I. POLICY

Sipuleucel-T (Provenge®) therapy may be considered medically necessary in the treatment of asymptomatic or minimally symptomatic prostate cancer; when all of the following are met:

- Metastatic androgen-independent (castration-resistant) prostate cancer; and
- Life expectancy of at least six months; and
- Serum prostate specific antigen (PSA) greater than or equal to 5.0 mg/dl; and
- Castrate level of testosterone less than 50 mg/dl; and
- Negative serology for HIV 1&2, Human T-cell lymphotropic virus type 1 (HTLV-1), and Hepatitis B and C.

Sipuleucel-T (Provenge®) therapy is considered 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. There is insufficient evidence to support a conclusion concerning the health outcomes or benefits associated with this procedure.

Administration of Sipuleucel-T (Provenge®) beyond the recommended course of therapy (three infusions) is considered not medically necessary.

Cross-references:
- MP-2.010 Clinical Trials
- MP-4.017 Adoptive Immunotherapy
- MP-2.039 Melanoma Vaccines
- MP-4.024 Lipid Apheresis

II. PRODUCT VARIATIONS

This policy is applicable to all programs and products administered by Capital BlueCross unless otherwise indicated below.
**III. DESCRIPTION/BACKGROUND**

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. The agent 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 are 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.

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 majority 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.
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.

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. The cells are administered as 3 intravenous (IV) infusions, each infusion given approximately 2 weeks apart. The proposed mechanism of action is that the treatment stimulates the patient’s own immune system to resist spread of the cancer.

**Regulatory Status**
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.

**IV. RATIONALE**

**Literature Review**

**Metastatic, Androgen-Independent Prostate Cancer**

Sipuleucel-T has been studied most definitively in a series of double-blind, placebo-controlled randomized controlled trials (RCTs).(3) These studies were published by Small et al (2006),(5) Higano et al (2009),(6) and Kantoff et al (2010),(7) and were extensively presented in a briefing document available from the U.S. Food and Drug Administration (FDA). Patients enrolled in these trials all had androgen-independent metastatic prostate cancer, were asymptomatic or mildly symptomatic, in good physical health characterized by Eastern Cooperative Oncology Group (ECOG) Performance Status 0 or 1, and had tumors with positive staining for prostatic acid phosphatase (PAP).

Table 1 describes the 2 early identically designed studies. (4-6) Patients with asymptomatic metastatic prostate cancer were randomized to receive either sipuleucel-T or a control infusion...
of untreated dendritic cells. Principal outcome 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).

Studies were not designed to establish efficacy based on overall survival. On 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 antigen (recombinant fusion protein comprising human PAP linked to granulocyte-macrophage colony-stimulating factor [GM-CSF]), but prepared from frozen dendritic cells harvested from their initial leukapheresis procedures.

Table 1. Description of Randomized Phase 3 Trials of Sipuleucel-T

<table>
<thead>
<tr>
<th>Study Name</th>
<th>Design</th>
<th>Eligibility</th>
<th>Treatment</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>9901A</td>
<td>Randomized double-blind, placebo-controlled</td>
<td>Metastatic prostate cancer by imaging, asymptomatic and progressing by imaging or rising PSA</td>
<td>Exp: 3 infusions of vaccine Ctl: 3 infusions of placebo dendritic cells</td>
<td>Primary: disease progression (radiologic, clinical, pain) Secondary: time to pain, time to progression</td>
</tr>
<tr>
<td>9902A</td>
<td>Randomized double-blind, placebo-controlled</td>
<td>Metastatic prostate cancer by imaging, asymptomatic and progressing by imaging or rising PSA</td>
<td>Exp: 3 infusions of vaccine Ctl: 3 infusions of placebo dendritic cells</td>
<td>Primary: overall survival Secondary: time to objective disease progression</td>
</tr>
<tr>
<td>IMPACT</td>
<td>Randomized double-blind, placebo-controlled</td>
<td>Metastatic prostate cancer by imaging, asymptomatic or minimally symptomatic and progressing by imaging or rising PSA</td>
<td>Exp: 3 infusions of vaccine Ctl: 3 infusions of placebo dendritic cells</td>
<td>Primary: overall survival Secondary: time to objective disease progression</td>
</tr>
</tbody>
</table>

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

As shown in Table 2, 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.
Table 2. Results of Randomized, Phase 3 Trials of Sipuleucel-T

<table>
<thead>
<tr>
<th>Study</th>
<th>Vaccine</th>
<th>Control</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Study 9901A</strong></td>
<td>n=82</td>
<td>n=45</td>
<td></td>
</tr>
<tr>
<td>Median time to progression, wk</td>
<td>11.7</td>
<td>10.0</td>
<td>0.052</td>
</tr>
<tr>
<td>Median time to clinical progression, wk</td>
<td>10.7</td>
<td>9.1</td>
<td>0.061</td>
</tr>
<tr>
<td>Overall median survival, mo</td>
<td>25.9</td>
<td>21.4</td>
<td>0.01</td>
</tr>
<tr>
<td>Overall survival at 36 mo, %</td>
<td>34</td>
<td>11</td>
<td>0.005 Multivariable adjusted, 0.002</td>
</tr>
<tr>
<td><strong>Study 9902A</strong></td>
<td>n=65</td>
<td>n=33</td>
<td></td>
</tr>
<tr>
<td>Median time to progression, wk</td>
<td>10.9</td>
<td>9.9</td>
<td>0.719</td>
</tr>
<tr>
<td>Overall median survival, mo</td>
<td>19.0</td>
<td>15.7</td>
<td>0.331</td>
</tr>
<tr>
<td><strong>IMPACT study</strong></td>
<td>n=341</td>
<td>n=171</td>
<td></td>
</tr>
<tr>
<td>Overall median survival, mo</td>
<td>25.8</td>
<td>21.7</td>
<td>0.032</td>
</tr>
<tr>
<td>Overall survival at 36 mo, %</td>
<td>31.7</td>
<td>23.0</td>
<td>0.036</td>
</tr>
<tr>
<td>Time to progression</td>
<td>Not reported</td>
<td>Not reported</td>
<td>HR=0.95, p=0.628</td>
</tr>
</tbody>
</table>

HR: hazard ratio.

A survival analysis of study 9901A was presented in the FDA briefing document, with 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. Using a log-rank test, median survival times were 25.9 months for vaccine-treated patients and 21.4 months for placebo-treated patients, a statistically significant difference (p=0.011). At 36 months, 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. (7) After disease progression, patients in both groups received chemotherapy, but the rate of chemotherapy was slightly higher in the placebo group (48% vs 36%, respectively). Examination of the causes of death did not reveal any obvious spurious elevation of noncancer deaths in the placebo group. The published version of study 9901A by Small et al (2006)(4) 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 to 3.44).

Because study 9901A did not meet its principal outcome end point for efficacy, enrollment for its partner study 9902A was suspended. Its sample size was therefore smaller, and the study subsequently had lower statistical power. As shown in Table 1, 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 median survival was 19 months in vaccine-treated patients and 15.7 months in control, which also was not statistically significant.

Higano et al (2009) pooled survival data from the 2 studies. (6) Pooled analysis showed a 33% reduction in the risk of death (HR=1.50; 95% CI, 1.10 to 2.05; p=0.011). The association was robust to adjustments in imbalances in baseline prognostic factors and postprogression chemotherapy use.

Because these earlier studies did not meet criteria for success for their principal end points, FDA did not approve sipuleucel-T in 2007. A larger phase 3 trial of similar design called IMPACT enrolling 512 patients was designed with a principal end point of overall survival.(6) Analyses used to support FDA approval reported a 22% reduction in overall mortality in patients treated with sipuleucel-T. Treatment extended median survival by 4.1 months, compared with placebo (25.8 months vs 21.7 months, respectively) and improved 3-year survival by a relative 38%, compared with placebo (31.7% vs 23.0%, respectively). 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. In retrospective, prespecified, multivariate subgroup analysis, several baseline factors were associated with overall survival: prostate-specific antigen (PSA), lactate dehydrogenase, hemoglobin, ECOG Performance Status, alkaline phosphatase, and Gleason score.(8) Analysis of PSA by quartiles showed that men in the lowest quartile had the greatest survival benefit with sipuleucel-T: 49% reduced mortality compared with 26% reduced mortality in the second quartile, 19% in the third quartile, and 16% in the highest quartile.

Small et al (2014) pooled data for time to disease-related pain and time to first use of opioid analgesics from all 3 RCTs.(10) Median time to disease-related pain was 5.6 months for sipuleucel-T versus 5.3 months for control (HR=0.82; 95% CI, 0.62 to 1.09). Median time to first use of opioid analgesics was 12.6 months for sipuleucel-T versus 9.7 months for control (HR=0.76; 95% CI, 0.58 to 0.99).

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, 1 difficulty in assessing potential adverse effects by comparing sipuleucel-T with placebo is that placebo comprised infusion of untreated dendritic cells, which may cause adverse effects. FDA reviewers expressed concern regarding a possible association of sipuleucel-T with cerebrovascular events, as 8 (5%) of 147 vaccine-treated patients experienced cerebrovascular-related adverse events, compared with zero placebo-treated patients in the 2 early trials.(7) In the latest available report of adverse effects reported in the full prescribing information,(3) incidence of stroke 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, incidence of stroke was 4.9% (17/345) in sipuleucel-T-treated patients and 1.7% (3/172) in placebo-treated patients.
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 1500 patients with prostate cancer who receive sipuleucel-T.

Section Summary

For patients with metastatic, androgen-independent prostate cancer, 3 RCTs of sipuleucel-T have been published. The 3 RCTs are consistent in reporting an improvement in overall survival of approximately 4 months compared with placebo. Two trials also reported that 36-month survival was significantly improved for patients receiving sipuleucel-T, with absolute improvements in survival of 9% and 23%. Time to progression was slightly longer in the sipuleucel-T groups, but this difference was not statistically significant. Serious adverse events were not increased in the sipuleucel-T group. There has been concern raised about a possible increase in stroke risk, but the available trials do not show a significantly increased incidence of stroke.

Other Indications

A phase 3 trial of sipuleucel-T in the setting of androgen-dependent, nonmetastatic prostate cancer was published in 2011.(9) Patients with prostate cancer detectable by PSA after radical prostatectomy received 3 to 4 months of androgen suppression therapy and were then randomized (2:1) to receive sipuleucel-T (n=117) or control (n=59). The primary end point was time to biochemical failure. There was no difference in this end point between groups; median time to biochemical failure was 18.0 months for sipuleucel-T and 15.4 months for control (HR=0.936; p=0.737). Sipuleucel-T patients had a 48% increase in PSA doubling time after testosterone recovery (155 vs 105 days; p=0.038). Sixteen percent of patients developed distant failure. The treatment effect favored sipuleucel-T but was not statistically significant (HR=0.728; p=0.421).

Section Summary

A single RCT has been performed in patients with nonmetastatic prostate cancer, and this trial did not show any benefit for sipuleucel-T compared with control. Therefore, evidence on treatment of nonmetastatic prostate cancer is not sufficient to determine that health outcomes are improved.

Ongoing and Unpublished Trials

Some currently unpublished trials that might influence this policy are listed in Table 3.
Summary of Evidence

For patients with metastatic, androgen-independent prostate cancer, 3 randomized controlled trials of sipuleucel-T reported an improvement in median survival of approximately 4 months. The 2 early studies of sipuleucel-T were not specifically designed to demonstrate a difference in overall mortality but did show a survival difference. The third study, which was designed to demonstrate a mortality difference, showed a similar improvement in overall survival. All 3 studies also were consistent in demonstrating that sipuleucel-T does not delay time to measureable progression of disease. In all studies, many patients had further chemotherapy treatment at the discretion of the treating physician; thus, the survival benefit accrues in the context of additional treatment as needed for symptomatic recurrence. This evidence is sufficient to conclude that sipuleucel-T is medically necessary for patients with androgen-independent, asymptomatic or minimally symptomatic, metastatic prostate cancer.

For patients who do not meet the above criteria, evidence does not demonstrate an improvement in health outcomes. One RCT of patients with androgen-dependent, nonmetastatic prostate
cancer showed no statistical difference between sipuleucel-T and control in time to biochemical failure or PSA doubling time. This evidence does not support the use of sipuleucel-T for these patients, and therefore sipuleucel-T is considered investigational for all other indications, including but not limited to hormone-responsive prostate cancer, treatment of moderate to severe symptomatic metastatic prostate cancer, and treatment of visceral (liver, lung, or brain) metastases.

Practice Guidelines and Position Statements

National Comprehensive Cancer Network (NCCN)

Current National Comprehensive Cancer Network Guidelines for prostate cancer (v.1.2015) recommend sipuleucel-T as a category 1 treatment for patients with metastatic castration-recurrent prostate cancer if asymptomatic or minimally symptomatic; Eastern Cooperative Oncology Group Performance Status 0-1; no liver metastasis; and life expectancy greater than 6 months. Sipuleucel-T also is recommended for second-line treatment of symptomatic patients with metastatic castration-recurrent prostate cancer who fail chemotherapy and otherwise meet criteria for treatment with sipuleucel-T (category 2A recommendation). This recommendation was based on further analysis of previously reviewed clinical trials, which showed similar benefit in those who had and had not received prior chemotherapy.(13) A footnote stating that “sipuleucel-T has not been studied in patients with visceral metastases” has been added.

American Society of Clinical Oncology-Cancer Care Ontario

In 2014, the American Society of Clinical Oncology and Cancer Care Ontario issued a joint, evidence-based clinical practice guideline on systemic therapy in men with metastatic castration-resistant prostate cancer.(14) The guideline includes a weak recommendation that “sipuleucel-T may be offered to men who are asymptomatic or minimally symptomatic (benefit: moderate; harm: low; evidence strength: moderate).”

European Consensus Panel

On September 7, 2013, 21 experts in the field of prostate cancer met in France to “evaluate current opinion regarding the most appropriate sequencing of available therapies for metastatic castration-resistant prostate cancer,” among other objectives.(12) The panel used a modified Delphi method to obtain consensus, based on the biannual St. Gallen Early Breast Cancer Consensus Conference. The panel agreed (≥70% consensus) that sipuleucel-T is a reasonable option for patients with asymptomatic or minimally symptomatic metastatic hormone-refractory prostate cancer and should be considered before docetaxel, abiraterone, and enzalutamide. The panel considered sipuleucel-T a new treatment option “during the time period between development of hormone-refractory disease and becoming a candidate for chemotherapy.”

U.S. Preventive Services Task Force

The use of sipuleucel-T for prostate cancer is not a preventive service.
Medicare National Coverage

On June 30, 2011 a national coverage determination was released by CMS approving sipuleucel-T for treatment of asymptomatic or minimally symptomatic castrate-resistant prostate cancer. (16) Coverage for off-label indications was left to the discretion of local Medicare administrative contractors.

V. DEFINITIONS

LEUKAPHERESIS refers to separation of the leukocytes from blood, which are then transfused back into the patient.

VI. BENEFIT VARIATIONS

The existence of this medical policy does not mean that this service is a covered benefit under the member's contract. Benefit determinations should be based in all cases on the applicable contract language. Medical policies do not constitute a description of benefits. A member’s individual or group customer benefits govern which services are covered, which are excluded, and which are subject to benefit limits and which require preauthorization. Members and providers should consult the member’s benefit information or contact Capital for benefit information.

VII. DISCLAIMER

Capital’s medical policies are developed to assist in administering a member’s benefits, do not constitute medical advice and are subject to change. Treating providers are solely responsible for medical advice and treatment of members. Members should discuss any medical policy related to their coverage or condition with their provider and consult their benefit information to determine if the service is covered. If there is a discrepancy between this medical policy and a member’s benefit information, the benefit information will govern. Capital considers the information contained in this medical policy to be proprietary and it may only be disseminated as permitted by law.

VIII. CODING INFORMATION

Note: This list of codes may not be all-inclusive, and codes are subject to change at any time. The identification of a code in this section does not denote coverage as coverage is determined by the terms of member benefit information. In addition, not all covered services are eligible for separate reimbursement.
Covered when medically necessary:

<table>
<thead>
<tr>
<th>HCPCS Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Q2043</td>
<td>Sipuleucel-t, minimum of 50 million autologous cd54+ cells activated with pap-gm-csf, including leukapheresis and all other preparatory procedures, per infusion</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>ICD-10-CM Diagnosis Code*</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>C61</td>
<td>Malignant neoplasm of prostate</td>
</tr>
<tr>
<td>Z51.12</td>
<td>Encounter for antineoplastic immunotherapy</td>
</tr>
</tbody>
</table>

*If applicable, please see Medicare LCD or NCD for additional covered diagnoses

IX. REFERENCES


Other:

X. POLICY HISTORY

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<th></th>
<th></th>
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<tbody>
<tr>
<td></td>
<td>CAC 9/28/10 Policy criteria revised. Adopted Highmark Medicare Services medical necessity criteria.</td>
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</table>
MEDICAL POLICY

<table>
<thead>
<tr>
<th>POLICY TITLE</th>
<th>CELLULAR IMMUNOTHERAPY FOR PROSTATE CANCER</th>
</tr>
</thead>
<tbody>
<tr>
<td>POLICY NUMBER</td>
<td>MP-2.151</td>
</tr>
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CAC 07/26/11 Administrative change. Medicare variation added to NCD 110.22 Autologous Cellular Immunotherapy Treatment. Preauthorization form revised for Medicare to refer to NCD specific indications.

CAC 4/24/12 Consensus review. FEP variation revised. Deleted Medicare variation reference to NCD 110.22 and Medicare Benefit Policy Manual (100-2, Chapter 15, Section 50.4.5- Off-Label Use of Drugs and Biologicals in an Anti-Cancer Chemotherapeutic Regimen. Added references to LCD L31686 Services That are Not Reasonable and Necessary.

Administrative change 9/13/12 Medicare variation removed.

CAC 1/29/13 Minor. Deleted requirement for adequate hematologic, renal and liver function from criteria list. Added Medicare variation to reference NCD 110.22 Autologous Cellular Immunotherapy Treatment and LCD L31686 Services That are Not Reasonable and Necessary. Codes reviewed 11/16/12

CAC 11/26/13 Consensus – no change to policy statements. References updated. Added rationale section.

CAC 11/25/14 Consensus review. References and rationale updated. No changes to the policy statements. Deleted notation regarding preauthorization requirement. All users should refer to officially posted preauthorization resources for requirements. Note LCD changed numbers from L31686 to L35094. Coding reviewed, no changes.

CAC 11/24/15 Consensus review. References and rationale updated. “Hormone-refractory” changed to the current clinically accepted term “castration-resistant” in the medically necessary policy statement and throughout the policy. Policy statements otherwise unchanged. Coding reviewed and updated.

CAC 11/29/16 Consensus. No change to policy statements. References updated. Variation reformatting. Coding reviewed and updated.

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