

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all of the information needed to use PROVENGE® (sipuleucel-T) safely and effectively. See Full Prescribing Information for PROVENGE®.

**PROVENGE® (sipuleucel-T) Intravenous Infusion
Initial U.S. Approval: YEAR**

----- INDICATIONS AND USAGE -----

PROVENGE® is indicated for the treatment of men with metastatic castrate resistant (hormone refractory) prostate cancer. (1.0)

----- DOSAGE AND ADMINISTRATION -----

- The recommended course of therapy for PROVENGE® is 3 complete doses, given at approximately 2-week intervals by intravenous infusion. (2.2)
- PROVENGE® should be administered via intravenous infusion over a period of approximately 60 minutes. (2.1)
- Patients should be premedicated orally with acetaminophen and an antihistamine such as diphenhydramine. (2.3)
- Dose Modification: see Full Prescribing Information. (2.4)

----- DOSAGE FORMS AND STRENGTHS -----

Each dose of PROVENGE® contains all the autologous mononuclear cells, including antigen presenting cells, that are activated ex vivo via culture with a recombinant PAP-GM-CSF fusion protein, suspended in 250 mL of Lactated Ringer's Injection, USP and provided in a sealed, patient-specific infusion bag. (3.0)

----- CONTRAINDICATIONS -----

- None known. (4.0)

----- WARNINGS AND PRECAUTIONS -----

- PROVENGE® is a product intended solely for autologous use. (5.0)
- PROVENGE® is not routinely tested for transmissible infectious diseases and may transmit diseases to health care professionals handling the product. Universal precautions should be followed. (5.0)
- Concomitant use of chemotherapy and immunosuppressive medications with PROVENGE® has not been studied. (5.1)
- Acute infusion reactions have been observed in patients treated with PROVENGE®. 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. Closely monitor patients with cardiac or pulmonary conditions. (2.4, 5.2)

----- ADVERSE REACTIONS -----

- The most common adverse reactions ($\geq 5\%$ and at least twice the control arm incidence) are chills, pyrexia (fever), headache, myalgia, influenza like illness, and hyperhidrosis (sweating). (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Dendreon Corporation (phone number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

**FULL PRESCRIBING INFORMATION:
CONTENTS***

- 1 INDICATIONS AND USAGE**
- 2 DOSAGE AND ADMINISTRATION**
 - 2.1 Administration
 - 2.2 Recommended Dose and Schedule
 - 2.3 Recommended Premedication
 - 2.4 Dose Modification
- 3 DOSAGE FORMS AND STRENGTHS**
- 4 CONTRAINDICATIONS**
- 5 WARNINGS AND PRECAUTIONS**
 - 5.1 Concomitant Chemotherapy or Immunosuppressive Therapy
 - 5.2 Acute Infusion Reactions
 - 5.3 General Precautions
- 6 ADVERSE REACTIONS**
 - 6.1 Clinical Trials Experience
- 7 DRUG INTERACTIONS**
- 8 USE IN SPECIFIC POPULATIONS**
 - 8.5 Geriatric
 - 8.6 Race
- 10 OVERDOSAGE**
- 11 DESCRIPTION**
- 12 CLINICAL PHARMACOLOGY**
 - 12.1 Mechanism of Action
- 14 CLINICAL STUDIES**
 - 14.1 IMPACT Study (D9902B)
 - 14.2 Study D9901
 - 14.3 Study D9902A
 - 14.4 Summary of Overall Survival
- 16 HOW SUPPLIED/STORAGE AND HANDLING**
- 17 PATIENT COUNSELING INFORMATION**
 - 17.1 Physician Information
 - 17.1.1 Preparation and Schedule
 - 17.1.2 Leukapheresis and Venous Access
 - 17.1.3 Acute Infusion Reactions
 - 17.1.4 Immunosuppressive Agents
 - 17.1.5 Prostate-Specific Antigen
 - 17.2 Patient Labeling

* Sections or subsections omitted from the Full Prescribing Information are not listed.

FULL PRESCRIBING INFORMATION

1.0 INDICATIONS AND USAGE

PROVENGE[®] (sipuleucel-T) is indicated for the treatment of men with metastatic castrate resistant (hormone refractory) prostate cancer.

2.0 DOSAGE AND ADMINISTRATION

2.1 Administration

PROVENGE[®] should be administered via intravenous infusion over a period of approximately 60 minutes. **DO NOT USE A CELL FILTER.** It is recommended that patients be observed for a minimum of 30 minutes following each infusion.

Each dose of PROVENGE[®] is labeled with a unique patient identifier that must be matched to the patient prior to infusion. The healthcare professional must ensure that the infusion of PROVENGE[®] does not begin until confirmation of product release has been received from Dendreon. Infusion must begin prior to the expiration date and time indicated on the Product Disposition Form and Product Label. **DO NOT INITIATE INFUSION OF EXPIRED PROVENGE[®].**

2.2 Recommended Dose and Schedule

The recommended course of therapy for PROVENGE[®] is 3 complete doses, given at approximately 2-week intervals. In controlled clinical trials, the median dosing interval between infusions of PROVENGE[®] was 2 weeks (range 1 to 15 weeks); the maximum dosing interval has not been established. Each dose of PROVENGE[®] is preceded by a standard leukapheresis procedure approximately 2 to 3 days prior to the infusion date. It is important that the physician and patient adhere to the personalized leukapheresis and infusion schedule.

2.3 Recommended Premedication

To minimize potential acute infusion reactions such as chills and/or pyrexia (fever), it is recommended that approximately 30 minutes prior to administration of PROVENGE[®], patients be premedicated orally with acetaminophen and an antihistamine such as diphenhydramine.

2.4 Dose Modification

Acute Infusion Reactions [*see Warnings and Precautions (5.2)*].

- 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 should be administered as needed. In controlled clinical trials, symptoms of acute infusion reactions

- In the event an infusion of PROVENGE[®] must be interrupted, the infusion should not be restarted if this period exceeds 60 minutes.

3.0 DOSAGE FORMS AND STRENGTHS

The composition of PROVENGE[®] is dependent on the cells obtained from the patient's leukapheresis. Each dose of PROVENGE[®] will contain all the autologous mononuclear cells, including antigen presenting cells that were activated ex vivo via culture with a recombinant PAP-GM-CSF fusion protein, suspended in 250 mL of Lactated Ringer's Injection, USP. Each dose of PROVENGE[®] will contain a minimum of 50×10^6 CD54⁺ antigen presenting cells.

PROVENGE[®] is supplied in a sealed, patient-specific infusion bag; the entire volume of the bag should be infused.

4.0 CONTRAINDICATIONS

None known.

5.0 WARNINGS AND PRECAUTIONS

PROVENGE[®] is intended solely for autologous use. PROVENGE[®] is not routinely tested for transmissible infectious diseases. Therefore, patient leukapheresis material and PROVENGE[®] may carry the risk of transmitting infectious diseases to health care professionals handling the product. Accordingly, health care professionals should employ universal precautions when handling leukapheresis material or PROVENGE[®].

If, for any reason, the patient is unable to receive an infusion of PROVENGE[®], the patient will need to undergo additional leukapheresis procedure(s) if the course of treatment is to be continued. Patients should be advised of this possibility prior to initiating treatment.

5.1 Concomitant Chemotherapy or Immunosuppressive Therapy

Use of either chemotherapy or immunosuppressive agents (such as systemic corticosteroids) given prior to the leukapheresis procedure, concurrently with PROVENGE[®], or following PROVENGE[®] therapy, has not been studied. The effect of these drugs on the safety and effectiveness of PROVENGE[®] is not known. PROVENGE[®] is designed to activate the immune system. Patients should be carefully evaluated to determine whether it is medically appropriate to reduce or discontinue immunosuppressive agents prior to treatment with PROVENGE[®].

5.2 Acute Infusion Reactions

Acute infusion reactions (occurring within 1 day of infusion) included, but were not limited to, pyrexia (fever), chills, respiratory events (dyspnea, hypoxia, and bronchospasm), nausea, vomiting, fatigue, hypertension, and tachycardia. In controlled clinical trials, 71.2% of patients in the PROVENGE[®] arm developed an acute infusion reaction. The most common events ($\geq 20\%$) were chills, pyrexia (fever), and fatigue. The majority of events were mild or moderate (NCI CTCAE Grade 1 or 2, respectively).

In controlled clinical trials, severe (Grade 3) acute infusion reactions occurred in 3.5% of PROVENGE[®] patients. They included chills, pyrexia (fever), fatigue, asthenia, dyspnea, hypoxia, bronchospasm, dizziness, headache, hypertension, myalgia, nausea, and vomiting. The incidence of severe events was greater following the second infusion (2.1% vs. 0.8% following the first infusion); and decreased to 1.3% following the third infusion. A total of 1.2% of PROVENGE[®] patients were hospitalized within 1 day of infusion for management of acute infusion reactions. No Grade 4 or 5 acute infusion reactions occurred in PROVENGE[®] patients.

In controlled clinical trials, 3 patients (0.5%) on the PROVENGE[®] arm experienced cardiac arrhythmias within 1 day of infusion. The 2 patients who developed atrial fibrillation had histories of atrial fibrillation and responded to treatment. One patient with a history of hypertension had a 1-minute episode of ventricular tachycardia that resolved without treatment.

Closely monitor patients with cardiac or pulmonary conditions.

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. [*See Dosage and Administration (2.4).*]

5.3 General Precautions

PROVENGE[®] is shipped following a preliminary sterility test with a 2-day incubation to determine absence of microbial growth. Final (7-day incubation) sterility test results are not available at the time of infusion.

6.0 ADVERSE REACTIONS

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The safety evaluation of PROVENGE[®] is based on 601 prostate cancer patients who received PROVENGE[®] in randomized Phase 3 controlled clinical trials. The most common adverse

reactions observed in PROVENGE[®] patients at a rate $\geq 5\%$ and at least twice the control arm rate, were chills, pyrexia (fever), headache, myalgia, influenza like illness, and hyperhidrosis (sweating). The majority of adverse reactions were mild or moderate in severity.

Serious adverse events observed in patients treated with PROVENGE[®] include acute infusion reactions [*see Warnings and Precautions (5.2)*], cerebrovascular events, and single case reports of eosinophilia, rhabdomyolysis, myasthenia gravis, myositis, and tumor flare.

PROVENGE[®] was discontinued in 1.5% of patients in the IMPACT trial due to adverse reactions. Some patients who required central venous catheters for treatment with PROVENGE[®] developed infections, including sepsis. A small number of these patients discontinued treatment as a result. Monitoring for infectious sequelae in patients with central venous catheters is recommended.

Each dose of PROVENGE[®] is preceded by a standard leukapheresis procedure approximately 2 to 3 days prior to the infusion. Adverse events that occurred ≤ 1 day following a leukapheresis procedure in $\geq 5\%$ of patients in controlled clinical trials included citrate toxicity (14.2%), paresthesia oral (12.6%), paresthesia (11.4%), and fatigue (8.3%).

Table 1 provides the frequency and severity of adverse events reported in $\geq 5\%$ of patients in the PROVENGE[®] arm of Phase 3, randomized, controlled trials of men with prostate cancer. The population included 485 PROVENGE[®] patients with metastatic castrate resistant prostate cancer and 116 PROVENGE[®] patients with non-metastatic androgen dependent prostate cancer who were scheduled to receive 3 infusions of PROVENGE[®] at approximately 2-week intervals. The population was age 40 to 91 years (median 70 years), and the majority of patients (90.6%) were Caucasian.

Table 1 Incidence of Adverse Events Occurring in $\geq 5\%$ of Patients Randomized to PROVENGE[®]

	PROVENGE [®] (N = 601)		Placebo (N = 303)	
	All Grades n (%)	Grade 3-5 n (%)	All Grades n (%)	Grade 3-5 n (%)
Chills	319 (53.1)	13 (2.2)	33 (10.9)	0 (0.0)
Fatigue	247 (41.1)	6 (1.0)	105 (34.7)	4 (1.3)
Pyrexia (fever)	188 (31.3)	6 (1.0)	29 (9.6)	3 (1.0)
Back pain	178 (29.6)	18 (3.0)	87 (28.7)	9 (3.0)
Nausea	129 (21.5)	3 (0.5)	45 (14.9)	0 (0.0)
Arthralgia	118 (19.6)	11 (1.8)	62 (20.5)	5 (1.7)
Headache	109 (18.1)	4 (0.7)	20 (6.6)	0 (0.0)
Citrate toxicity	89 (14.8)	0 (0.0)	43 (14.2)	0 (0.0)
Paresthesia	85 (14.1)	1 (0.2)	43 (14.2)	0 (0.0)
Vomiting	80 (13.3)	2 (0.3)	23 (7.6)	0 (0.0)
Anemia	75 (12.5)	11 (1.8)	34 (11.2)	7 (2.3)
Constipation	74 (12.3)	1 (0.2)	40 (13.2)	3 (1.0)
Pain	74 (12.3)	7 (1.2)	20 (6.6)	3 (1.0)
Paresthesia oral	74 (12.3)	0 (0.0)	43 (14.2)	0 (0.0)
Pain in extremity	73 (12.1)	5 (0.8)	40 (13.2)	1 (0.3)
Dizziness	71 (11.8)	2 (0.3)	34 (11.2)	0 (0.0)
Myalgia	71 (11.8)	3 (0.5)	17 (5.6)	0 (0.0)
Asthenia	65 (10.8)	6 (1.0)	20 (6.6)	2 (0.7)
Diarrhea	60 (10.0)	1 (0.2)	34 (11.2)	3 (1.0)
Influenza like illness	58 (9.7)	0 (0.0)	11 (3.6)	0 (0.0)
Musculoskeletal pain	54 (9.0)	3 (0.5)	31 (10.2)	3 (1.0)
Dyspnea	52 (8.7)	11 (1.8)	14 (4.6)	3 (1.0)
Edema peripheral	50 (8.3)	1 (0.2)	31 (10.2)	1 (0.3)
Hot flush	49 (8.2)	2 (0.3)	29 (9.6)	1 (0.3)
Hematuria	46 (7.7)	6 (1.0)	18 (5.9)	3 (1.0)
Muscle spasms	46 (7.7)	2 (0.3)	17 (5.6)	0 (0.0)
Hypertension	45 (7.5)	3 (0.5)	14 (4.6)	0 (0.0)

	PROVENGE[®] (N = 601)		Placebo (N = 303)	
	All Grades n (%)	Grade 3-5 n (%)	All Grades n (%)	Grade 3-5 n (%)
Anorexia	39 (6.5)	1 (0.2)	33 (10.9)	3 (1.0)
Bone pain	38 (6.3)	4 (0.7)	22 (7.3)	3 (1.0)
Upper respiratory tract infection	38 (6.3)	0 (0.0)	18 (5.9)	0 (0.0)
Insomnia	37 (6.2)	0 (0.0)	22 (7.3)	1 (0.3)
Musculoskeletal chest pain	36 (6.0)	2 (0.3)	23 (7.6)	2 (0.7)
Cough	35 (5.8)	0 (0.0)	17 (5.6)	0 (0.0)
Neck pain	34 (5.7)	3 (0.5)	14 (4.6)	2 (0.7)
Weight decreased	34 (5.7)	2 (0.3)	24 (7.9)	1 (0.3)
Urinary tract infection	33 (5.5)	1 (0.2)	18 (5.9)	2 (0.7)
Rash	31 (5.2)	0 (0.0)	10 (3.3)	0 (0.0)
Hyperhidrosis	30 (5.0)	1 (0.2)	3 (1.0)	0 (0.0)
Tremor	30 (5.0)	0 (0.0)	9 (3.0)	0 (0.0)

Cerebrovascular Events

In controlled clinical trials of PROVENGE[®], cerebrovascular events (hemorrhagic, ischemic, or bleeding from dural metastatic lesions) were observed in 3.5% of patients in the PROVENGE[®] arm compared with 2.6% of patients in the placebo arm. No increased incidence of non-neurologic arterial vascular events or non-neurologic venous vascular events was observed for patients in the PROVENGE[®] arm compared with placebo. Whether there is a causal relationship of cerebrovascular events to PROVENGE[®] remains unclear.

7.0 DRUG INTERACTIONS

There have been no reports of drug interactions associated with the administration of PROVENGE[®].

8.0 USE IN SPECIFIC POPULATIONS

8.5 Geriatric

In controlled clinical trials, 72.9% of patients (438 of 601) treated with PROVENGE[®] were \geq 65 years of age and 27.1% (163 of 601) were $<$ 65 years of age. There were no apparent differences in the safety of PROVENGE[®] between patients \geq 65 years of age and younger patients.

In a survival analysis of the controlled clinical trials of PROVENGE[®] in castrate resistant prostate cancer, 78.3% of patients (382 of 488) were \geq 65 years of age. The median survival in the PROVENGE[®] patients \geq 65 years of age was 23.4 months (95% confidence interval [CI]: 22.0, 27.1) and in the PROVENGE[®] patients < 65 years of age was 29.0 months (95% CI: 22.8, 34.2).

8.6 Race

In controlled clinical trials, 90.6% of patients were Caucasian, 5.8% were African American, and 3.7% were Other. Due to the high percentage of patients who were Caucasian, no conclusions can be made regarding the safety or efficacy of PROVENGE[®] by race.

10.0 OVERDOSAGE

Given that each PROVENGE[®] infusion comprises the maximum number of cells that can be manufactured from a single leukapheresis procedure, there are no known instances of overdose from either a single infusion or a full course of therapy with PROVENGE[®].

11.0 DESCRIPTION

PROVENGE[®] is an autologous active cellular immunotherapy product designed to stimulate an immune response against prostate cancer. PROVENGE[®] consists of autologous peripheral blood mononuclear cells, including antigen presenting cells, that have been activated ex vivo via culture with a recombinant fusion protein consisting of prostatic acid phosphatase (PAP), an antigen expressed in prostate cancer tissue, linked to granulocyte-macrophage colony-stimulating factor (GM-CSF), an immune cell activator.

The composition of PROVENGE[®] is dependent on the composition of cells obtained from the patient's leukapheresis. Each dose of PROVENGE[®] must contain a minimum of 50×10^6 CD54⁺ antigen presenting cells. In addition to antigen presenting cells, the final product also includes T cells, B cells, and natural killer (NK) cells. Each dose of PROVENGE[®] is suspended in 250 mL of Lactated Ringer's Injection, USP.

12.0 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

PROVENGE[®] is classified as an active cellular immunotherapy. Such immunotherapy products are designed to elicit a specific immune response to a target antigen.

In vivo, anti-tumor immune responses are mediated by antigen presenting cells (APCs) and T cells. APCs take up and display tumor antigen-derived peptides on their surface. T cells bind to and recognize the target antigen peptides on the APC surface, eliciting a response

characterized by the T cell activation and proliferation. Activated T cells are the effector cells thought to be responsible for recognition and destruction of cancer cells in vivo.

While the precise mechanism of action is unknown, PROVENGE[®] is designed to induce a cellular immune response targeted against PAP, an antigen expressed in most prostate cancers. During ex vivo culture with the PAP-GM-CSF antigen, APCs are activated to take up and process the recombinant target antigen into small peptides that are then displayed on the APC surface. PROVENGE[®] has been shown to stimulate the proliferation of PAP-specific T cell hybridomas in vitro.

In the IMPACT clinical trial, 237 of the 512 patients randomized were evaluated for the development of humoral and/or T cell responses to the target antigen. Significant antibody responses against both the fusion protein and the PAP antigens were observed in the PROVENGE[®] group compared to the placebo control group ($P \leq 0.001$ at Weeks 6, 14, and 26, Wilcoxon Rank Sum). These antibody responses persisted to at least 26 weeks. ELISPOT responses to the fusion protein increased after treatment with PROVENGE[®] and the increases were significantly greater than those observed for the placebo arm (each $P \leq 0.02$ ANOVA of ranked ELISPOT medians). T cell proliferative responses to the fusion protein were significantly greater than those observed for the placebo arm ($P < 0.001$ at Weeks 6 and 14, and $P = 0.009$ at Week 26, mixed model ANOVA of log-transformed stimulation index) and a smaller response to PAP was also observed. Overall, treatment-related responses showed a positive correlation with overall survival in the IMPACT study.

Exploratory analyses from Phase 3 clinical trials support the role of activated APCs in the mechanism of action for PROVENGE[®]. CD54 is a cell surface molecule that plays a role in the immunologic interactions between APCs and T cells, and it is considered a marker of immune cell activation. When immune cells are activated, cell surface expression of CD54 increases, a phenomenon known as CD54 upregulation. In the analyses of Phase 3 controlled clinical trials in castrate resistant prostate cancer, there was a positive correlation between prolongation of overall survival and cumulative CD54 upregulation on APCs ($P = 0.041$, Cox model), cumulative total nucleated cell (TNC) count ($P < 0.001$, Cox model), and cumulative CD54⁺ APC count ($P = 0.005$, Cox model) in patients who received at least 1 infusion of PROVENGE[®].

14.0 CLINICAL STUDIES

14.1 IMPACT Study (D9902B)

The efficacy and safety of PROVENGE[®] in the treatment of metastatic castrate resistant prostate cancer were assessed in this Phase 3, randomized, double blind, placebo-controlled, multicenter trial. Patients with asymptomatic or minimally symptomatic metastatic castrate resistant prostate cancer were randomized 2:1 to receive PROVENGE[®] (active treatment, n=341 patients) or placebo (control, n=171 patients). Stratification factors included primary Gleason grade (≤ 3 ,

≥ 4), number of bone metastases (0 to 5, 6 to 10, >10), and bisphosphonate use (yes, no). Following randomization, patients from both treatment groups were scheduled to undergo a series of 3 leukapheresis procedures (at approximately Weeks 0, 2, and 4), each followed 2 to 3 days later by infusion of PROVENGE[®] or placebo. Patients were followed for safety and efficacy until independent confirmation of objective disease progression. Following independent confirmation of objective disease progression, patients could be unblinded to have their treatment assignment revealed; patients randomized to the placebo arm had the option to enter a Phase 2, open label salvage protocol and receive antigen loaded (PAP-GM-CSF) APCs prepared from autologous APC precursors that had been cryopreserved at the time of placebo generation. Patients randomized to the PROVENGE[®] arm were not eligible to participate in the salvage study.

The primary endpoint of the study was overall survival. The secondary endpoint was time to objective disease progression as determined by independent assessment of serial imaging studies. Prostate-specific antigen (PSA) was not used as a measure of progression in this study. Baseline demographic and disease characteristics were well balanced between the treatment groups (Table 2).

Table 2 IMPACT Study, Baseline Demographic and Disease Characteristics, Intent-to-Treat Population

Patient Characteristic	PROVENGE[®] (N = 341)	Placebo (N = 171)
Age (yrs)		
Median (min, max)	72 (49, 91)	70 (40, 89)
Race (%)		
Caucasian	89.4	91.2
African American	6.7	4.1
Asian, Hispanic, or Other	3.8	4.7
ECOG Performance Status (%)		
0	82.1	81.3
Gleason Sum (%)		
≤ 7	75.4	75.4
Weight		
Median lbs (min, max)	194 (116, 384)	190 (132, 300)
Median kgs (min, max)	88 (53, 175)	86 (60, 136)
Time from Diagnosis to Randomization (yrs)		
Median (min, max)	7.1 (0.8, 24.5)	7.1 (0.9, 21.5)

Patient Characteristic	PROVENGE® (N = 341)	Placebo (N = 171)
Disease Localization (%)		
Bone only	50.7	43.3
Soft tissue only	7.0	8.2
Bone and soft tissue	41.9	48.5
Laboratory Values		
Serum PSA, median ng/mL	51.7	47.2
Serum PAP, median U/L	2.7	3.2
Alkaline phosphatase, median U/L	99.0	109.0
LDH, median U/L	194.0	193.0
Hemoglobin, median g/dL	12.9	12.7
White blood cell count, median x 10 ³ /μL	6.2	6.0
Total absolute neutrophil count, median x 10 ³ /μL	4.0	4.1
Stratification Factors, n (%)		
Primary Gleason Grade		
≤ 3	144 (42.2)	71 (41.5)
≥ 4	197 (57.8)	100 (58.5)
Bone Metastases		
0 – 5	146 (42.8)	73 (42.7)
6 – 10	49 (14.4)	25 (14.6)
> 10	146 (42.8)	73 (42.7)
Bisphosphonate Use		
Yes	164 (48.1)	82 (48.0)
No	177 (51.9)	89 (52.0)
Prior Prostate Cancer Therapy, n (%)		
Hormone therapy received	341 (100.0)	171 (100.0)
Combined androgen blockade	279 (81.8)	141 (82.5)
Orchiectomy	32 (9.4)	13 (7.6)
Chemotherapy	67 (19.6)	26 (15.2)
Docetaxel	53 (15.5)	21 (12.3)
Radical prostatectomy	121 (35.5)	59 (34.5)
Radiotherapy (to the prostate bed)	185 (54.3)	91 (53.2)

Abbreviations: ECOG = Eastern Cooperative Oncology Group

Of the 171 patients randomized to the placebo arm, 109 patients (63.7%) crossed over to receive antigen loaded (PAP-GM-CSF) APCs prepared from autologous cryopreserved APC precursors as part of the salvage study. Following randomization, 57.2% of patients in the PROVENGE[®] arm and 50.3% of patients in the placebo arm received subsequent treatment with docetaxel.

The clinical benefit of PROVENGE[®] as measured in the intent-to-treat population demonstrated that patients treated with PROVENGE[®] had a statistically significant survival advantage compared with placebo ($P = 0.032$, Cox model). Patients randomized to PROVENGE[®] had a 22.5% reduction in the risk of death compared with placebo (HR = 0.775 [95% CI = 0.614, 0.979]). The median survival for patients randomized to PROVENGE[®] was 25.8 months compared to 21.7 months for patients randomized to placebo. The percentage of patients alive at 3 years by Kaplan Meier estimate was 32% in the PROVENGE[®] arm compared with 23% in the placebo arm. Survival results are presented in Table 3, Table 4, and Figure 1.

Table 3 IMPACT Study, Analysis of Overall Survival, Intent-to-Treat Population

	PROVENGE[®] (N = 341)	Placebo (N = 171)
Events, n (%)	210 (61.6)	121 (70.8)
Median Survival Time (Months; 95% CI)	25.8 (22.8, 27.7)	21.7 (17.7, 23.8)
Primary Model		
p-value (Cox) ¹	0.032	
Hazard Ratio (95% CI)	0.775 (0.614, 0.979)	
Unadjusted Analysis		
p-value (log-rank) ²	0.023	
Hazard Ratio (95% CI)	0.766 (0.608, 0.965)	

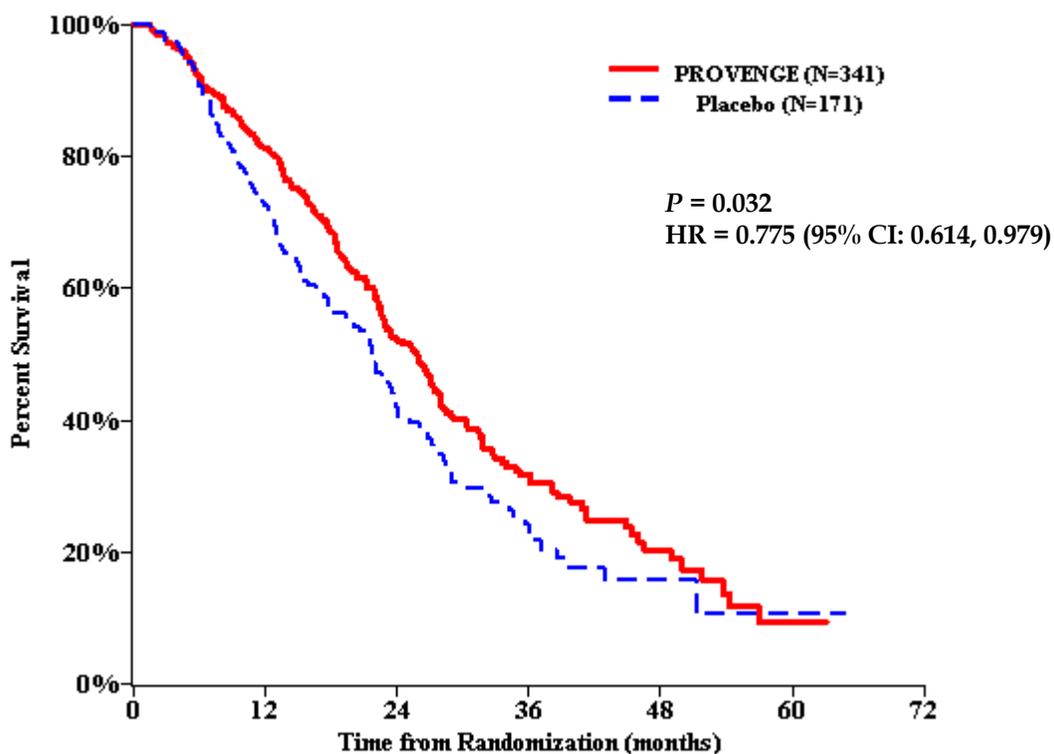
¹ From a Cox regression model with treatment, PSA (ln), and LDH (ln) as the independent variables, stratified by randomization strata.

² P-value was obtained from log-rank test and HR was obtained from a Cox regression model with treatment as the independent variable, both stratified by randomization strata.

Table 4 IMPACT Study, Kaplan-Meier Survival Rate Estimates (Percent), Intent-to-Treat Population

Treatment	12 Months	24 Months	36 Months	48 Months
PROVENGE [®]	81.1	52.1	31.7	20.5
Placebo	72.4	41.2	23.0	16.0

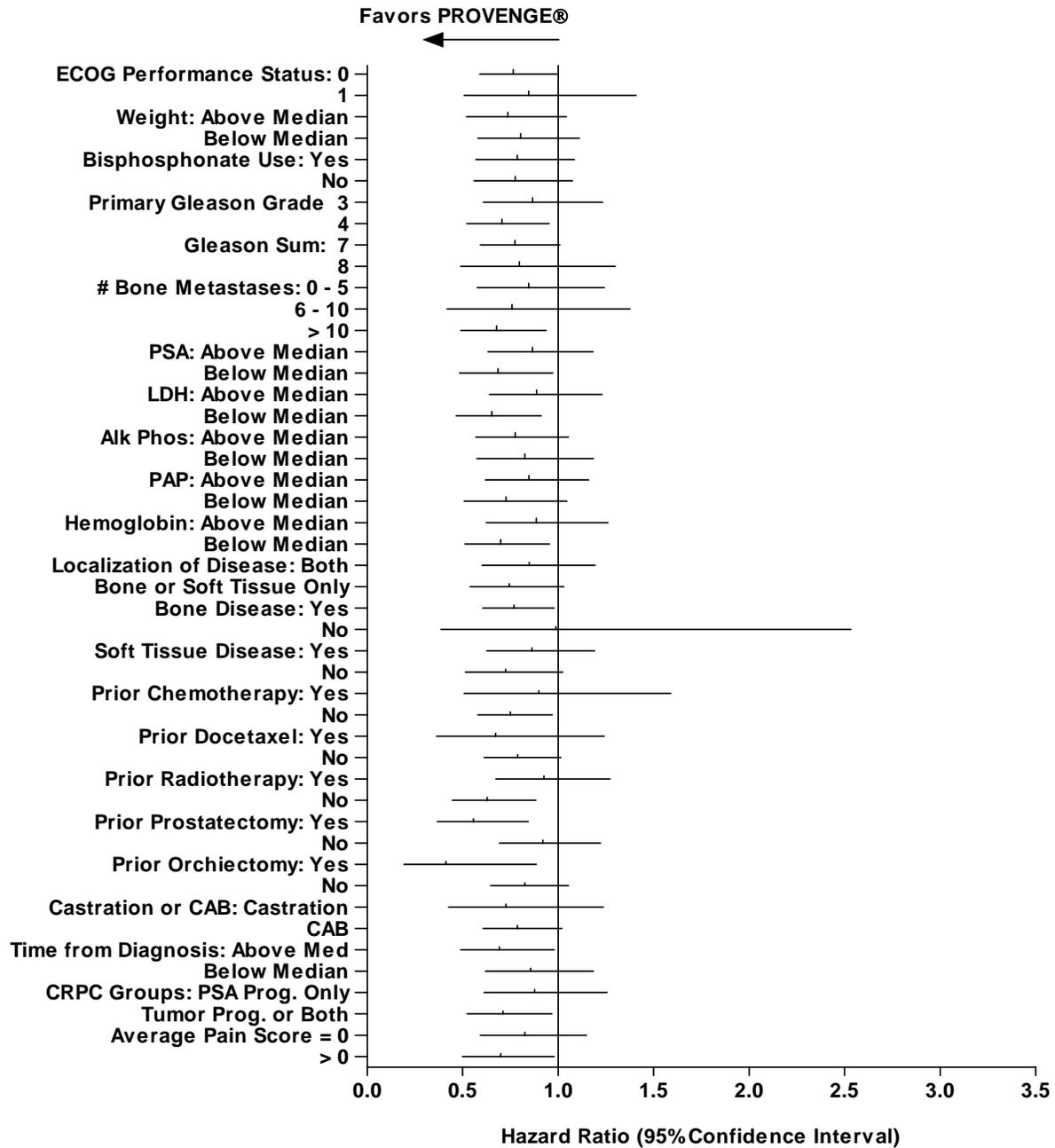
Figure 1 IMPACT Study, Kaplan-Meier Overall Survival Curve, Intent-to-Treat Population



Patients at Risk	0	12	24	36	48	60
	Months	Months	Months	Months	Months	Months
PROVENGE®	341	274	129	49	14	1
Placebo	171	123	55	19	4	1

A number of patient subsets were examined in sensitivity analyses. The results of these analyses are shown in [Figure 2](#). The effect of PROVENGE® on survival was consistent across the multiple subsets.

Figure 2 IMPACT Study, Survival Consistency in Study Subgroups as Defined by Baseline Covariates



There was no significant delay in time to objective disease progression as determined by independent assessment of serial imaging studies for patients treated with PROVENGE[®] compared to placebo (HR = 0.951 [95% CI: 0.773, 1.169]; *P* = 0.628, log rank).

14.2 Study D9901

Study D9901 was a Phase 3, randomized, double blind, placebo-controlled, multicenter trial in patients with asymptomatic metastatic castrate resistant prostate cancer. A total of 127 patients were randomized 2:1 to receive PROVENGE[®] (active treatment, *n* = 82 patients) or placebo (control, *n* = 45 patients). Following randomization, patients from both treatment groups were scheduled to undergo a series of 3 leukapheresis procedures (at approximately Weeks 0, 2, and 4), each followed 2 to 3 days later by infusion of PROVENGE[®] or placebo. Patients were followed for safety and efficacy until they reached disease progression. Following disease progression, patients could be unblinded to have their treatment assignment revealed; patients randomized to the placebo arm had the option to enter a Phase 2, open label salvage protocol and receive antigen loaded (PAP-GM-CSF) APCs prepared from autologous APC precursors that had been cryopreserved at the time of placebo generation. Patients randomized to the PROVENGE[®] arm were not eligible to participate in the salvage study.

The primary endpoint of this study was time to disease progression defined as progressive disease on serial radiographic imaging tests, new cancer-related pain associated with a radiographic anatomical correlation, or other clinical events consistent with progression such as spinal cord compression, nerve root compression, or pathologic fracture. PSA was not used as a measure of progression in this study. Overall survival was not a study endpoint but was a pre-specified analysis to be performed after all patients had been followed for 36 months or until death, whichever occurred first.

Baseline demographics and disease characteristics were well balanced between the treatment groups. Of the 45 patients randomized to placebo, 34 patients (75.6%) crossed over to receive antigen loaded (PAP-GM-CSF) APCs prepared from autologous cryopreserved APC precursors as part of the salvage study. Following randomization, 37.2% of patients in the PROVENGE[®] arm and 48.8% of patients in the placebo arm received subsequent treatment with docetaxel.

Patients randomized to PROVENGE[®] had a 31% reduction in the risk of disease progression (HR = 0.691 [95% CI: 0.473, 1.010]; *P* = 0.052, log rank) and a 41% reduction in the risk of death compared to patients randomized to placebo (HR = 0.586 [95% CI: 0.388, 0.884]; *P* = 0.010, log rank). The median survival for patients randomized to PROVENGE[®] was 25.9 months compared to 21.4 months for patients randomized to placebo. The percentage of patients alive at 3 years by Kaplan Meier estimate was 34% in the PROVENGE[®] arm compared with 11% in the placebo arm.

14.3 Study D9902A

Study D9902A was a randomized, double blind, placebo-controlled, multicenter trial in patients with asymptomatic metastatic castrate resistant prostate cancer. A total of 98 patients were randomized 2:1 to receive PROVENGE[®] (active treatment, n=65) or placebo (control, n=33). Study D9902A was identical in design to Study D9901.

Baseline demographics and disease characteristics were generally well balanced between the treatment groups. Several prognostic factors, including the percentage of patients with more than 10 bone metastases, and median values for PSA, LDH and alkaline phosphatase favored the placebo arm. Of the 33 patients randomized to placebo, 22 patients (66.7%) crossed over to receive antigen loaded (PAP-GM-CSF) APCs prepared from autologous APC precursors that had been cryopreserved at the time of placebo generation as part of the salvage study. Following disease progression, 38.6% of patients in the PROVENGE[®] arm and 34.4% of patients in the placebo arm received subsequent treatment with docetaxel.

There was no significant delay in time to disease progression (HR = 0.921 [95% CI: 0.588, 1.443]; *P* = 0.719, log rank) and no significant difference in overall survival for patients treated with PROVENGE[®] compared to placebo (HR = 0.786 [95% CI: 0.484, 1.278]; *P* = 0.331, log rank). The median survival for patients randomized to PROVENGE[®] was 19.0 months compared to 15.7 months for patients randomized to placebo. The percentage of patients alive at 3 years by Kaplan Meier estimate was 32% in the PROVENGE[®] arm compared with 21% in the placebo arm.

14.4 Summary of Overall Survival

Table 5 presents overall survival results observed in the randomized, Phase 3 studies of PROVENGE[®] in men with metastatic, castrate resistant prostate cancer.

Table 5 IMPACT Study, Study D9901, and Study D9902A, Summary of Overall Survival

	IMPACT Study		Study D9901 ^a		Study D9902A ^a	
	PROVENGE [®] (N=341)	Placebo (N=171)	PROVENGE [®] (N=82)	Placebo (N=45)	PROVENGE [®] (N=65)	Placebo (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 (0.614, 0.979)		0.586 (0.388, 0.884)		0.786 (0.484, 1.278)	
p-value	0.032 ^b		0.010 ^c		0.331 ^c	
36-Month survival (%)	32%	23%	34%	11%	32%	21%

^a Overall survival was a pre-specified analysis at 36 months.

^b Test statistic 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.

^c Hazard ratio is based on the unadjusted Cox Model and nominal p-values by log-rank.

Abbreviations: CI = confidence interval.

16.0 HOW SUPPLIED/STORAGE AND HANDLING

PROVENGE[®] IS A PRODUCT INTENDED SOLELY FOR AUTOLOGOUS USE.

PROVENGE[®] is suspended in 250 mL of Lactated Ringer's Injection, USP, and supplied in an infusion bag labeled for the specific recipient. The identity of the recipient must be matched with the information contained in the product label prior to infusion. PROVENGE[®] is not routinely tested for transmissible infectious diseases. Therefore, patient leukapheresis material and PROVENGE[®] may carry the risk of transmitting infectious diseases to health care professionals handling the product. Accordingly, health care professionals should employ universal precautions when handling leukapheresis material or PROVENGE[®].

PROVENGE[®] is shipped directly to the infusing provider. The insulated shipping carton and gel packs are designed to maintain the appropriate storage temperature and cell viability until infusion. The product must remain within the insulated carton until the time of administration.

Upon receipt it is important to review the technical data sheet placed on top of the insulated carton. The infusion of PROVENGE[®] must not begin until confirmation of product release via the Product Disposition Form has been received. Infusion must begin prior to the expiration date and time indicated on the technical data sheet and product label. **DO NOT INITIATE INFUSION OF EXPIRED PROVENGE[®].**

17.0 PATIENT COUNSELING INFORMATION

17.1 Physician Information

See FDA-Approved Patient Labeling (17.2)

17.1.1 Preparation and Schedule

The recommended course of therapy for PROVENGE[®] is 3 complete doses. The manufacturing process includes strict expiration times for both the leukapheresis material and PROVENGE[®]. To help ensure that expiration times are not exceeded and that infusions are appropriately spaced, patients should be counseled regarding the importance of maintaining all scheduled appointments and arriving at each appointment prepared and on time. If, for any reason, the patient is unable to receive an infusion of PROVENGE[®], the patient will need to undergo additional leukapheresis procedure(s) if the course of treatment is to be continued.

17.1.2 Leukapheresis and Venous Access

All patients should be appropriately counseled on the leukapheresis procedure, including the possible side effects. Some patients may not have adequate peripheral venous access to accommodate the leukapheresis procedure. Prior to the initial leukapheresis procedure, patients should be evaluated to assess the adequacy of peripheral venous access. Patients with inadequate venous access may require a central venous catheter for leukapheresis and infusion of PROVENGE[®]. In the IMPACT trial, 23.0% of patients required an in-dwelling venous catheter. Patients should be counseled on the importance of catheter care. Patients should be instructed to tell their doctor if they are experiencing any unexplained fevers as this may be attributable to an infected catheter.

Patients should be provided with preparation instructions for the leukapheresis procedure, including nutritional recommendations and hydration requirements, as well as post-procedure care.

17.1.3 Acute Infusion Reactions

Patients should be advised to report signs and symptoms of acute infusion reactions such as fever, chills, breathing problems, nausea, vomiting, headache, or muscle aches. In addition, they should report any symptoms suggestive of a cardiac arrhythmia.

17.1.4 Immunosuppressive Agents

Patients should be advised to inform their doctor if they are taking immunosuppressive agents. [*See Warnings and Precautions (5.1)*].

17.1.5 Prostate-Specific Antigen

Physicians should counsel their patients that PSA measurements may not necessarily reflect response to treatment with PROVENGE[®].

17.2 Patient Labeling

Patient Information about PROVENGE[®] (sipuleucel-T)

This leaflet is designed to help you understand therapy with PROVENGE[®]. The more you understand your treatment, the better you will be able to participate in your care. This leaflet does not take the place of talking with your doctor or healthcare professional about your medical condition or your treatment. If you have any questions, speak with your doctor.

What is PROVENGE[®]?

PROVENGE[®] is an active cellular immunotherapy for the treatment of advanced prostate cancer. PROVENGE[®] is designed to use your body's own immune system to target and attack prostate cancer. PROVENGE[®] is not considered chemotherapy or hormone therapy.

What is in PROVENGE[®]?

PROVENGE[®] is made by combining some of your own immune cells with a cancer targeting protein. Only your own immune system cells can be used to make PROVENGE[®] for you.

How is PROVENGE[®] designed to work?

PROVENGE[®] is designed to activate your immune system to fight prostate cancer.

What should I tell my doctor before receiving PROVENGE[®]?

You should tell your doctor about all your medical conditions, including if you have:

- heart problems
- lung problems
- a history of stroke

You should tell your doctor about all the medicines you take, including prescription and nonprescription medicines. Especially tell your doctor if you take or are receiving:

- chemotherapy
- immunosuppressive agents (such as prednisone, dexamethasone, and hydrocortisone)

How will I receive PROVENGE®?

You will receive PROVENGE® as 3 infusions generally 2 weeks apart. PROVENGE® is typically infused in your doctor's office. Each infusion is given over approximately a 60 minute period.

Since each dose of PROVENGE® is made from your own immune cells, 2 to 3 days before each scheduled infusion of PROVENGE® you will need to go to a blood bank or apheresis center identified by Dendreon to undergo a procedure called leukapheresis. This procedure collects your immune cells and takes about 4 hours. Once collected, your immune cells are sent to a Dendreon manufacturing facility where they are activated to help your immune system recognize and attack prostate cancer cells.

Your doctor will provide you with a personalized schedule of your leukapheresis and infusion appointments. It is very important that you adhere to this treatment schedule.

What is leukapheresis?

For this procedure, an intravenous (IV) catheter will be placed into veins in each arm or in a vein in your upper chest or neck. Blood will flow from your vein into a machine where certain types of white blood cells will be separated from the other blood cells and saved. The rest of your blood will then flow back into your body. During leukapheresis you will be lying in bed for about 4 hours. Leukapheresis occurs approximately 2 or 3 days prior to each infusion of PROVENGE®.

What are the possible side effects of the leukapheresis procedure required to manufacture PROVENGE®?

You should talk to your doctor about what to expect when undergoing a leukapheresis procedure. You may experience side effects as part of the leukapheresis procedure. These side effects include tingling in the fingers and around the mouth, dizziness, feeling light-headed, nausea, and feeling cold. Your doctor may recommend or administer calcium to prevent or treat these side effects.

If you have poor venous access, you may need to have an in-dwelling catheter (which is a thin tube placed into a large vein for a period of time) to collect immune system cells. In the IMPACT clinical trial, 23.0% of patients needed an in-dwelling catheter.

Contamination of venous catheters can result in infections, which may interrupt your treatment with PROVENGE® and cause additional complications that lead to serious injury, hospitalization, or death. Symptoms of infections could include fever and redness or pain at the catheter site. These symptoms should be reported to your doctor immediately. If you experience

an unexplained fever, you should contact your doctor or medical provider and seek emergency treatment.

How do I get started?

Your doctor's staff will work with you to schedule your leukapheresis appointments at the blood bank or apheresis center and your infusion appointments. It is important that you keep all of your scheduled appointments.

What happens if I miss an appointment or my product cannot be infused?

If you miss a leukapheresis appointment your doctor's staff will schedule a new appointment at the blood bank or apheresis center as well as a new infusion appointment.

If you miss an infusion appointment it is likely that your PROVENGE[®] dose will expire and will not be usable. There may be other reasons that may prevent you from receiving your scheduled infusion. If this happens, your doctor's staff will work with you to schedule a new appointment at the blood bank or apheresis center as well as a new infusion appointment.

What are the possible side effects of PROVENGE[®]?

Serious side effects observed in patients who received PROVENGE[®] include the following acute infusion reactions that occurred within 1 day of infusion: chills, fever, fatigue, lack of energy, shortness of breath, low blood oxygen levels, wheezing, dizziness, headache, high blood pressure, muscle aches, nausea, vomiting, and abnormal heart rhythms.

Strokes have been observed in patients who received PROVENGE[®]; the causal relationship of these events to PROVENGE[®] is not clear.

Common side effects observed in patients who received PROVENGE[®] include: chills, fever, headache, muscle aches, flu-like symptoms, and sweating. These side effects are typically mild to moderate, generally resolve within 24 to 48 hours, and can usually be managed at home with over-the-counter remedies as recommended by your doctor. It is important to tell your doctor about any side effects you may experience when receiving PROVENGE[®].

Rare side effects observed in patients who received PROVENGE[®] include: increase in blood eosinophil count, pain and inflammation of cancer sites, skeletal muscle damage, muscle inflammation, or muscle weakness.

These are not all the possible side effects of PROVENGE[®]. For more information, ask your doctor.

What will happen to my PSA level when I receive PROVENCE®?

Changes in your PSA values may not reflect your response to treatment with PROVENCE®. Talk with your doctor about the need to monitor your PSA values.

General Information

This leaflet provides a brief summary of information about PROVENCE®. It is important that you speak with your doctor to obtain more information about PROVENCE®.

Web site and toll-free number:

www.provenge.com

(phone number)