The following Protocol contains medical necessity criteria that apply for this service. It is applicable to Medicare Advantage products unless separate Medicare Advantage criteria are indicated. If the criteria are not met, reimbursement will be denied and the patient cannot be billed. Preauthorization is required and must be obtained through Case Management. Please note that payment for covered services is subject to eligibility and the limitations noted in the patient’s contract at the time the services are rendered.

**Description**

**Hematopoietic Stem-Cell Transplantation**

Hematopoietic stem-cell transplantation (HSCT) refers to a procedure in which hematopoietic stem cells are infused to restore bone marrow function in cancer patients who receive bone-marrow-toxic doses of cytotoxic drugs with or without whole-body radiation therapy. Hematopoietic stem cells may be obtained from the transplant recipient (autologous HSCT) or from a donor (allogeneic HSCT). They can be harvested from bone marrow, peripheral blood, or umbilical cord blood shortly after delivery of neonates. Although cord blood is an allogeneic source, the stem cells in it are antigenically “naïve” and thus are associated with a lower incidence of rejection or graft-versus-host disease (GVHD).

**Background**

Immunologic compatibility between infused hematopoietic stem cells and the recipient is not an issue in autologous HSCT. However, immunologic compatibility between donor and patient is a critical factor for achieving a good outcome of allogeneic HSCT. Compatibility is established by typing of human leukocyte antigens (HLA) using cellular, serologic, or molecular techniques. HLA refers to the tissue type expressed at the Class I and Class II loci on each arm of chromosome 6. Depending on the disease being treated, an acceptable donor will match the patient at all or most of the HLA loci (with the exception of umbilical cord blood).

**Conventional Preparative Conditioning for HSCT**

The conventional (“classical”) practice of allogeneic HSCT involves administration of cytotoxic agents (e.g., cyclophosphamide, busulfan) with or without total body irradiation at doses sufficient to destroy endogenous hematopoietic capability in the recipient. The beneficial treatment effect in this procedure is due to a combination of initial eradication of malignant cells and subsequent graft-versus-malignancy (GVM) effect mediated by non-self immunologic effector cells that develop after engraftment of allogeneic stem cells within the patient’s bone marrow space. While the slower GVM effect is considered to be the potentially curative component, it may be overwhelmed by extant disease without the use of pretransplant conditioning. However, intense conditioning regimens are limited to patients who are sufficiently fit medically to tolerate substantial adverse effects that include pre-engraftment opportunistic infections secondary to loss of endogenous bone marrow function and organ damage and failure caused by the cytotoxic drugs. Furthermore, in any allogeneic
HSCT, immunosuppressant drugs are required to minimize graft rejection and GVHD, which also increases susceptibility of the patient to opportunistic infections.

The success of autologous HSCT is predicated on the ability of cytotoxic chemotherapy with or without radiation to eradicate cancerous cells from the blood and bone marrow. This permits subsequent engraftment and repopulation of bone marrow space with presumably normal hematopoietic stem cells obtained from the patient prior to undergoing bone marrow ablation. As a consequence, autologous HSCT is typically performed as consolidation therapy when the patient’s disease is in complete remission. Patients who undergo autologous HSCT are susceptible to chemotherapy-related toxicities and opportunistic infections prior to engraftment, but not GVHD.

Reduced-Intensity Conditioning for Allogeneic HSCT

Reduced-intensity conditioning (RIC) refers to the pretransplant use of lower doses or less-intense regimens of cytotoxic drugs or radiation than are used in traditional full-dose myeloablative conditioning treatments. The goal of RIC is to reduce disease burden but also to minimize as much as possible associated treatment-related morbidity and non-relapse mortality (NRM) in the period during which the beneficial GVM effect of allogeneic transplantation develops. Although the definition of RIC remains arbitrary, with numerous versions employed, all seek to balance the competing effects of NRM and relapse due to residual disease. RIC regimens can be viewed as a continuum in effects, from nearly totally myeloablative to minimally myeloablative with lymphoablation, with intensity tailored to specific diseases and patient condition. Patients who undergo RIC with allogeneic HSCT initially demonstrate donor cell engraftment and bone marrow mixed chimerism. Most will subsequently convert to full-donor chimerism, which may be supplemented with donor lymphocyte infusions to eradicate residual malignant cells.

For the purposes of this Protocol, the term “reduced-intensity conditioning” will refer to all conditioning regimens intended to be non-myeloablative, as opposed to fully myeloablative (traditional) regimens.

Multiple Myeloma

Multiple myeloma (MM) is a systemic malignancy of plasma cells that represents approximately 10% of all hematologic cancers. It is treatable but rarely curable, with estimated new cases and deaths in 2010 in the U.S. of 20,180 and 10,650, respectively. (1) At the time of diagnosis most patients have generalized disease, and, the selection of treatment is influenced by patient age, general health, prior therapy, and the presence of complications of the disease. (1, 2)

The disease is staged by estimating tumor mass, based on various clinical parameters such as hemoglobin, serum calcium, number of lytic bone lesions, and the presence or absence of renal failure. (1) Multiple myeloma usually evolves from an asymptomatic premalignant stage (termed “monoclonal gammopathy of undetermined significance” or MGUS). Treatment is usually reserved for patients with symptomatic disease (usually progressive myeloma), whereas asymptomatic patients are observed, as there is little evidence that early treatment of asymptomatic multiple myeloma prolongs survival when compared to therapy delivered at the time of symptoms or end-organ damage. (1, 2) In some patients, an intermediate asymptomatic but more advanced premalignant stage is recognized and referred to as smoldering multiple myeloma. (3) The overall risk of disease progression from smoldering to symptomatic multiple myeloma is 10% per year for the first five years, approximately 3% per year for the next five years, and 1% for the next 10 years. (1, 2)

POEMS Syndrome

POEMS syndrome (also known as osteosclerotic myeloma, Crow-Fukase syndrome, or Takasuki syndrome) is a rare, paraneoplastic disorder secondary to a plasma cell dyscrasia. (3, 4) This complex, multiorgan disease was first described in 1938, but the acronym POEMS was coined in 1980, reflecting hallmark characteristics of the syndrome: polyneuropathy, organomegaly, endocrinopathy, M protein, and skin changes. (5) No single test
establishes the presence of POEMS syndrome. Its pathogenesis is undefined, although some evidence suggests it is mediated by imbalance of proinflammatory cytokines including interleukin-1β (IL-1β), IL-6, and tumor necrosis factor-α; vascular endothelial growth factor may also be involved. (4, 6) However, specific criteria have been established, and the syndrome may entail other findings in the constellation of signs and symptoms, as shown in the Table. Both major criteria and at least one of the minor criteria are necessary for diagnosis. (6)

Criteria for the diagnosis of POEMS syndrome (4, 6)

<table>
<thead>
<tr>
<th>Major Criteria</th>
<th>Minor Criteria</th>
<th>Known Associations</th>
<th>Possible Associations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Polyneuropathy</td>
<td>Sclerotic bone lesions</td>
<td>Clubbing</td>
<td>Pulmonary hypertension</td>
</tr>
<tr>
<td>Monoclonal plasmoproliferative disorder</td>
<td>Castleman disease</td>
<td>Weight loss</td>
<td>Restrictive lung disease</td>
</tr>
<tr>
<td>Organomegaly</td>
<td>Sclerotic bone lesions</td>
<td>Thrombocytosis</td>
<td>Thrombotic diatheses</td>
</tr>
<tr>
<td>(spleenomegaly, hepatomegaly, or lymphadenopathy)</td>
<td>Polycythemia</td>
<td></td>
<td>Arthralgias</td>
</tr>
<tr>
<td>Edema</td>
<td>(edema, pleural effusion, or ascites)</td>
<td>Hyperhidrosis</td>
<td>Cardiomyopathy (systolic dysfunction)</td>
</tr>
<tr>
<td>Endocrinopathy</td>
<td>(adrenal, thyroid, pituitary, gonadal, parathyroid, pancreatic)</td>
<td></td>
<td>Fever</td>
</tr>
<tr>
<td>Skin changes</td>
<td>(hyperpigmentation, hypertrichosis, plethora, hemangiomata, white nails)</td>
<td></td>
<td>Low vitamin B12 values</td>
</tr>
<tr>
<td>Papilledema</td>
<td></td>
<td></td>
<td>Diarrhea</td>
</tr>
</tbody>
</table>

The prevalence of POEMS syndrome is unclear. A national survey in Japan showed a prevalence of about 0.3 per 100,000. (7) Other large series have been described in the United States (4, 6, 8) and in India. (9) In general, patients with POEMS have a superior overall survival compared with that of MM, nearly 14 years in a large series from the Mayo Clinic. (6) However, given the rarity of POEMS, no randomized controlled trials of therapies have been reported. (10) Numerous approaches have included ionizing radiation, plasmapheresis, intravenous immunoglobulin, interferon alfa, corticosteroids, alkylating agents, azathioprine, tamoxifen, transretinoic acid, and high-dose chemotherapy with autologous HSCT support. (4, 6) Optimal treatment involves eliminating the plasma cell clone, for example by surgical excision or local radiation therapy for an isolated plasmacytoma, or systemic chemotherapy in patients with disseminated disease, such as medullary disease or multiple plasmacytomas. Given the underlying plasma cell dyscrasia of POEMS, newer approaches to MM, including bortezomib, lenalidomide, and thalidomide, are also under investigation. (4, 11)

Corporate Medical Guideline

**Multiple myeloma**

A single or second (salvage) autologous hematopoietic stem-cell transplantation may be considered **medically necessary** to treat multiple myeloma.
Tandem autologous-autologous hematopoietic stem-cell transplantation may be considered **medically necessary** to treat multiple myeloma in patients who fail to achieve at least a near-complete or very good partial response after the first transplant in the tandem sequence. (For definitions of near-complete response and very good partial response, see Policy Guidelines.)

Tandem transplantation with an initial round of autologous hematopoietic stem-cell transplantation followed by a non-marrow-ablative conditioning regimen and allogeneic hematopoietic stem-cell transplantation (i.e., reduced-intensity conditioning transplant) may be considered **medically necessary** to treat newly diagnosed multiple myeloma patients.

Allogeneic hematopoietic stem-cell transplantation, myeloablative or nonmyeloablative, as upfront therapy of newly diagnosed multiple myeloma or as salvage therapy, is considered **investigational**.

**POEMS syndrome**

Autologous hematopoietic stem-cell transplantation may be considered **medically necessary** to treat disseminated POEMS syndrome. (See Policy Guidelines)

Allogeneic and tandem hematopoietic stem-cell transplantation are considered **investigational** to treat POEMS syndrome.

**Policy Guideline**

A complete response has been defined by the International Myeloma Working Group of the International Myeloma Foundation as negative immunofixation on the serum and urine, disappearance of any soft tissue plasmacytomas and ≥ 5% plasma cells in bone marrow. Other response criteria have been determined by them for these categories: stringent complete response, very good partial response, partial response, and stable disease. (48)

Patients with disseminated POEMS syndrome may have diffuse sclerotic lesions or disseminated bone marrow involvement.

**Benefit Application**

Individual transplant facilities may have their own **additional** requirements or protocols that must be met in order for the patient to be eligible for a transplant at their facility.

**Medicare Advantage**

If a transplant is needed, we arrange to have the transplant center review and decide whether the patient is an appropriate candidate for the transplant.

| Protocol | Hematopoietic Stem-Cell Transplantation for Plasma Cell Dyscrasias, Including Multiple Myeloma and POEMS Syndrome | Last Review Date: 09/13 |

Services that are the subject of a clinical trial do not meet our Technology Assessment Protocol criteria and are considered investigational. **For explanation of experimental and investigational, please refer to the Technology Assessment Protocol.**

It is expected that only appropriate and medically necessary services will be rendered. We reserve the right to conduct prepayment and postpayment reviews to assess the medical appropriateness of the above-referenced
procedures. Some of this Protocol may not pertain to the patients you provide care to, as it may relate to products that are not available in your geographic area.

References
We are not responsible for the continuing viability of web site addresses that may be listed in any references below.


