8.01.53 Cellular Immunotherapy for Prostate Cancer

Policy Statement

Sipuleucel-T therapy may be considered medically necessary in the treatment of asymptomatic or minimally symptomatic, androgen-independent (castration-resistant) metastatic prostate cancer.

Sipuleucel-T therapy is considered investigational for the treatment of prostate cancer in all other situations, including but not limited to:

- Treatment of hormone-responsive prostate cancer
- Treatment of moderate-to-severe symptomatic metastatic prostate cancer
- Treatment of visceral (liver, lung, or brain) metastases

Policy Guidelines

The following HCPCS code is available for this product:

- Q2043: Sipuleucel-T, minimum of 50 million autologous cd54+ cells activated with PAP-GM-CSF, including leukapheresis and all other preparatory procedures, per infusion

Description

Sipuleucel-T (Provenge®) is a new class of therapeutic agent used to treat asymptomatic—or minimally symptomatic—castration-resistant, metastatic prostate cancer. The agent comprises specially treated dendritic cells obtained from the patient through leukapheresis. The cells are then exposed in vitro to proteins that contain prostate antigens and immunologic-stimulating factors and reinfused into the patient. The proposed mechanism of action is that treatment stimulates the patient’s own immune system to resist cancer spread.

Related Policies

- Genetic and Protein Biomarkers for the Diagnosis and Cancer Risk Assessment of Prostate Cancer

Benefit Application

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. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

Some state or federal mandates [e.g., Federal Employee Program (FEP)] prohibits plans from denying Food and Drug Administration (FDA)-approved technologies as investigational. In these instances, plans may have to consider the coverage eligibility of FDA-approved technologies on the basis of medical necessity alone.

Regulatory Status

In April 2010, the U.S. Food and Drug Administration approved Provenge® (Sipuleucel-T; Dendreon Corp, now Sanpower, Jiangsu, China) via a biologics licensing application for “the treatment of asymptomatic or minimally symptomatic metastatic castrate resistant (hormone refractory) prostate cancer.” Approval was contingent on the manufacturer conducting a
postmarketing study, based on a registry design, to assess the risk of cerebrovascular events in 1500 men with prostate cancer who receive Sipuleucel-T.

**Rationale**

**Background**

**Prostate Cancer**

Prostate cancer is the second leading cause of cancer-related deaths among American men, with an estimated incidence of 220,800 cases and an estimated number of 27,540 deaths in 2015. In most cases, prostate cancer is diagnosed at a localized stage and is treated with prostatectomy or radiotherapy. However, some patients are diagnosed with metastatic or recurrent disease after treatment of localized disease.

**Treatment**

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

Cancer immunotherapy has been investigated as a treatment that could 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 is thought to be relatively low, and it is thought that an effective immune response to the cancer during this interval could effectively delay or prevent progression. Such a delay could allow a course of effective chemotherapy, such as docetaxel, to be deferred or delayed until necessary, thus providing an overall survival benefit.

Sipuleucel-T (Provenge®) is a new class of therapeutic agent used to treat asymptomatic or minimally symptomatic, androgen-independent (castration-resistant), metastatic prostate cancer. The agent comprises specially treated dendritic cells obtained from the patient through leukapheresis. The cells are then exposed in vitro to proteins that contain prostate antigens and immunologic-stimulating factors and reinfused into the patient. The cells are administered as 3 intravenous infusions given approximately 2 weeks apart. The proposed mechanism of action is that the treatment stimulates the patient’s own immune system to resist cancer spread.

**Literature Review**

**Metastatic, castration-resistant Prostate Cancer**

**Systematic Reviews**

In 2016, Yi et al reported on a meta-analysis that identified 3 randomized controlled trials (RCTs) on Sipuleucel-T for treating castration-resistant prostate cancer. A pooled analysis of the 3 RCTs found significantly improved overall survival (OS) with Sipuleucel-T compared with placebo (hazard ratio [HR], 0.73; 95% confidence interval [CI], 0.61 to 0.88; P=0%). There was no significant difference between Sipuleucel-T and placebo in time to progression of prostate cancer (HR=0.88; 95% CI, 0.74 to 1.06; P=4%). Rates of individual adverse events were pooled, and there were no significant differences between Sipuleucel-T and placebo in any of the adverse events, which consisted of fatigue, back pain, headache, arthralgia, and constipation. Stroke rates were not reported.
**Randomized Controlled Trials**

Sipuleucel-T has been studied in 3 double-blind, placebo-controlled randomized trials. These trials were published by Small et al (2006), Higano et al (2009), and Kantoff et al (2010), 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 castration-resistant metastatic prostate cancer, were asymptomatic or mildly symptomatic, in good physical health characterized by the Eastern Cooperative Oncology Group Performance Status at 0 or 1, and had tumors with positive staining for prostatic acid phosphatase.

Table 1 describes the 2 early identically designed studies. Patients with asymptomatic metastatic prostate cancer were randomized to Sipuleucel-T or to a control infusion of untreated dendritic cells. The 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, e.g., pathologic fracture), or pain progression (based on onset of pain corresponding to the anatomic location of the disease).

Studies were not designed to establish efficacy based on overall survival. On progression of cancer, patients were allowed additional treatment as needed, including chemotherapy. Patients originally assigned to a placebo were allowed to cross over by receiving their own dendritic cells pulsed with PA2024 antigen (recombinant fusion protein comprising human prostatic acid phosphatase linked to granulocyte-macrophage colony-stimulating factor) 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</th>
<th>Design</th>
<th>Eligibility</th>
<th>Treatment</th>
<th>Outcomes</th>
</tr>
</thead>
</table>
| 9901A,7   | 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 (radiologic, clinical, pain)  
• Secondary: time to pain, time to progression |
| 9902A8    | 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.

As shown in Table 2, results of study 9901A for the principal outcome of time to progression did not show a significant difference between the vaccine and infusion 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 Group</th>
<th>Control Group</th>
<th>p</th>
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<tbody>
<tr>
<td>Study 9901A,7 n</td>
<td>82</td>
<td>45</td>
<td>0.052</td>
</tr>
<tr>
<td>Median time to progression, wk</td>
<td>11.7</td>
<td>10.0</td>
<td></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</td>
</tr>
<tr>
<td>(multivariable adjusted, 0.002)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Study 9902A,8 n</td>
<td>65</td>
<td>33</td>
<td>0.719</td>
</tr>
<tr>
<td>Median time to progression, wk</td>
<td>10.9</td>
<td>9.9</td>
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<tr>
<td>Overall median survival, mo</td>
<td>19.0</td>
<td>15.7</td>
<td>0.331</td>
</tr>
<tr>
<td>IMPACT study,9 n</td>
<td>341</td>
<td>171</td>
<td>0.032</td>
</tr>
<tr>
<td>Overall median survival, mo</td>
<td>25.8</td>
<td>21.7</td>
<td></td>
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</table>
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. 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 in the survival analysis. After disease progression, patients in both groups received chemotherapy; however, 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) analyzed the survival data after adjusting for prognostic factors and found a significant association between Sipuleucel-T treatment and survival (HR=2.12; 95% CI, 1.31 to 3.44).7

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 2, 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.8 Pooled analysis showed a 33% reduction in the risk of death (HR=1.9; 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, the 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 OS.9 Analyses used to support the 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 a 2013 retrospective, prespecified, multivariate subgroup analysis, several baseline factors were associated with OS: prostate-specific antigen (PSA) levels, lactate dehydrogenase levels, hemoglobin levels, the Eastern Cooperative Oncology Group Performance Status scores, alkaline phosphatase levels, and Gleason scores.11 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.12 Median time to disease-related pain was 5.6 months for Sipuleucel-T and 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 and 9.7 months for control (HR=0.76; 95% CI, 0.58 to 0.99).
Regarding the safety of Sipuleucel-T, most adverse events were grade 1 and 2 and resolved within 48 hours. The rate of serious adverse events did not differ statistically between vaccine- and placebo-treated patients. However, a difficulty in assessing potential adverse events by comparing Sipuleucel-T with placebo is that placebo comprised infusion of untreated dendritic cells, which may cause adverse events. The FDA reviewers expressed concern on a possible association of Sipuleucel-T with cerebrovascular events; 8 (5%) of 147 vaccine-treated patients experienced cerebrovascular-related adverse events, compared with zero placebo-treated patients in the 2 early trials. 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 (p=0.092). The FDA review called the cerebrovascular event rate a “potential safety signal” and included as part of its 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: Metastatic, Castration-Resistant Prostate Cancer
For patients with metastatic, castration-resistant prostate cancer, 3 RCTs of Sipuleucel-T have been published. The 3 RCTs are consistent in reporting an improvement in OS of approximately 4 months compared with placebo. Additionally, 2 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. A meta-analysis of the 3 RCTs found significantly improved OS, but not time to progression, with Sipuleucel-T compared with placebo. Serious adverse events were not increased in the Sipuleucel-T group. However, given data reported to the FDA, there was a concern about a possible increase in stroke risk and this is being studied in an ongoing postmarketing study.

Nonmetastatic, Androgen-dependent Prostate Cancer
In 2011, Beer et al published an RCT evaluating Sipuleucel-T in the setting of nonmetastatic, androgen-dependent prostate cancer. 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 Sipuleucel-T (n=117) or to control (n=59). The primary end point was time to biochemical failure. The median time to biochemical failure was 18.0 months for Sipuleucel-T and 15.4 months for control. The difference between groups was not statistically significant (HR=0.936, p=0.737). The PSA doubling time after testosterone recovery was 155 days in the Sipuleucel-T group and 105 days in the placebo group (p=0.038). At the data cutoff point, 16% developed distant failure. The risk of distant failure did not significantly favor the Sipuleucel-T group (p=0.021); however, the authors noted that this analysis had limited power.

Section Summary: Nonmetastatic, Androgen-Dependent Prostate Cancer
Only 1 RCT has evaluated Sipuleucel-T in patients with nonmetastatic, androgen-dependent prostate cancer. This trial did not show a statistically significant 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.

Summary of Evidence
For individuals who have a symptomatic or minimally symptomatic, metastatic, castration-resistant prostate cancer who receive Sipuleucel-T (Provenge®), the evidence includes 3 randomized controlled trials (RCTs) and a systematic review of these RCTs. Relevant outcomes are overall survival, disease-specific survival, change in disease status, and treatment-related morbidity. The 2 earlier RCTs of Sipuleucel-T were not specifically designed to demonstrate a difference in overall mortality but did show a survival difference. The third RCT, which was designed to demonstrate a mortality difference, showed a similar improvement in overall survival. All 3 studies were consistent in demonstrating that Sipuleucel-T does not delay time to a measurable progression of the disease. A meta-analysis of the 3 RCTs found significantly improved overall survival, but not time to progression, with Sipuleucel-T compared with placebo. Serious adverse events did not increase in the Sipuleucel-T group. However, the available data
suggested, but did not confirm, an increase in stroke risk; this risk is being evaluated in a postmarketing study. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have nonmetastatic, androgen-dependent prostate cancer who receive Sipuleucel-T (Provenge®), the evidence includes a RCT. Relevant outcomes are overall survival, disease-specific survival, change in disease status, and treatment-related morbidity. The RCT did not find a statistically significant difference between Sipuleucel-T and a control in time to biochemical failure. The RCT was not designed to evaluate the impact of Sipuleucel-T on mortality. The evidence is insufficient to determine the effects of the technology on health outcomes.

Supplemental Information
Practice Guidelines and Position Statements

European Association of Urology et al
In 2016, the European Association of Urology, the European Society for Radiotherapy & Oncology, and the International Society of Geriatric Oncology published joint guidelines on the treatment of relapsing, metastatic, castration-resistant prostate cancer. The guidelines stated that the choice of first-line treatment should be based on factors including performance status, symptoms, comorbidities, and the extent of disease, and that recommended treatment options are in “(alphabetic order: abiraterone, cabazitaxel docetaxel, enzalutamide, Ra 223 and Sipuleucel-T).”

American Urological Association
In 2013 (amended 2015), the American Urological Association published guidelines on castration-resistant prostate cancer. The guidelines included the following statements on Sipuleucel-T:

“Clinicians should offer abiraterone + prednisone, enzalutamide, docetaxel, or Sipuleucel-T to patients with asymptomatic or minimally symptomatic mCRPC [metastatic castration-resistant prostate cancer] with good performance status and no prior docetaxel chemotherapy. [Standard; Evidence Level Grade A (abiraterone + prednisone and enzalutamide)/B (docetaxel and Sipuleucel-T)]"

“Clinicians should not offer treatment with either estramustine or Sipuleucel-T to patients with symptomatic, mCRPC with poor performance status and no prior docetaxel chemotherapy. (Recommendation; Evidence Level Grade C)”

National Comprehensive Cancer Network
Current National Comprehensive Cancer Network guidelines for prostate cancer (v.2.2017) recommend Sipuleucel-T as a category 1 treatment for patients with metastatic castration-recurrent prostate cancer, symptomatic or minimally symptomatic; Eastern Cooperative Oncology Group Performance Status 0 or 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).

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

U.S. Preventive Services Task Force Recommendations
Not applicable.
Medicare National Coverage
In 2011, a national coverage determination was released by the Centers for Medicare & Medicaid Services approving Sipuleucel-T for treatment of asymptomatic or minimally symptomatic castrate-resistant prostate cancer. Coverage for off-label indications was left to the discretion of local Medicare administrative contractors.

Ongoing and Unpublished Clinical Trials
Some currently unpublished trials that might influence this policy are listed in Table 3.

Table 3. Summary of Key Trials

<table>
<thead>
<tr>
<th>NCT No.</th>
<th>Trial Name</th>
<th>Planned Enrollment</th>
<th>Completion Date</th>
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</thead>
<tbody>
<tr>
<td>Ongoing</td>
<td></td>
<td></td>
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<tr>
<td>NCT01487863</td>
<td>A Randomized, Open-label, Phase 2 Trial of Sipuleucel-T With Concurrent Versus Sequential Administration of Abiraterone Acetate Plus Prednisone in Men With Metastatic Castrate Resistant Prostate Cancer (mCRPC)</td>
<td>69</td>
<td>Jun 2016 (ongoing)</td>
</tr>
<tr>
<td>NCT01981122</td>
<td>A Randomized, Open-label, Phase 2 Study of Sipuleucel-T With Concurrent Versus Sequential Administration of Enzalutamide in Men With Metastatic Castrate-Resistant Prostate Cancer</td>
<td>52</td>
<td>Jul 2017 (ongoing)</td>
</tr>
<tr>
<td>NCT01560923</td>
<td>A Randomized, Double-Blind Phase II Study of Sipuleucel-T (Provenge ®) Followed by Indoximod or Placebo in the Treatment of Patients With Asymptomatic or Minimally Symptomatic Metastatic Castration Resistant Prostate Cancer</td>
<td>47</td>
<td>Nov 2017</td>
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<tr>
<td>NCT01807065</td>
<td>Randomized Phase II Trial of Sipuleucel-T Immunotherapy Preceded by Sensitizing Radiation Therapy and Sipuleucel-T Alone in Patients With Castrate Resistant Metastatic Prostate Cancer</td>
<td>50</td>
<td>Jan 2018</td>
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<tr>
<td>NCT01804465</td>
<td>A Randomized Phase 2 Trial of Combining Sipuleucel-T With Immediate vs. Delayed CTLA-4 Blockade for Prostate Cancer</td>
<td>54</td>
<td>Dec 2018</td>
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<tr>
<td>NCT03024216</td>
<td>Clinical Study of Atezolizumab (Anti-PD-L1) and Sipuleucel-T in Patients Who Have Asymptomatic or Minimally Symptomatic Metastatic Castrate Resistant Prostate Cancer</td>
<td>34</td>
<td>Jan 2019</td>
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<tr>
<td>Unpublished</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>NCT02159950</td>
<td>A Phase II Randomized Open Label Study of Sipuleucel-T vs. Sipuleucel-Tand Tasquinimod in Patients With Metastatic Castrate-Resistant Prostate Cancer (CRPC)</td>
<td>2</td>
<td>Apr 2015 (completed)</td>
</tr>
<tr>
<td>NCT01306890</td>
<td>A Registry of Sipuleucel-T Therapy in Men With Advanced Prostate Cancer (PROCEED)</td>
<td>1973</td>
<td>Jan 2017 (completed)</td>
</tr>
</tbody>
</table>

NCT: national clinical trial.
* Denotes industry-sponsored or cosponsored trial.

References


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Documentation for Clinical Review

Please provide the following documentation (if/when requested):

- History and physical and/or consultation notes including:
  - Previous treatment and response

Post Service
- Procedure report(s)

Coding

This Policy relates only to the services or supplies described herein. Benefits may vary according to product design; therefore, contract language should be reviewed before applying the terms of the Policy. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement.

MN/IE

The following services may be considered medically necessary in certain instances and investigational in others. Services may be considered medically necessary when policy criteria are met. Services may be considered investigational when the policy criteria are not met or when the code describes application of a product in the position statement that is investigational.

<table>
<thead>
<tr>
<th>Type</th>
<th>Code</th>
<th>Description</th>
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<tbody>
<tr>
<td>CPT®</td>
<td>36511</td>
<td>Therapeutic apheresis; for white blood cells</td>
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<tr>
<td></td>
<td>96365</td>
<td>Intravenous infusion; for therapy, prophylaxis, or diagnosis (specify substance or drug); initial, up to 1 hour</td>
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<td>HCPCS</td>
<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>
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<td>ICD-10 Procedure</td>
<td>30233Q0</td>
<td>Transfusion of Autologous White Cells into Peripheral Vein, Percutaneous Approach</td>
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<td>30243Q0</td>
<td>Transfusion of Autologous White Cells into Central Vein, Percutaneous Approach</td>
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<td>6A551Z1</td>
<td>Pheresis of Leukocytes, Multiple</td>
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<td>ICD-10 Diagnosis</td>
<td>All Diagnoses</td>
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Policy History

This section provides a chronological history of the activities, updates and changes that have occurred with this Medical Policy.

<table>
<thead>
<tr>
<th>Effective Date</th>
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<tbody>
<tr>
<td>01/07/2011</td>
<td>BCBSA Medical Policy adoption</td>
<td>Medical Policy Committee</td>
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<tr>
<td>04/05/2011</td>
<td>Administrative Review</td>
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<tr>
<td>09/30/2014</td>
<td>Policy revision without position change</td>
<td>Medical Policy Committee</td>
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</table>
Definitions of Decision Determinations

Medically Necessary: A treatment, procedure, or drug is medically necessary only when it has been established as safe and effective for the particular symptoms or diagnosis, is not investigational or experimental, is not being provided primarily for the convenience of the patient or the provider, and is provided at the most appropriate level to treat the condition.

Investigational/Experimental: A treatment, procedure, or drug is investigational when it has not been recognized as safe and effective for use in treating the particular condition in accordance with generally accepted professional medical standards. This includes services where approval by the federal or state governmental is required prior to use, but has not yet been granted.

Split Evaluation: Blue Shield of California/Blue Shield of California Life & Health Insurance Company (Blue Shield) policy review can result in a split evaluation, where a treatment, procedure, or drug will be considered to be investigational for certain indications or conditions, but will be deemed safe and effective for other indications or conditions, and therefore potentially medically necessary in those instances.

Prior Authorization Requirements (as applicable to your plan)

Within five days before the actual date of service, the provider must confirm with Blue Shield that the member's health plan coverage is still in effect. Blue Shield reserves the right to revoke an authorization prior to services being rendered based on cancellation of the member's eligibility. Final determination of benefits will be made after review of the claim for limitations or exclusions.

Questions regarding the applicability of this policy should be directed to the Prior Authorization Department. Please call (800) 541-6652 or visit the provider portal at www.blueshieldca.com/provider.

Disclaimer: This medical policy is a guide in evaluating the medical necessity of a particular service or treatment. Blue Shield of California may consider published peer-reviewed scientific literature, national guidelines, and local standards of practice in developing its medical policy. 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 covered services. Member contracts may differ in their benefits. Blue Shield reserves the right to review and update policies as appropriate.