Policy Replaced by NCD 110.22
Effective June 30, 2011

BlueCross BlueShield of Alabama

Name of Blue Advantage Policy:

Cellular Immunotherapy for Prostate Cancer

Policy #: 432
Category: Medical

Latest Review Date: May 2011
Policy Grade: A

Background:

Blue Advantage *medical policy does not conflict with Local Coverage Determinations (LCDs), Local Medical Review Policies (LMRPs) or National Coverage Determinations (NCDs) or with coverage provisions in Medicare manuals, instructions or operational policy letters. In order to be covered by Blue Advantage the service shall be reasonable and necessary under Title XVIII of the Social Security Act, Section 1862(a)(1)(A). The service is considered reasonable and necessary if it is determined that the service is:*

1. *Safe and effective;*
2. *Not experimental or investigational*;*
3. *Appropriate, including duration and frequency that is considered appropriate for the service, in terms of whether it is:*
   - *Furnished in accordance with accepted standards of medical practice for the diagnosis or treatment of the patient's condition or to improve the function of a malformed body member;*
   - *Furnished in a setting appropriate to the patient's medical needs and condition;*
   - *Ordered and furnished by qualified personnel;*
   - *One that meets, but does not exceed, the patient's medical need; and*
   - *At least as beneficial as an existing and available medically appropriate alternative.*

Routine costs of qualifying clinical trial services with dates of service on or after September 19, 2000 which meet the requirements of the Clinical Trials NCD are considered reasonable and necessary by Medicare. Providers should bill* ***Original Medicare* *for covered services that are related to* ***clinical trials*** *that meet Medicare requirements (Refer to Medicare National Coverage Determinations Manual, Chapter 1, Section 310 and Medicare Claims Processing Manual Chapter 32, Sections 69.0-69.11).*

Description of Procedure or Service:

Sipuleucel-T (Provenge®, Dendreon Corp.) is a new class of therapeutic agent used in the treatment of asymptomatic or minimally symptomatic, androgen-independent (hormone-refractory), metastatic prostate cancer. It consists of specially treated dendritic cells obtained from the patient with leukapheresis. The cells are then exposed in vitro to proteins that contain prostate antigens and immunologic stimulating factors, and then reinfused back into the patient*. The proposed mechanism of action is that the treatment stimulates the patient's own immune system to resist spread of the cancer.

***A course of treatment is 3 doses at approximately 2 week intervals.**

Cancer immunotherapy has been investigated as a treatment which might be instituted at the point of detection of androgen-independent metastatic disease before significant symptomatic manifestations have occurred. The quantity of cancer cells in the patient during this time interval is thought to be relatively low, and it is thought that an effective immune response against the cancer during this time period could effectively delay or prevent progression. Such a delay could allow effective chemotherapy such as docetaxel to be deferred or delayed until necessary, thus providing an overall survival benefit.

Policy:

Effective for dates of service on or after April 29, 2010 and prior to June 30, 2011:
Blue Advantage will treat **sipuleucel-T therapy** as a **covered** benefit for the **treatment of asymptomatic or minimally symptomatic, metastatic, androgen-independent (hormone-refractory) prostate cancer for a single course of treatment (3 infusions)**.

Blue Advantage will treat **sipuleucel-T therapy** as a non-covered benefit and as **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 (liver, lung or brain) metastases.**

Blue Advantage does not approve or deny procedures, services, testing, or equipment for our members. Our decisions concern coverage only. The decision of whether or not to have a certain test, treatment or procedure is one made between the physician and his/her patient. Blue Advantage administers benefits based on the members' contract and medical policies. Physicians should always exercise their best medical judgment in providing the care they feel is most appropriate for their patients. Needed care should not be delayed or refused because of a coverage determination.

Key Points:

Prostate cancer is the second leading cause of cancer-related deaths among American men with an estimated incidence of 218,890 cases and an estimated number of 27,050 deaths in 2007. The majorities of cases are diagnosed at a localized stage and are treated with prostatectomy or radiation therapy. However, some patients are diagnosed with metastatic disease or recurrent disease after treatment of localized disease. Androgen ablation is the standard treatment for

metastatic or recurrent disease. However, most patients who survive long enough eventually develop androgen-independent prostate cancer. At this stage of metastatic disease docetaxel, a chemotherapeutic agent has been demonstrated to confer a survival benefit of 1.9 to 2.4 months in randomized clinical trials. Chemotherapy with docetaxel causes adverse effects in large proportions of patients, including alopecia, fatigue, neutropenia, neuropathy, and other symptoms. The trials evaluating docetaxel included both asymptomatic and symptomatic patients, and results suggested a survival benefit for both symptomatic and asymptomatic patients. Because of the burden of treatment and its side effects, most patients therefore defer docetaxel treatment until the cancer recurrence is symptomatic.

Sipuleucel-T has been studied most definitively in a series of double-blind, placebo-controlled studies. Results of two of these studies have been published by Small and co-workers and Higano et al, and extensively presented in a briefing document available from the U.S. Food and Drug Administration (FDA). The third and largest trial is not published, but results were presented at the American Urological Association meeting in April 2009 and summarized in an FDA press release in April 2010. Patients enrolled in these trials all had androgen-independent metastatic prostate cancer, were asymptomatic or mildly symptomatic, in good physical health characterized by ECOG performance status 0 or 1, and had tumors with positive staining for prostatic acid phosphatase.

In the two early identically designed studies, patients with asymptomatic metastatic prostate cancer were randomized to receive either sipuleucel-T or a control infusion of untreated dendritic cells. The principal outcome of these studies was time to disease progression, defined as the time from randomization to the first observation of disease progression. Disease progression could be defined as radiologic progression (based on several imaging criteria), clinical progression (based on prostate cancer-related clinical events such as pathologic fracture), or pain progression (based on onset of pain corresponding to anatomic location of disease).

The studies were not designed to establish efficacy based on overall survival. Upon progression of cancer, patients were allowed to have additional treatment as needed including chemotherapy. Patients originally assigned to placebo were allowed to "cross-over" by receiving their own dendritic cells pulsed with PA2024, but prepared from frozen dendritic cells harvested from their initial leukapheresis procedures.

Table 1: Description of randomized phase III trials of sipuleucel-T

Study name	Design	Eligibility	Treatment	Outcomes
9901A 9902A	Randomized, double blind, placebo-controlled	Metastatic prostate cancer by imaging, asymptomatic and progressing by imaging or rising PSA	Exp: 3 infusions of vaccine Ctl: 3 infusions of placebo dendritic cells	Primary: Disease progression (radiological, clinical, pain) Secondary: time to pain, time to progression

IMPACT	Randomized, double blind, placebo-controlled	Metastatic prostate cancer by imaging, asymptomatic or minimally symptomatic and progressing by imaging or rising PSA	Exp: 3 infusions of vaccine Ctl: 3 infusions of placebo dendritic cells	Primary: Overall survival Secondary: time to objective disease progression

Ctl: control arm; Exp: experimental arm; PSA: prostate-specific antigen

Results of study 9901A for the principal outcome of time-to-progression did not show a significant difference between vaccine and control. Median time to progression was 11.7 weeks for the vaccine group and 10.0 weeks for the control group.

A survival analysis of study 9901A was presented in the FDA briefing document, with the caveats that the study was not powered to show a survival effect, and that a primary method of survival analysis was not prespecified in the protocol. The median survival times for vaccine-treated patients was 25.9 months and for placebo-treated patients was 21.4 months, which was statistically significant (p=0.011 log-rank test). At 36 months, the survival rate was 34% for vaccine-treated patients and 11% for placebo-treated patients.

The FDA briefing document shows analyses of possible confounders regarding the survival analysis. After disease progression, patients in both groups received chemotherapy, but the rate of chemotherapy was slightly higher in the placebo-treated groups (48% versus 36%).

Examination of the causes of death did not reveal any obvious spurious elevation of non-cancer causes of death in the placebo group. The published version of study 9901A by Small et al. analyzed the survival data after adjusting for prognostic factors and found a significant association of sipuleucel-T treatment and survival (hazard ratio [HR]: 2.12; 95% confidence interval [CI]: 1.31–3.44).

Because study 9901A did not meet its principal outcome endpoint for efficacy, enrollment for its partner study 9902A was suspended. Its sample size was therefore smaller and the study subsequently had lower statistical power. Results for study 9902A showed a median time-to-progression of 10.9 weeks in the vaccine group versus 9.9 weeks in the placebo group, which was not statistically significant. A survival analysis of study 9902A showed that vaccine-treated patients had a median survival of 19 months and control patients had a median survival of 15.7 months, which was also not statistically significant.

The two studies' survival data was pooled in the study by Higano et al. The pooled analysis showed a 33% reduction in the risk of death (HR: 1.50; 95% CI: 1.10–2.05, p=0.011). The association was robust to adjustments in imbalances in baseline prognostic factors and post-progression chemotherapy use.

Because these earlier studies did not meet criteria for success for their principal endpoints, the FDA did not approve sipuleucel-T in 2007. A larger Phase III trial of similar design called

IMPACT enrolling 512 patients was designed with a principal endpoint of overall survival. Analyses reported at the American Urological Association in April 2009 and used to support FDA approval reported a 22% reduction in overall mortality in the patients treated with sipuleucel-T. Treatment extended median survival by 4.1 months compared to placebo (25.8 months versus 21.7 months) and improved 3-year survival by a relative 38% compared to placebo (31.7% versus 23.0%). Results adjusted for subsequent docetaxel use and timing, as well as analyses examining prostate cancer-specific survival showed similar magnitude and statistical significance of the survival benefit. Of note, 14% of enrolled subjects in this trial had received prior docetaxel treatment.

Regarding the safety of sipuleucel-T, most adverse effects were grade 1 and 2 and resolved within 48 hours. The rate of serious adverse events was not statistically different between vaccine- and placebo-treated patients. However, one difficulty in assessing the potential adverse effects by comparing sipuleucel-T to placebo is that the placebo consisted of infusion of untreated dendritic cells, which may cause some adverse effects. There was concern expressed in the FDA review regarding a possible association with cerebrovascular events, as 8/147 vaccine-treated patients experienced cerebrovascular-related adverse events, compared to zero placebo-treated patients in the two early trials. In the latest available report of adverse effects reported in the full prescribing information documents, the stroke rate was 3.5% in the sipuleucel-T group and 2.6% in the control group, but these figures appear to include data from trials evaluating a different indication. In the FDA review summarizing cerebrovascular event rates from studies 9901A, 9902A, and interim data from IMPACT, the rate was 4.9% (17/345) in the sipuleucel-T-treated subjects, and 1.7% (3/172) in placebo-treated subjects (p=0.092). The FDA review called the cerebrovascular event rate a “potential safety signal” and included as part of the approval, a postmarketing study, based on a registry design, to assess the risk of cerebrovascular events in 1,500 patients with prostate cancer who receive sipuleucel-T.

The results of three randomized, controlled trials of sipuleucel-T given in the setting of asymptomatic or mildly symptomatic androgen-independent metastatic prostate cancer show an improvement in median survival of four months. The two early studies of sipuleucel-T were not specifically designed to demonstrate a difference in overall mortality, but showed survival effects consistent with the third study which was designed to demonstrate a mortality difference. All three studies are also consistent in demonstrating that sipuleucel-T treatment does not delay time to measureable progression of disease. In all studies, many patients had further chemotherapy treatment at the discretion of their physician; thus, the survival benefit accrues in the context of additional treatment as needed for symptomatic recurrence.

Table 2: Results of randomized, Phase III trials of sipuleucel-T

Study 9901A			
	Vaccine n=82	Control n=45	p value
Median time-to-progression	11.7 weeks	10.0 weeks	0.052
Median time-to-clinical progression	10.7 weeks	9.1 weeks	0.061
Overall median survival	25.9 months	21.4 months	0.01
Overall survival at 36	34%	11%	0.005

months			Multivariable adjusted 0.002
Study 9902A			
	Vaccine n=65	Control n=33	p value
Median time-to-progression	10.9 weeks	9.9 weeks	0.719
Overall median survival	19.0 months	15.7 months	0.331
IMPACT study			
	Vaccine n=341	Control n=171	p value
Overall median survival	25.8 months	21.7 months	0.032
Overall survival at 36 months	31.7%	23.0%	0.036
Time-to-progression	Not reported	Not reported	Hazard ratio=0.95 p=0.628

Other Indications

A phase III trial of sipuleucel-T in the setting of androgen-dependent, nonmetastatic prostate cancer has completed enrollment (Provenge for the Treatment of Hormone Sensitive Prostate Cancer [PROTECT], NCT00779402) and has released some preliminary findings. No published studies are yet available from this study. According to news reports, preliminary findings include an increase in prostate-specific antigen doubling time in sipuleucel-T-treated subjects compared to placebo-treated subjects, and a statistically nonsignificant delay in detecting metastasis. According to the ClinicalTrials.gov website, this study is no longer recruiting participants.

Key Words:

Provenge, Sipuleucel-T therapy, Cellular immunotherapy

Approved by Governing Bodies:

On April 29, 2010, the U.S. Food and Drug Administration (FDA) approved Provenge® (sipuleucel-T, Dendreon Corp.) via a Biologics Licensing Application (BLA) for "the treatment of asymptomatic or minimally symptomatic metastatic castrate resistant (hormone refractory) prostate cancer (for autologous use only)."

Approval was contingent on agreement of the manufacturer to conduct a postmarketing study, based on a registry design, to assess the risk of cerebrovascular events in 1,500 patients with prostate cancer who receive sipuleucel-T.

Benefit Application:

Coverage is subject to member's specific benefits. Group specific policy will supersede this policy when applicable.

Current Coding:

HCPCS Codes:

Q2043 Sipuleucel-T, minimum of 50 million autologous CD54+ cells activated with PAP-GM-CSF, including leukapheresis and all other preparatory procedures, per infusion **(Effective July 1, 2011)**

J3590 Unclassified biologics

Previous Coding:

There is not a specific CPT code for Sipuleucel-T therapy. The following codes may be used

36511 Therapeutic apheresis; for white cells

96365 Intravenous infusion, for therapy, prophylaxis, or diagnosis; initial, up to 1 hour **(Deleted effective July 1, 2011)**

References:

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2. Dendreon Corporation. Provenge® (sipuleucel-T) prescribing information. Seattle, WA; April 2010. Available online at www.provenge.com/pdf/prescribing-information.pdf. Last accessed May 2010.
3. 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(16):3670-9.
4. 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.
5. Tannock IF, de Wit R, Berry WR, et al. Docetaxel plus prednisone or mitoxantrone plus prednisone for advanced prostate cancer. N Engl J Med 2004; 351(15):1502-12.
6. U.S. Food and Drug Administration. Cellular, Tissue and Gene Therapies Advisory Committee Meeting, March 29, 2007. Clinical Briefing Document: Provenge (Sipuleucel T). Available online at www.fda.gov/ohrms/dockets/ac/07/briefing/2007-4291B1_2a.pdf. Last accessed May 2010.
7. U.S. Food and Drug Administration. Press release: FDA Approves a Cellular Immunotherapy for Men with Advanced Prostate Cancer. Available online at www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm210174.htmm. Last accessed May 2010.

Policy History:

Adopted for Blue Advantage, June 2010
Available for comment June 18-August 2, 2010
Medical Policy Group, December, 2010; 2011 Coding update
Medical Policy Group, May 2011 **(1)** Coding update

This medical policy is not an authorization, certification, explanation of benefits, or a contract. Eligibility and benefits are determined on a case-by-case basis according to the terms of the member's plan in effect as of the date services are rendered. All medical policies are based on (i) research of current medical literature and (ii) review of common medical practices in the treatment and diagnosis of disease as of the date hereof. Physicians and other providers are solely responsible for all aspects of medical care and treatment, including the type, quality, and levels of care and treatment.

This policy is intended to be used for adjudication of claims (including pre-admission certification, pre-determinations, and pre-procedure review) in Blue Cross and Blue Shield's administration of plan contracts.