Medication Policy Manual

Policy No: dru216

Topic: Provenge®, sipuleucel-T

Date of Origin: August 11, 2010

Committee Approval: January 13, 2017

Next Review Date: January 2018

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IMPORTANT REMINDER

This Medication Policy has been developed through consideration of medical necessity, generally accepted standards of medical practice, and review of medical literature and government approval status.

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control.

The purpose of Medication Policy is to provide a guide to coverage. Medication Policy is not intended to dictate to providers how to practice medicine. Providers are expected to exercise their medical judgment in providing the most appropriate care.

Description

Sipuleucel-T (Provenge) is indicated for the treatment of asymptomatic or minimally symptomatic metastatic castration-resistant prostate cancer. It is an immunotherapy designed to stimulate a patient's own immune system against prostate cancer.

Some of the patient's immune cells are collected via a process called leukapheresis. These immune cells are then exposed to a protein intended to stimulate and direct them against the prostate cancer. After this exposure, the activated immune cells are then returned to the patient via intravenous infusion, to treat the prostate cancer.

Policy/Criteria

I. Most contracts require prior authorization approval of sipuleucel-T (Provenge) prior to coverage. Sipuleucel-T (Provenge) may be considered medically necessary when criteria A, B, C, D, E and F below are met.

A. Metastatic prostate cancer confirmed with histology as adenocarcinoma of the prostate.

AND

B. Radiographic evidence of metastases beyond the primary tumor, (such as bone and soft tissue) except visceral metastases; specifically, liver, lung or brain metastases. [1]

AND

C. Hormone refractory (also known as castration-resistant, castration-recurrent, or androgen-independent) disease when both criteria 1 and 2 below are met:

1. Documented progression or metastasis despite removal of testes OR despite treatment with anti-androgen medications such as leuprolide (Lupron)

AND

2. Current testosterone level is < 50 ng/mL.

AND

D. Asymptomatic or minimally symptomatic disease [e.g. no narcotic (opioid) use for prostate cancer-related pain].

AND

E. If cytotoxic chemotherapy [e.g. docetaxel, cabazitaxel (Jevtana)] has been previously administered, it must have been stopped for at least 3 months prior to initiation of leukapheresis for sipuleucel-T (Provenge) therapy.

AND

F. If immunosuppressants such as systemic corticosteroids at doses > 5 mg prednisone or equivalent) and/or radiation have been administered, it must have been stopped for at least 28 days prior to initiation of leukapheresis for sipuleucel-T (Provenge) therapy.

II. Administration, Quantity Limitations, and Authorization Period

A. OmedaRx does not consider sipuleucel-T (Provenge) to be a self-administered medication.

B. When prior authorization is approved, sipuleucel-T (Provenge) may be authorized one-time for a maximum of three infusions, each of which includes harvest and re-infusion of activated leucocytes. When criteria for coverage are met, up to 3 completed infusions (one course of therapy) may be authorized per lifetime.

C. Additional courses of therapy are considered investigational.

III. Sipuleucel-T (Provenge) is considered investigational when used for all other conditions, including but not limited to:

A. Localized (non-metastatic) prostate cancer.

B. Treatment of patients with moderate to severe prostate cancer-related pain that requires treatment with opioid analgesics.

C. Treatment of metastatic prostate cancer when there is metastasis to the liver, lung, or brain with or without additional metastases.

D. Concomitant use with of either chemotherapy or immunosuppressive agents (such as systemic corticosteroids) with the leukapheresis procedure or sipuleucel-T (Provenge).

Position Statement

- Sipuleucel-T (Provenge) may improve overall survival as a first-line therapy in men with metastatic castration-resistant (mCRPC). However, there is uncertainty as to the magnitude of its benefit and its effectiveness relative to docetaxel (Taxotere). [1,2]
- Medical or surgical castration (hormonal intervention) is considered first-line therapy for patients with metastatic prostate cancer. Approximately 15% of patients do not respond to or eventually become refractory to hormonal intervention. [3]
- Docetaxel plus prednisone is considered first-line salvage therapy in patients with mCRPC based on its overall survival advantage over mitoxantrone (Novantrone) plus prednisone, a chemotherapy regimen used for palliative treatment. [3]
- In the sipuleucel-T (Provenge) clinical trials, the population studied had radiologically confirmed mCRPC which was asymptomatic or minimally symptomatic. No data exists for its use in moderately or severely symptomatic patients and it has not been studied in patients with visceral metastases. [2,3]
- Patients in the clinical trials had castration levels of serum testosterone below 50 ng/mL and a serum PSA of at least 5.0 ng/mL. Disease progression was based on imaging studies or PSA measurements, despite surgical or medical castration. [1,2]
- Pain related to prostate cancer is considered a prognostic factor in metastatic prostate cancer and people with pain tend to have higher tumor burden.[7]
- The use of either chemotherapy or immunosuppressive agents (such as systemic corticosteroids) given at the same time with the leukapheresis procedure for sipuleucel-T (Provenge) has not been studied. Sipuleucel-T (Provenge) is designed to stimulate the immune system, and using immunosuppressive agents at the same time may alter the effectiveness and/or safety of sipuleucel-T (Provenge). [1,4]

Clinical Efficacy

- The evidence for sipuleucel-T (Provenge) in the first-line salvage treatment of mCRPC is unreliable. The magnitude of survival benefit relative to placebo is uncertain.
- The efficacy of sipuleucel-T (Provenge) relative to docetaxel, another potential first-line therapy in this setting, has not been studied.[1]

- There are three studies that compared sipuleucel-T (Provenge) with "placebo" (Note: a large proportion of subjects initially randomized to placebo crossed over to a product similar to sipuleucel-T (Provenge) after progression of disease).[2,5,6]
- The evidence from one pivotal published randomized controlled published trial comparing sipuleucel-T (Provenge) with placebo in men with mCRPC disease. At a median follow-up of 34 months, patients who received sipuleucel-T (Provenge) had a statistically significant improvement in overall survival. This trial was appraised as unreliable for reasons that included: [2]
  - Unblinding, which was allowed after disease progression was confirmed.
  - Crossover to alternative therapies after disease progression was allowed at the discretion of the investigator. (This occurred in a large proportion of subjects).
- Both of these flaws may impact the overall survival endpoint. The follow up use of a product similar to sipuleucel-T (Provenge) in the placebo treatment arm has the potential to improve survival in these patients, while follow up use of docetaxel in the sipuleucel-T (Provenge) treatment arm has the potential to improve survival in these patients. This crossover allows for confounding variables and makes it difficult to assess whether the reported overall survival benefit is valid and, if the benefit is real, to quantify the benefit.
- The evidence from two smaller published trials comparing sipuleucel-T (Provenge) with placebo in men with mCRPC disease were appraised as not reliable for reasons that included: [5,6]
  - Use of time to progression (TTP) of disease as a primary endpoint. TTP does not predict overall survival, a clinically relevant endpoint, in men with mCRPC.
  - Crossover to other therapies was allowed after progression of disease.
  - Post hoc analysis of overall survival (did not define statistical methods in advance).
  - One study was stopped before it met its enrollment goal.
- Sipuleucel-T (Provenge) is recognized in the National Comprehensive Cancer Network (NCCN) prostate cancer guidelines as a category 1 recommendation for men with mCRPC with asymptomatic or minimally symptomatic disease with ECOG scores of 0 to 1, and is not recommended for patients with visceral metastases and a life expectancy of less than 6 months. It is also recommended as category 2A in patients who have failed first-line therapy for metastatic disease. [3]

OmedaRx performs independent analyses of oncology medications. The OmedaRx analysis and coverage policy may differ from NCCN guidelines.

Safety [7]

- The most common adverse reactions include: chills, fatigue, fever, back pain, nausea, joint ache, and headache.

- There are no published head-to-head clinical trials to support the claim that sipuleucel-T (Provenge) has less toxicity than docetaxel.
- There were more cerebrovascular events (CVEs), including hemorrhagic and ischemic strokes, reported in patients receiving sipuleucel-T (Provenge) than placebo (3.5% vs. 2.6%). The difference was not statistically significant. Nevertheless, the Food and Drug Administration listed it as a safety concern in their review of the safety of this medication.

Cross References
Jevtana®, cabazitaxel, Medication Policy Manual, Policy No. 232
Xtandi®, enzalutamide, Medication Policy Manual, Policy No. 280
Zytiga™, abiraterone, Medication Policy Manual, Policy No.252

Codes	**Number**	**Description**
HCPCS	Q2043	Sipuleucel-T, minimum of 50 million autologous cd54+ cells activated with pap-gm-csf, including leukapheresis and all other preparatory procedures, per infusion
ICD-9	185	Malignant neoplasm of prostate
ICD-9	V10.46	Personal history of malignant neoplasm of prostate
ICD-10	C61	Malignant neoplasm of prostate
ICD-10	Z85.46	Personal history of malignant neoplasm of prostate
CPT code	36511	Therapeutic apheresis; for white cells (leukapheresis procedure).
NCD	110.22	National Coverage Determination (NCD) for Autologous Cellular Immunotherapy Treatment

References

1. Price, TJ, Peeters, M, Kim, TW, et al. Panitumumab versus cetuximab in patients with chemotherapy-refractory wild-type KRAS exon 2 metastatic colorectal cancer (ASPECCT): a randomised, multicentre, open-label, non-inferiority phase 3 study. *The Lancet Oncology*. 2014 May;15(6):569-79. PMID: 24739896
2. Kantoff, PW, Higano, CS, Shore, ND, et al. Sipuleucel-T immunotherapy for castration-resistant prostate cancer. *The New England journal of medicine*. 2010 Jul 29;363(5):411-22. PMID: 20818862
3. Belsomra® [package insert]. Whitehouse Station, NJ: Merck & Co., Inc; 10/2014.
4. Schwartzberg, LS, Rivera, F, Karthaus, M, et al. PEAK: a randomized, multicenter phase II study of panitumumab plus modified fluorouracil, leucovorin, and oxaliplatin (mFOLFOX6) or bevacizumab plus mFOLFOX6 in patients with previously untreated, unresectable, wild-type KRAS exon 2 metastatic colorectal cancer. United States, 2014. p. 2240-7.
5. 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 Aug 15;115(16):3670-9. PMID: 19536890
6. 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 Jul 1;24(19):3089-94. PMID: 16809734
7. Douillard, JY, Siena, S, Cassidy, J, et al. Randomized, phase III trial of panitumumab with infusional fluorouracil, leucovorin, and oxaliplatin (FOLFOX4) versus FOLFOX4 alone as first-line treatment in patients with previously untreated metastatic colorectal cancer: the PRIME study. United States, 2010. p. 4697-705.

Revision History

Revision Date	Revision Summary
1/13/2017	No criteria changes with this annual update
1/8/2016	Reorganization of criteria, including splitting some individual criterion into two criterion, for clarity and ease of use. The intent of the policy has not changed.