge

Like all medicines, Provenge can cause side effects, although not everybody gets them.

The most severe side effects are described below:

Infusion-related side effects
During or within 24 hours of the infusion, you may develop very common symptoms such as chills, fever, tiredness, feeling weak, headache, feeling sick (nausea), being sick (vomiting), muscle ache, and dizziness,. Common symptoms include a fainting episode, bluish discoloration of the skin, lips and/or nail beds due to low levels of oxygen in the blood, wheezing, high or low blood pressure and difficulty breathing.

Tell your doctor or nurse if you develop any of these symptoms, as the infusion may need to be slowed down or stopped. You may also be given other medicines if needed.

If you experience any of the following side effects **several days after** the infusion, **contact a doctor immediately**:

- shortness of breath, wheezing, dizziness, rash, or fever.

Infection
Tell your doctor after your Provenge treament if you get any symptoms of an infection, for example, a fever or high temperature above 38°C, chills, a fast heartbeat, fast breathing, dizziness on standing up, confusion or feeling/being sick.

Stroke
Contact a doctor immediately if you experience sudden vision loss in one eye, difficulty speaking, numbness and/or weakness affecting one side of the body as any of these may be signs of a stroke.

Heart attack
Contact a doctor immediately if you experience chest pain, pain in the left arm and/or shortness of breath as any of these may be signs of a heart attack.

Other side effects with Provenge include:

Very common side effects (may affect more than 1 in 10 patients):
- pain
- joint ache or pain (arthralgia)
- tingling, numbness or abnormal sensation (paraesthesia) around lips, in mouth, or in the arms and/or legs during the leukapheresis procedure
- muscle spasms, chest pain, and low blood pressure during the leukapheresis procedure (caused by a medicine (citrate) used to prevent blood clotting).
- anaemia (decrease in number of red blood cells) due tothe leukapheresis procedure

Common side effects (may affect up to 1 in 10 patients):
- flu-like illness
- abdominal pain
- tremor
- rash, including raised itchy rash (urticaria), or itching
- excessive sweating
- bacteria in the blood (bacteraemia)
- reduced sense of touch or sensation (hypoaesthesia)
- collapse of one of the bones in the spine (spinal cord compression)
- irregular or rapid heart rate
- stroke
- temporary symptoms of a stroke
- blood in the urine
- chest discomfort
- decrease of platelets in the blood due to the leukapheresis procedure

Uncommon side effects (may affect up to 1 in 100 patients
- severe infection in the blood(sepsis)
- severe infection in the blood from a contaminated catheter (catheter sepsis)
- infection from a contaminated catheter (catheter-related infection)
- skin infection of the area where the infusion drip was inserted
- heart attack
- symptoms of a heart attack
- increase in a type of white blood cells called eosinophils
- infusion site reaction (a reaction of the skin area where the infusion drip was inserted)

Reporting side effects
If you get any side effects, talk to your doctor or nurse. This includes any possible side effects not listed in this leaflet. You can also report any side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Provenge

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiration date and time, which is stated on the insulated container and the infusion bag.

Store the bag in the insulated container to maintain the correct storage temperature (2°C–8°C) until infusion.
Do not refrigerate or freeze the container.

After removal from the insulated container, the medicinal product should be used immediately. If not used immediately, in-use storage times and conditions should not exceed 3 hours at room temperature (25°C).

Do not throw away any medicines via wastewater. Since this medicine will be given by a qualified doctor or nurse, they are responsible for the correct disposal of the product. These measures will help to protect the environment.

6. Contents of the pack and other information

What Provenge contains
The **active substance** is autologous peripheral blood mononuclear cells activated with PAP-GM-CSF (prostatic acid phosphatase-granulocyte macrophage-colony stimulating factor), including a minimum of 50 x 10^6 autologous $CD54^+$ cells.
The **other ingredients** are: sodium chloride, sodium lactate, potassium chloride, and calcium chloride.

What Provenge looks like and contents of the pack
Provenge is a slightly cloudy dispersion of cream-to-pink colour and is supplied in a plastic bag with 3 sample ports.

Each Provenge bag contains one individual infusion treatment and the container will only be opened when you are ready to receive your treatment. Your doctor or nurse will confirm that your details (name and date of birth) correspond to the details provided with the Provenge container.

Marketing Authorisation Holder

Dendreon UK Limited
41 Chalton Street
London, NW1 1JD
United Kingdom
Tel: (0)20 7554 2222
Fax: (0)20 7554 2201
dendreonuk@dendreon.com

Manufacturer

PharmaCell
Oxfordlaan 70
NL-6229 EV, Maastricht
The Netherlands

This leaflet was last revised in

Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu.

This leaflet is available in all EU/EEA languages on the European Medicines Agency website.

The following information is intended for medical or healthcare professionals only:

Practical information for medical or healthcare professionals on handling and administration of Provenge dispersion for infusion

Provenge must be administered under the supervision of a physician experienced in the medical treatment of prostate cancer and in an environment where availability of resuscitation equipment must be ensured.

It is important that you read the entire content of this procedure prior to administering Provenge.

Dose and course of treatment
One bag containins autologous peripheral blood mononuclear cells activated with PAP-GM-CSF, including a minimum of 50 x 10^6 autologous $CD54^+$ cells.

The recommended course of treatment is 3 doses at approximately 2 week intervals. Each dose of Provenge is preceded by a standard leukepheresis procedure approximately 3 days prior to the scheduled infusion date. Prior to the first leukapheresis proceedure, a complete blood count (CBC) test should be performed. Additional CBC tests may be performed in accordance with local requirements.

Handling instructions

Before handling or administering Provenge

- Provenge is shipped directly to the medical facility where the infusion will be administered. The infusion bag is placed inside an insulated polyurethane container and packed in a shipping box. The insulated container and the gel packs within are designed to maintain the appropriate transportation and storage temperature of Provenge until infusion. Do not irradiate.
- The outer shipping box should be opened to verify the product and patient-specific labels located on the top of the insulated container. Do not remove this insulated container from the shipping box, or open the lid of the insulated container, until the patient is ready for infusion.
- Provenge is prepared from human blood of the specific patient and is not tested for transmissible infectious agents. Patient leukapheresis material is tested for transmissible infectious agents in line with applicable local requirements. However, as Provenge is an autologous product, a positive test does not preclude the manufacture of the product. Therefore, Provenge may carry the risk of transmitting infectious viruses (HIV 1 and 2, hepatitis B and C) to health care professionals handling the product. Accordingly, healthcare professionals should employ appropriate precautions when handling the leukapheresis material or Provenge.

Preparing the infusion

- Take care to ensure aseptic handling when preparing the infusion.

What to check prior to infusion

- It must be ensured that the Final Product Disposition Notification form containing the patient identifiers, expiration date and time, and the disposition status (approved for infusion or rejected), has been received from the market authorisation holder.
- It must be ensured that the patient's identity matches the essential unique patient information on the Provenge bag and the Final Product Disposition Notification form.
- Once the patient is prepared for infusion and the APPROVED Final Product Disposition Notification form has been received, the Provenge bag should be removed from the insulated container and inspected for leaks, external damage, foreign particulate matter, or clumps/clots.
- Contents of the bag will be slightly cloudy, with a cream to pink colour. Gently mix and re-suspend the contents of the bag, inspecting for clumps and clots. Small clumps of cellular material should disperse with gentle manual mixing.
- If the Provenge bag leaks, is damaged, or if particles or clumps remain in the bag after gentle manual mixing, the product **must not be used**.

Administration

- Infusion must begin prior to the expiration date and time indicated on the Final Product Disposition Notification form and bag label. **Do not initiate infusion of expired Provenge**.
- Only one of the 2 spike ports should be used and should not be opened prior to administration in order to avoid contamination.
- Provenge is infused over a period of approximately 60 minutes through a large bore needle appropriate for transfusion of red blood cells. This peripheral delivery system is commonly used in clinical practice for the transfusion of blood components. **Do not use a cell filter for infusion.** The entire volume of the infusion bag should be used.
- If the infusion of Provenge must be interrupted, it should not be resumed if the infusion bag has been held at room temperature (25°C) for more than 3 hours.

After the infusion

- Upon completion of the infusion, the patient specific label on the infusion bag should be removed and adhered to the patient file.
- Any unused product or waste material should be disposed of in accordance with local requirements.

IMPORTANT - Do not infuse Provenge if

- You have not received the Final Product Disposition Notification form.
- The Final Product Disposition Notification form is marked REJECTED.
- The expiration date and time have passed.
- The essential unique patient information on the infusion bag does not match that of the scheduled patient.
- The product integrity has been breached in any way (the infusion bag is damaged, leaks, or particles/clumps remain in the bag after gentle manual mixing).

Shelf life and special precautions for storage

Provenge has a shelf life of 18 hours in the insulated container that is shipped to the medical facility where the infusion will be administered. Store the bag in the insulated container to maintain the correct storage temperature (2°C–8°C) until infusion. Do not refrigerate or freeze the container.

After removal from the insulated container, Provenge should be used immediately. If not used immediately, in use storage times and conditions should not exceed 3 hours at room temperature (25°C).

Disposal

Any unused product or waste material should be disposed of in accordance with local requirements.