sipuleucel-T (Provenge®)

Policy # 00264
Original Effective Date: 07/21/2010
Current Effective Date: 11/11/2024

Applies to all products administered or underwritten by Blue Cross and Blue Shield of Louisiana and its subsidiary, HMO Louisiana, Inc.(collectively referred to as the "Company"), unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.

When Services May Be Eligible for Coverage

Coverage for eligible medical treatments or procedures, drugs, devices or biological products may be provided only if:

- *Benefits are available in the member's contract/certificate, and*
- *Medical necessity criteria and guidelines are met.*

Based on review of available data, the Company may consider the use of sipuleucel-T (Provenge®)‡ for the treatment of metastatic castrate resistant prostate cancer to be **eligible for coverage.****

Patient Selection Criteria

Coverage eligibility for the use of sipuleucel-T (Provenge) will be considered when ALL of the following criteria are met:

- Patient has documented metastatic prostate cancer in soft tissues and/or bone; AND
- Patient has documented hormone refractory prostate cancer with evidence of disease progression as indicated by serial measurement of serum prostate specific antigen and testosterone level measurement < 50 ng/dL; AND
- Patient is NOT on narcotics for cancer-related pain management; AND
- Patient is asymptomatic or minimally symptomatic; AND
- Patient does NOT have visceral (liver, lung, or brain) metastases

When Services Are Considered Investigational

Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

Based on review of available data, the Company considers the use of sipuleucel-T (Provenge) when patient selection criteria have not been met to be **investigational.***

sipuleucel-T (Provenge®)

Policy # 00264
Original Effective Date: 07/21/2010
Current Effective Date: 11/11/2024

Background/Overview

Provenge is a cellular immunotherapy consisting of autologous peripheral blood mononuclear cells (PBMC's), obtained by leukapheresis and cultured (activated) with a recombinant human protein (PAP-GM-CSF) consisting of prostatic acid phosphatase linked to granulocyte-macrophage colony-stimulating factor. Provenge is indicated for the treatment of asymptomatic or minimally symptomatic metastatic castrate resistant (hormone refractory) prostate cancer.

Provenge is personalized for each patient, produced by taking cells from a patient's tumor, and incubating them with a protein often found on prostate tumors and, an immune system booster. The treated cells are then infused back into the patient three times at approximately 2-week intervals.

The active components of Provenge are autologous antigen presenting cells (APCs) and the protein called PAP-GM-CSF. Antigen presenting cells are activated during a defined culture period with a recombinant human protein, PAP-GM-CSF, 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 cellular composition of Provenge will vary, depending on the cells obtained from the individual patient during leukapheresis. In addition to the APCs, the product also contains T cells, B cells, natural killer (NK) cells, and other cells.

Metastatic Prostate Cancer

Metastatic castrate-resistant (hormone refractory) prostate cancer is usually incurable. Currently available therapies are intended for palliation and/or prolonging survival. These therapeutic options include additional hormonal manipulations, bisphosphonates to reduce effects of bony metastases, chemotherapy, palliative radiation and pain control.

Current National Comprehensive Cancer Network (NCCN) guidelines for prostate cancer recommend Provenge as a category 1 treatment only for patients with metastatic castrate-resistant prostate cancer who are asymptomatic or minimally symptomatic with an ECOG status of 0 or 1 with no liver metastases and life expectancy greater than 6 months. The American Urological Association has a similar recommendation encouraging clinicians not to offer Provenge treatment to patients with symptomatic castrate-resistant prostate cancer.

sipuleucel-T (Provenge®)

Policy # 00264
Original Effective Date: 07/21/2010
Current Effective Date: 11/11/2024

FDA or Other Governmental Regulatory Approval

U.S. Food and Drug Administration (FDA)
Provenge received FDA approval on April 29, 2010 for use in the treatment of prostate cancer patients with hormone-resistant cancer that has spread in the body but is not causing significant symptoms.

Rationale/Source

This medical policy was developed through consideration of peer-reviewed medical literature generally recognized by the relevant medical community, U.S. Food and Drug Administration approval status, nationally accepted standards of medical practice and accepted standards of medical practice in this community, technology evaluation centers, reference to federal regulations, other plan medical policies, and accredited national guidelines.

The approval of this drug by the FDA was based on results from a randomized, double-blind, placebo-controlled, multicenter trial (Study 9902B). Overall survival (OS) was the primary efficacy endpoint of this trial. Eligible patients had metastatic disease in soft tissue and/or bone with evidence of disease progression determined at either of these sites or by serial measurement of prostate specific antigen (PSA).

All patients had prior adequate hormonal therapies with castrate testosterone levels attained. Patients with visceral (liver, lung, or brain) metastases or who reported moderate to severe prostate cancer-related pain and/or use of narcotics for cancer-related pain were excluded. Patients were randomized to receive either the sipuleucel-T treatment or a control (peripheral blood mononuclear cells which were not activated). Patients in both groups underwent 3 leukapheresis procedures (approximately Weeks 0, 2, and 4), followed 3 days later with an infusion of either sipuleucel-T or the non-activated control. Patients who had disease progression during the trial were treated at the physician's discretion. Five hundred twelve patients were randomized (2:1) to either sipuleucel-T (n = 341) or control (n = 171). Eighty-two percent had received prior combined androgen blockade, 54% local radiotherapy, 35% radical prostatectomies, 18% prior chemotherapy including docetaxel. The median age was 71 years (range 40-89); 90% were Caucasian.

Patients treated with sipuleucel-T had an improvement in median OS (25.8 months versus 21.7 months, p = 0.032, HR 0.775, 95% CI 0.61, 0.98). There was no difference in time-to-progression.

Fifty-seven percent of patients in the sipuleucel-T arm and 50.3% in the control arm received docetaxel after disease progression. A second trial (Study 9901) provided supportive evidence to the results of Study 9902B. Study 9901 was a smaller, randomized, double-blind, placebo-controlled, multicenter trial of 127 patients with metastatic, castrate resistant prostate cancer. Patients were randomized (2:1) to receive either sipuleucel-T (n = 82) or control (n = 45). The primary endpoint was time to disease progression. All patients were followed for OS, although the method of survival analysis was not pre-specified. Analysis of the primary endpoint did not reach statistical significance. The median OS of patients treated with sipuleucel-T was 25.9 months compared to 21.45 months for patients in the control group.

The safety evaluation of Provenge is based on 601 prostate cancer patients in the Provenge group who underwent at least 1 leukapheresis procedure in 4 randomized, controlled clinical trials. The control was non-activated autologous peripheral blood mononuclear cells.

Almost all (98.3%) patients in the Provenge group and 96.0% in the control group reported an adverse event. The most common adverse events, reported in patients in the Provenge group at a rate ≥ 15%, were chills, fatigue, fever, back pain, nausea, joint ache, and headache. In 67.4% of patients in the Provenge group, these adverse events were mild or moderate in severity. Severe (Grade 3) and life-threatening (Grade 4) adverse events were reported in 23.6% and 4.0% of patients in the Provenge group compared with 25.1% and 3.3% of patients in the control group. Fatal (Grade 5) adverse events were reported in 3.3% of patients in the Provenge group compared with 3.6% of patients in the control group. The most common (≥ 2%) Grade 3-5 adverse events reported in the Provenge group were back pain and chills.

Serious adverse events were reported in 24.0% of patients in the Provenge group and 25.1% of patients in the control group. Serious adverse events in the Provenge group included acute infusion reactions, cerebrovascular events, and single case reports of eosinophilia, rhabdomyolysis, myasthenia gravis, myositis, and tumor flare.

Provenge was discontinued in 1.5% of patients in Study 1 due to adverse events. 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. In controlled clinical trials,

cerebrovascular events, including hemorrhagic and ischemic strokes, were observed in 3.5% of patients in the Provenge group compared with 2.6% of patients in the control group

Each dose of Provenge requires a standard leukapheresis procedure approximately 3 days prior to the infusion. Adverse events that were reported ≤ 1 day following a leukapheresis procedure in ≥ 5% of patients in controlled clinical trials included citrate toxicity (14.2%), oral paresthesia (12.6%), paresthesia (11.4%), and fatigue (8.3%).

References

1. Provenge [package insert]. Dendreon Corporation; November, 2020.
2. Berger ER. Treatment options for the advanced asymptomatic prostate cancer patient: an active immunotherapy approach. Commun Oncol. 2007;447-452.
3. Chang SS. Treatment options for hormone-refractory prostate cancer. Rev Urol. 2007;9 (suppl 2):S13-S18.
4. Armstrong AJ, George DJ. New drug development in metastatic prostate cancer. Urol Oncol. 2008;26:430-437.
5. WeinerLM, Dhokapkar MV, FeroneS. Monoclonal antibodies for cancer immunotherapy. Lancet. 2009;373:1033-1040.
6. June CH. Adoptive T cell therapy for cancer in the clinic. J Clin Invest. 2007;117:1466-1476.
7. Eggermont AM. Therapeutic vaccines in solid tumors: can they be harmful? Eur J Cancer. 2009;45:2087-2090.
8. Harzstark AL, Small EJ. Immunotherapy for prostate cancer using antigen-loaded antigen-presenting cells:APC08015(Provenge) Expert Opin Biol Ther. 2007;7:1275-1280.
9. Lin AM, Hershberg RM, Small EJ. Immunotherapy for prostate cancer using prostatic acid phosphatase loaded antigen presenting cells Urol Oncol. 2006;24:434-441.
10. Kalinski P, Urban J, Narang R, Berk E, Wieckowski E, Muthuswamy R. Dendritic cell-based therapeutic cancer vaccines: what we have what we need. Future Oncol. 2009;5:379-390.
11. Burch PA, Croghan GA, Gastineau DA, et al. Immunotherapy (ACC8015, Provenge) targeting prostatic acid phosphatase can induce durable remission of metastatic androgen-independent protstate cancer: a phase 2 trial. Prostate.2004;60:197-204.
12. Small EJ, Schellhammer PF, Higano CS, et al. Placebo-controlled phase III trial of immunologic therapy with sipuleucel-T (APC8015) in patients with metastatic, asymptomatic hormone refractory prostate cancer. J Clin Oncol. 2006;34:3089-3094.

13. Higano CS, Schellhammer PF, Small EJ, et al. Integrated data from 2 randomized, double-blind, placebo-controlled, phase 3 trials of active cellular immunotherapy with sipuleucel-T in advanced prostate cancer. Cancer. 2009;115:3670-3679.
14. Kantoff P, Higano CS, Berger ER, et al. Updated survival results of the D9902B trial of sipuleucel-T for metastatic castration-resistant prostate cancer (CRPC). In: Proceedings from the 2010 Genitourinary Cancer Symposium; March 5-7, 2010; San Francisco, CA Abstract 8.
15. James ND, Caty A, Borre M, et al. Safety and efficacy of the specific Endothelin-A receptor antagonist ZD4054 in patients with hormone-resistant prostate cancer and bone metastases who were pain free or mildly symptomatic: a double-blind, placebo-controlled, randomized, phase 2 trial. Eur Urol. 2008;55:1112-1123.
16. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: prostate cancer. Version 2.2021.
17. Cookson MS, Roth BJ, Dahm P, et al. Castration-resistant prostate cancer: AUA Guideline. J Urol. Aug 2013; 190(2):429-38.

Policy History

Original Effective Date: 07/21/2010
Current Effective Date: 11/11/2024

07/03/2010	Medical Policy Committee review
07/21/2010	Medical Policy Implementation Committee approval. New policy.
08/04/2011	Medical Policy Committee review
08/17/2011	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
08/02/2012	Medical Policy Committee review
08/15/2012	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
08/01/2013	Medical Policy Committee review
08/21/2013	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
08/07/2014	Medical Policy Committee review
08/20/2014	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
10/08/2015	Medical Policy Committee review

sipuleucel-T (Provenge®)

Policy # 00264
Original Effective Date: 07/21/2010
Current Effective Date: 11/11/2024

10/21/2015	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
10/06/2016	Medical Policy Committee review
10/19/2016	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
01/01/2017	Coding update: Removing ICD-9 Diagnosis Codes
10/05/2017	Medical Policy Committee review
10/18/2017	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
10/04/2018	Medical Policy Committee review
10/17/2018	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
10/03/2019	Medical Policy Committee review
10/09/2019	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
10/01/2020	Medical Policy Committee review
10/07/2020	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
10/07/2021	Medical Policy Committee review
10/13/2021	Medical Policy Implementation Committee approval. Background information updated. No change to coverage eligibility.
10/06/2022	Medical Policy Committee review
10/11/2022	Medical Policy Implementation Committee approval. No change to coverage.
10/05/2023	Medical Policy Committee review
10/11/2023	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
10/03/2024	Medical Policy Committee review
10/08/2024	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.

Next Scheduled Review Date: 10/2025

sipuleucel-T (Provenge®)

Policy # 00264
Original Effective Date: 07/21/2010
Current Effective Date: 11/11/2024

Coding

The five character codes included in the Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines are obtained from Current Procedural Terminology (CPT®)‡, copyright 2023 by the American Medical Association (AMA). CPT is developed by the AMA as a listing of descriptive terms and five character identifying codes and modifiers for reporting medical services and procedures performed by physician.

The responsibility for the content of Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines is with Blue Cross and Blue Shield of Louisiana and no endorsement by the AMA is intended or should be implied. The AMA disclaims responsibility for any consequences or liability attributable or related to any use, nonuse or interpretation of information contained in Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines. Fee schedules, relative value units, conversion factors and/or related components are not assigned by the AMA, are not part of CPT, and the AMA is not recommending their use. The AMA does not directly or indirectly practice medicine or dispense medical services. The AMA assumes no liability for data contained or not contained herein. Any use of CPT outside of Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines should refer to the most current Current Procedural Terminology which contains the complete and most current listing of CPT codes and descriptive terms. Applicable FARS/DFARS apply.

CPT is a registered trademark of the American Medical Association.

Codes used to identify services associated with this policy may include (but may not be limited to) the following:

Code Type	Code
CPT	No codes
HCPCS	Q2043
ICD-10 Diagnosis	All related diagnoses

sipuleucel-T (Provenge®)

Policy # 00264
Original Effective Date: 07/21/2010
Current Effective Date: 11/11/2024

*Investigational – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and it has not been incorporated into standard medical practice. Any determination we make that a medical treatment, procedure, drug, device, or biological product is Investigational will be based on a consideration of the following:

A. Whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. Food and Drug Administration (FDA) and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or
B. Whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:
    1. Consultation with technology evaluation center(s);
    2. Credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
    3. Reference to federal regulations.

**Medically Necessary (or "Medical Necessity") - Health care services, treatment, procedures, equipment, drugs, devices, items or supplies that a Provider, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury, disease or its symptoms, and that are:

A. In accordance with nationally accepted standards of medical practice;
B. Clinically appropriate, in terms of type, frequency, extent, level of care, site and duration, and considered effective for the patient's illness, injury or disease; and
C. Not primarily for the personal comfort or convenience of the patient, physician or other health care provider, and not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient's illness, injury or disease.

For these purposes, "nationally accepted standards of medical practice" means standards that are based on credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community, Physician Specialty Society recommendations and the views of Physicians practicing in relevant clinical areas and any other relevant factors.

sipuleucel-T (Provenge®)

Policy # 00264
Original Effective Date: 07/21/2010
Current Effective Date: 11/11/2024

‡ Indicated trademarks are the registered trademarks of their respective owners.

NOTICE: If the Patient's health insurance contract contains language that differs from the BCBSLA Medical Policy definition noted above, the definition in the health insurance contract will be relied upon for specific coverage determinations.

NOTICE: Medical Policies are scientific based opinions, provided solely for coverage and informational purposes. Medical Policies should not be construed to suggest that the Company recommends, advocates, requires, encourages, or discourages any particular treatment, procedure, or service, or any particular course of treatment, procedure, or service.

NOTICE: Federal and State law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over Medical Policy and must be considered first in determining eligibility for coverage.