09-J1000-29

Original Effective Date: 08/01/10

Reviewed: 03/13/19

Revised: 04/15/19

Subject: Sipuleucel-T (Provenge®)

THIS MEDICAL COVERAGE GUIDELINE IS NOT AN AUTHORIZATION, CERTIFICATION, EXPLANATION OF BENEFITS, OR A GUARANTEE OF PAYMENT, NOR DOES IT SUBSTITUTE FOR OR CONSTITUTE MEDICAL ADVICE. ALL MEDICAL DECISIONS ARE SOLELY THE RESPONSIBILITY OF THE PATIENT AND PHYSICIAN. BENEFITS ARE DETERMINED BY THE GROUP CONTRACT, MEMBER BENEFIT BOOKLET, AND/OR INDIVIDUAL SUBSCRIBER CERTIFICATE IN EFFECT AT THE TIME SERVICES WERE RENDERED. THIS MEDICAL COVERAGE GUIDELINE APPLIES TO ALL LINES OF BUSINESS UNLESS OTHERWISE NOTED IN THE PROGRAM EXCEPTIONS SECTION.

DESCRIPTION:

Prostate cancer remains the most common non-cutaneous malignancy among men worldwide. Prostate cancer is a complex disease, with many controversial aspects of management. Sipuleucel-T (Provenge) was approved by the US Food and Drug Administration (FDA) in April 2010 and represents a novel class of cancer immunotherapeutic agents. Sipuleucel-T is an autologous cancer “vaccine” and involves collection of the white blood cell fraction containing antigen-presenting cells from each individual, exposure of the cells to the prostatic acid phosphatase-granulocyte macrophage colony-stimulating factor (PAP-GM-CSF recombinant fusion protein), and subsequent reinfusion of the cells into the member. Sipuleucel’s approval was based principally on a phase III, multi-center, randomized double-blind study of 512 subjects with asymptomatic or minimally symptomatic castration-resistant prostate cancer (CRPC). Subjects were randomized to receive either sipuleucel-T or placebo. Median survival in the vaccine arm was 25.8 months compared to 21.7 months in the control arm. Treatment with sipuleucel-T resulted in a 22% reduction in mortality risk (HR=0.78; 95% CI, 0.61-0.98, p=0.03).

The National Comprehensive Cancer Network (NCCN) guidelines (Version 4.2018) for the treatment of prostate cancer recommend sipuleucel-T for the initial treatment of metastatic CRPC (category 1) for individuals who are asymptomatic or minimally symptomatic, have good performance status (ECOG 0-1), have no hepatic metastases, and have a life expectancy of at least 6 months. In addition, sipuleucel-T is an option after failure of or treatment with other initial therapies for metastatic CRPC (category 2A). However, persons with rapidly progressing disease, liver metastasis, or a life expectancy of less than 6 months should not be considered for sipuleucel-T. The NCCN recommends that patients whose disease progresses to CRPC during primary androgen deprivation therapy (ADT) should receive a laboratory assessment to assure a castrate level of testosterone (<50 ng/dL) has been achieved.

POSITION STATEMENT:

Sipuleucel-T (Provenge) meets the definition of **medical necessity** when **ALL** of the following criteria are met ("1" to "6"):

1. Member is diagnosed with metastatic, castration-recurrent prostate cancer (CRPC, a.k.a., castration-resistant or hormone-refractory prostate cancer) - lab documentation of a recent (past 90 days) serum testosterone level at castrate level (<50 ng/dL) must be submitted for members receiving medical castration. A chart note documenting a bilateral orchiectomy must be submitted for members who have received surgical castration.
2. Member is asymptomatic or minimally symptomatic
3. Member has an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 (**see TABLE 1**)
4. Member has no visceral metastases (e.g., brain, liver, lung, adrenal gland, or peritoneum)
5. Sipuleucel-T is **NOT** used concomitantly with **ANY** of the following:
    a. Abiraterone (Zytiga, Yonsa)
    b. Apalutamide (Erleada)
    c. Cabazitaxel (Jevtana)
    d. Docetaxel (Taxotere)
    e. Enzalutamide (Xtandi)
    f. Ipilimumab (Yervoy)
    g. Mitoxantrone (Novantrone)
    h. Radium-223 (Xofigo)
6. Member has not exceeded three (3) lifetime injections

Approval duration: 12 weeks (maximum of 3 total doses)

Sipuleucel-T therapy is considered **experimental and investigational** in all other situations, including but not limited to treatment of hormone-responsive prostate cancer, treatment of those with moderate to severe symptomatic metastatic prostate cancer, and those with visceral metastases.

DOSAGE/ADMINISTRATION:

THIS INFORMATION IS PROVIDED FOR INFORMATIONAL PURPOSES ONLY AND SHOULD NOT BE USED AS A SOURCE FOR MAKING PRESCRIBING OR OTHER MEDICAL DETERMINATIONS. PROVIDERS SHOULD REFER TO THE MANUFACTURER'S FULL PRESCRIBING INFORMATION FOR DOSAGE GUIDELINES AND OTHER INFORMATION RELATED TO THIS MEDICATION BEFORE MAKING ANY CLINICAL DECISIONS REGARDING ITS USAGE.

FDA-approved: sipuleucel-T is an autologous cellular immunotherapy indicated for the treatment of asymptomatic or minimally symptomatic metastatic castrate resistant (hormone refractory) prostate cancer. Sipuleucel-T should be administered as an intravenous (IV) infusion only over a period of 60 minutes. A cell filter should **NOT** be used. Sipuleucel-T is indicated for autologous use only; prior to infusion, confirm that the member's identity matches the identifiers on the infusion bag. The recommended course of therapy is 3 doses at approximately 2-week intervals. Premedication with oral acetaminophen and an antihistamine (e.g., diphenhydramine) 30 minutes prior to the infusion is recommended to minimize potential for acute infusion reactions. The member should be observed for at least 30 minutes following each infusion. Additional details on administration can be found in the product labeling.

Drug Availability: each dose of sipuleucel-T contains a minimum of 50 million autologous $CD54^+$ cells activated with PAP-GM-CSF, suspended in 250 mL of Lactated Ringer's Injection, USP in a sealed, member-specific infusion bag.

PRECAUTIONS:

Contraindications: None

Warnings and Precautions

Administration: Sipuleucel-T is intended solely for autologous use.

Acute infusion reactions: Acute infusion reactions (reported within 1 day of infusion) included, but were not limited to, fever, chills, respiratory reactions (dyspnea, hypoxia, and bronchospasm), nausea, vomiting, fatigue, hypotension, syncope, 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 therapy should be administered as needed. Closely monitor members with pulmonary or cardiac conditions.

Thromboembolic Events: Thromboembolic events, including deep venous thrombosis and pulmonary embolism, can occur following infusion of sipuleucel-T; however, the clinical significance and causal relationship are uncertain. Most patients had multiple risk factors. Use with caution in members with thromboembolic risk factors.

Infectious diseases: Sipuleucel-T is not routinely tested for transmissible infectious diseases and may transmit disease to health care professionals handling the product. Universal precautions should be followed.

Concomitant chemotherapy: Concomitant use of chemotherapy and immunosuppressive medications (including systemic corticosteroids) with sipuleucel-T has not been studied.

BILLING/CODING INFORMATION:

HCPCS Coding

Q2043	Sipuleucel-T, minimum of 50 million autologous CD54+ cells activated with pap-gm-cst, including leukapheresis and all other preparatory procedures, per infusion

ICD-10 Diagnosis Codes That Support Medical Necessity

C61	Malignant neoplasm of prostate

REIMBURSEMENT INFORMATION:

Refer to section entitled **POSITION STATEMENT**.

PROGRAM EXCEPTIONS:

Federal Employee Program (FEP): Follow FEP guidelines.

State Account Organization (SAO): Follow SAO guidelines.

Medicare Part D: Not applicable.

Medicare Advantage:

- The following National Coverage Determination (NCD) was reviewed on the last guideline review date: Autologous Cellular Immunotherapy Treatment (110.22) located at cms.gov.
- No Local Coverage Determination (LCD) was found at the time of the last guideline review date.

DEFINITIONS:

Autologous: Derived from the same organism or from one of its parts.

Dendritic Cells: Dendritic cells in the periphery capture and process antigens, express lymphocyte co-stimulatory molecules, migrate to lymphoid organs and secrete cytokines to initiate immune responses.

Castrate-resistant/recurrent prostate cancer (CRPC): disease progression despite androgen deprivation therapy (ADT) with either medication or surgery (i.e., removal/destruction of testicles), and may present as either a continuous rise in serum prostate-specific antigen (PSA) levels, the progression of pre-existing disease, and/or the appearance of new metastases.

RELATED GUIDELINES:

Abiraterone acetate (Zytiga, Yonsa), 09-J1000-36

Apalutamide (Erleada), 09-J3000-03

Cabazitaxel (Jevtana), 09-J1000-77

Cryosurgical Ablation of the Prostate (CSAP), 02-54000-14

Docetaxel (Taxotere) IV, 09-J0000-95

Enzalutamide (Xtandi), 09-J1000-85

Gonadotropin Releasing Hormone Analogs and Antagonists, 09-J0000-48

Radium Ra 223 (Xofigo) Injection, 09-J2000-01

OTHER:

TABLE 1

ECOG PERFORMANCE STATUS*	
Grade	**ECOG**
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair
5	Dead

*As published in Am. J. Clin. Oncol.

Oken, M.M., Creech, R.H., Tormey, D.C., Horton, J., Davis, T.E., McFadden, E.T., Carbone, P.P.: Toxicity And Response Criteria Of The Eastern Cooperative Oncology Group. Am J Clin Oncol 5:649-655, 1982.

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11. Schellhammer PF, Chodak G, Whitmore JB, et al. Lower baseline prostate-specific antigen is associated with a greater overall survival benefit from sipuleucel-T in the immunotherapy for prostate adenocarcinoma treatment (IMPACT) trial. Urology. 2013;81(6):1297–302.
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;24(19):3089–94.

COMMITTEE APPROVAL:

This Medical Coverage Guideline (MCG) was approved by the Florida Blue Pharmacy Policy Committee on 03/13/19.

GUIDELINE UPDATE INFORMATION:

08/01/10	New Medical Coverage Guideline.
01/15/11	Revision to guideline; consisting of adding ICD-10 codes.

04/15/11	Review and revision to guideline; consisting of updating precautions, references and coding.
07/01/11	Revision to guideline; consisting of updating coding.
04/15/12	Review and revision to guideline; consisting of updating dosage and administration, precautions, and references.
04/15/13	Review and revision to guideline; consisting of revising position statement, description section, dosage/administration section, and precautions section; updating references; adding related guidelines and pertinent definitions.
04/15/14	Review and revision to guideline; consisting of description, position statement, program exceptions, references
04/15/15	Review and revision to guideline; consisting of description, precautions, program exceptions, and references.
11/01/15	Revision: ICD-9 Codes deleted.
04/15/16	Review and revision to guideline consisting of updating the description section, dosage/administration, definitions, and references.
04/15/17	Review and revision to guideline consisting of updating the description section, position statement, and references.
04/15/18	Review and revision to guideline consisting of updating the description section, position statement, and references.
12/15/18	Revision to guideline consisting of updating the position statement.
04/15/19	Review and revision to guideline consisting of updating the description section, position statement, related guidelines, and references.