Policy

*Please see amendment for Pennsylvania Medicaid at the end of this CPB.*

Aetna considers plerixafor injection (Mozobil) in combination with granulocyte-colony stimulating factor (G-CSF) (filgrastim (Neupogen), filgrastim-aafi (Nivestym), filgrastim-sndz (Zarxio), or tbo-filgrastim (Granix, Neutroval) medically necessary to mobilize hematopoietic stem cells to the peripheral blood for collection and subsequent autologous transplantation in persons with non-Hodgkin's lymphoma (NHL) or multiple myeloma.

Aetna considers concomitant use of plerixafor injection with sargramostim or within 7 days of pegfilgrastim dose experimental and investigational because the safety and effectiveness of these approaches has not been established.

Aetna considers use of plerixafor beyond 4 consecutive days or use after completion of stem cell harvest/apheresis experimental and investigational.

Aetna considers plerixafor injection experimental and investigational for all other indications including the following (not an all-inclusive list) because its effectiveness for indications other than the ones listed above has not been established.

- Acute lymphoblastic leukemia
- Acute myeloid leukemia
- Antibody-mediated rejection in lung transplantation
- Chronic lymphocytic leukemia
- Chronic myeloid leukemia
- Glioma
- Lung cancer
- Malaria
- Post-herpetic neuralgia
- Prevention of acute renal injury
- Sickle cell disease
- Treatment or prophylaxis of neutropenia or febrile neutropenia
- WHIM (warts, hypogammaglobulinemia, infections and myelokathexis) syndrome

See also CPB 0055 - Hematopoietic Colony-Stimulating Factors (CSFs) (../1_99/0055.html).

Dosing Recommendations

Plerixafor is available as Mozobil single-use vial containing 1.2 mL of a 20 mg/mL solution (containing 24 mg of plerixafor) for subcutaneous injection.

- Initiate Mozobil (plerixafor) treatment after the person has received G-CSF once daily for 4 days
- Repeat Mozobil dose up to 4 consecutive days
- Dose based on individual weight:
  - Less than or equal to 83 kg: 20 mg dose or select dose based on 0.24 mg/kg actual body weight
  - Greater than 83 kg: select dose based on 0.24 mg/kg actual body weight

- Administer by subcutaneous injection approximately 11 hours prior to initiation of apheresis
- Renal impairment: If creatinine clearance is less than or equal to 50 mL/min, decrease dose by one-third to 0.16 mg/kg.

Source: Genzyme, 2019

Background
Mozobil (plerixafor) is an inhibitor of the CXCR4 chemokine receptor and blocks binding of its cognate ligand, stromal cell-derived factor-1α (SDF-1α). SDF-1α and CXCR4 are recognized to play a role in the trafficking and homing of human hematopoietic stem cells (HSCs) to the marrow compartment. Once in the marrow, stem cell CXCR4 can act to help anchor these cells to the marrow matrix, either directly via SDF-1α or through the induction of other adhesion molecules.

Mozobil (plerixafor) has been approved by the U.S. Food and Drug Administration (FDA) for use in combination with granulocyte-colony stimulating factor (G-CSF) to mobilize hematopoietic stem cells to the peripheral blood for collection and subsequent autologous transplantation in patients with non-Hodgkin’s lymphoma and multiple myeloma.

There has been a steady rise in the use of peripheral blood stem cells (PBSC) as a source of hematopoietic stem cells. In general, less than 0.05 % of white blood cells (WBC) are CD34+ cells. Chemotherapy results in a 5- to 15-fold increase of PBSC. Chemotherapy in combination with growth factors increases CD34+ cells up to 6 % of WBC. In the allogeneic setting, granulocyte-colony stimulating factor (G-CSF) is used alone for mobilization of PBSC. Several factors affect PBSC mobilization; including age, gender, type of growth factor, dose of the growth factor, and in the autologous setting, the patient’s diagnosis, chemotherapy regimen and number of previous chemotherapy cycles or radiation. Muscle and bone pain are common side effects in allogeneic stem cell mobilization, but are usually tolerated with the use of analgesics. Spleen enlargement followed by rupture is a serious complication in allogeneic donors (Arslan and Moog, 2007).

While G-CSF is the standard mobilizing agent for PBSC donors, it is associated with some significant side effects and requires a multi-day dosing regimen. The other cytokine approved for stem cell mobilization, granulocyte-macrophage colony stimulating factor (GM-CSF), alters graft composition and may reduce the development of graft-versus-host disease (GVHD), but a significant minority of donors fails to provide sufficient CD34+ cells with GM-CSF and some experience unacceptable toxicity. Plerixafor (AMD3100) is a new mobilizing agent that may have several advantages over G-CSF for donor mobilization. As it is a direct antagonist of the interaction between the chemokine stromal-derived factor-1 and its receptor, CXC chemokine receptor 4 (CXCR4), plerixafor mobilizes PBSC more readily and is also well-tolerated. Studies of autologous and allogeneic transplantation of plerixafor-mobilized grafts have shown prompt and stable engraftment (Cashen et al, 2007).

Flomenberg et al (2005) tested the hypotheses that the combination of AMD3100 plus G-CSF (A + G) would be superior to G-CSF alone (G) in mobilizing hematopoietic progenitor cells (HPC) and that A + G-mobilized cells would engraft as well as G-mobilized cells. The primary objective
was to determine whether patients mobilized more progenitor cells per unit of blood volume of apheresis after A + G administration versus G alone. Secondary objectives were to determine whether patients mobilized with A + G compared with G alone required fewer apheresis procedures to reach the target level of at least 5 x 10(6) CD34(+) cells/kg for transplant and to determine whether patients mobilized with A + G had at least a 90 % success rate of autologous transplantation as indexed by neutrophil engraftment by day 21. Each patient served as his or her own control in a sequential mobilization design. All study objectives were met without significant toxicity. The results demonstrated that the combination of A + G is generally safe, effective, and superior to G alone for autologous HPC mobilization.

Lymphoma and Multiple Myeloma

In a phase II clinical trial, Gazitt and associates (2007) evaluated the effect of AMD3100 on the mobilization of CD34+ cells, dendritic cells (DC) and lymphoma cells in patients with refractory or relapsed non-Hodgkin's lymphoma (NHL). A total of 11 patients received 16 microg/kg daily of G-CSF for 4 days followed by 240 microg/kg of AMD3100 given subcutaneously on a new schedule of 9 to 10 hours before apheresis collection on day 5. Administration of G-CSF and AMD3100 were continued daily until greater than or equal to 2 x 10(6) CD34+ cells/kg were collected. Adequate collection of the target of CD34+ cells was achieved in all but 1 patient within 2 days, and 10/11 patients were transplanted within 2 months. All transplanted patients engrafted with a mean of 10 and 12 days for neutrophils and platelets, respectively. Addition of AMD3100 to G-CSF resulted with greater than 2.5-fold increase in CD34+ cells/microl (p = 0.0001) and in a greater than 2-fold increase in precursor dendritic cell type 1 and precursor dendritic cell type 2 cells/microl (p = 0.003). Adverse events related to AMD3100 were minimal. AMD3100 was generally safe and improved PBSC and DC cell mobilization with no apparent contamination of lymphoma cells.

Cashen and colleagues (2008) examined the safety and effectiveness of hematopoietic stem cell mobilization with plerixafor in patients with Hodgkin lymphoma (HL). A total of 22 patients with HL who were candidates for autologous stem cell transplantation (ASCT) underwent hematopoietic stem cell mobilization with a combination of G-CSF, 10 microg/kg daily, and plerixafor, 240 microg/kg subcutaneous, 10 to 11 hours prior to apheresis. The primary endpoint was the proportion of patients who collected greater than or equal to 5 x 10(6) CD34+ cells/kg. Outcomes were compared to a historical control population of HL patients mobilized with G-CSF alone. Pharmacokinetic (PK) analysis of plerixafor was performed in a subset of patients. Fifteen patients (68 %) collected greater than or equal to 5 x 10(6) CD34+ cells/kg, and 21 patients (95 %) achieved the minimum collection of greater than or equal to 2 x 10(6) CD34+ cells/kg, in a median 2 apheresis procedures. Both the proportion of patients collecting greater than or equal to 5 x 10(6) CD34+ cells/kg and the median CD34+ cells collected in days 1 to 2 of...
apheresis were significantly improved over historical controls. The PK of plerixafor in this patient population was similar to that previously seen in healthy volunteers. The regimen was generally safe and well-tolerated.

Calandra and colleagues (2008) reported that AMD3100 plus G-CSF can successfully mobilize CD34+ cells from NHL, HL and multiple myeloma (MM) patients previously failing mobilization with chemotherapy and/or cytokine treatment. A cohort of 115 data-audited poor mobilizers was assessed, with the objective being to collect greater than or equal to $2 \times 10^6$ CD34+ cells per kg following AMD3100 plus G-CSF mobilization. The rates of successful CD34+ cell collection were similar for patients who previously failed chemotherapy mobilization or cytokine-only mobilization: NHL -- 60.3 %, MM -- 71.4 % and HL -- 76.5 %. Following transplantation, median times to neutrophil and platelet engraftment were 11 days and 18 days, respectively. Engraftment was durable. There were no drug-related serious adverse events. Of the adverse events considered related to AMD3100, 2 (1.6 %) were severe (headache, n = 1; nightmares, n = 1). Other AMD3100-related adverse events were mild (84.8 %) or moderate (13.6 %). The most common AMD3100-related adverse events were paresthesias, gastrointestinal reactions, and injection site reactions.

Devine et al (2008) discussed their findings on rapid mobilization of functional donor hematopoietic cells without G-CSF using AMD3100. Donors (n = 25) were treated with AMD3100 at a dose of 240 mug/kg by subcutaneous injection, and leukapheresis was then initiated just 4 hours later. Two-thirds of the donors collected an allograft with a CD34(+) cell dose sufficient for transplantation after just 1 dose of AMD3100. No donor experienced more than grade 1 toxicity. After a myeloablative regimen, 20 patients with hematologic malignancies received allografts collected after AMD3100 alone. All patients engrafted neutrophils (median day 10) and platelets (median day 12) promptly. Acute GVHD grades 2 through 4 occurred in 35 % of patients; 1 patient died of complications related to acute GVHD. No unexpected adverse events were observed in any of the recipients. All 14 patients surviving in remission have robust trilineage hematopoiesis and are transfusion-free with a median follow-up of 277 days (range of 139 to 964 days).

Pusic et al (2008) examined historic institutional autologous stem cell mobilization practices and assessed factors influencing mobilization failure and kinetics. In this retrospective study, these researchers analyzed clinical records of 1834 patients who underwent stem cell mobilization for autologous transplantation from November 1995 to October 2006 at the Washington University in St. Louis. Successful mobilization was defined as collection of greater than or equal to $2 \times 10^6$ CD34(+) cells/kg. From 1834 consecutive patients, 1040 met the investigators' inclusion criteria (502 NHL, 137 HL, and 401 MM). A total of 976 patients received G-CSF and 64 received G-CSF plus chemotherapy (G/C) for the initial mobilization. Although the median CD34(+) cell yield
was higher in G/C group than in G-CSF alone group, the failure rates were similar: 18.8 % and 18.6 %, respectively. Overall, 53 % of patients collected greater than or equal to 2 x 10(6) CD34(+) cells/kg during the first apheresis with either mobilization regimen. Regardless of mobilization regimen used, MM patients had the highest total CD34(+) cell yield and required less aphereses to collect greater than or equal to 2 x 10(6) CD34(+) cells/kg. Mobilized, pre-apheresis, peripheral blood CD34(+) count correlated with first day apheresis yield (r = 0.877, p < 0.001) and 20 cells/microl was the minimum threshold needed for a successful day 1 collection. For the re-mobilization analysis, these investigators included patients from the whole database. A total of 269 of 1834 patients underwent re-mobilization using G/C, G-CSF, and/or GM-CSF, and G-CSF plus plerixafor. Only 23 % of re-mobilized patients achieved greater than or equal to 2 x 10(6) CD34(+) cells/kg and 29.7 % failed to pool sufficient number of stem cells from both collections. Patients receiving G-CSF plus plerixafor had lowest failure rates, p = 0.03. Non-Hodgkin’s lymphoma patients re-mobilized with G-CSF who waited greater than or equal to 25 days before re-mobilization had lower CD34(+) cell yield than those who waited greater than or equal to 16 days, p = 0.023. Current mobilization regimens are associated with a substantial failure rate irrespective of underlying disease. Patients who fail initial mobilization are more likely to fail re-mobilization. These findings suggested that there is a need for more effective first-line mobilization agents.

On December 18, 2008, the U.S. Food and Drug Administration (FDA) approved Mozobil (plerixafor injection) to be used in combination with G-CSF for the treatment of adults with MM or NHL. The FDA approval is based on the findings of two clinical studies: one in patients with MM, the other with NHL. In these two placebo-controlled clinical trials (Studies 1 and 2, Genzyme, 2008), patients were randomized to receive either plerixafor 0.24 mg/kg or placebo on each evening prior to apheresis. Patients received daily morning doses of G-CSF 10 micrograms/kg for 4 days prior to the first dose of plerixafor or placebo and on each morning prior to apheresis. In Study 1, a total of 298 NHL patients were included in the primary effectiveness analyses. The mean age was 55.1 years (range of 29 to 75) and 57.5 years (range of 22 to 75) in the plerixafor and placebo groups, respectively, and 93 % of subjects were Caucasian. In Study 2, a total of 302 MM patients were included in the primary effectiveness analyses. The mean age was 58.2 years (range of 28 to 75) and 58.5 years (range of 28 to 75) in the plerixafor and placebo groups, respectively, and 81 % of subjects were Caucasian.

In Study 1, 59 % of NHL patients who were mobilized with plerixafor and G-CSF collected greater than or equal to 5 x 10(6) CD34+ cells/kg from the peripheral blood in 4 or fewer apheresis sessions, compared with 20 % of patients who were mobilized with placebo and G-CSF (p < 0.001). Other CD34+ cell mobilization outcomes showed similar findings. The median number of days to reach greater than or equal to 5 x 10(6) CD34+ cells/kg was 3 days for the plerixafor group and not evaluable for the placebo group.
In Study 2, 72% of MM patients who were mobilized with plerixafor and G-CSF collected greater than or equal to 6 x 10^6 CD34+ cells/kg from the peripheral blood in 2 or fewer apheresis sessions, compared with 34% of patients who were mobilized with placebo and G-CSF (p < 0.001). Other CD34+ cell mobilization outcomes showed similar findings. The median number of days to reach greater than or equal to 6 x 10^6 CD34+ cells/kg was 1 day for the plerixafor group and 4 days for the placebo group. Multiple factors can influence time to engraftment and graft durability following stem cell transplantation. For transplanted patients in the phase 3 studies, time to neutrophil and platelet engraftment and graft durability were similar across the treatment groups.

Common side effects reported in these clinical trials and other smaller studies include diarrhea, fatigue, headaches, nausea, joint pain, injection site reactions, as well as dizziness and vomiting.

According to the FDA-approved labeling of Mozobil, the recommended dose of plerixafor for stem cell mobilization is 0.24 mg/kg body weight by subcutaneous injection.

When Mozobil (plerixafor) is used in combination with G-CSF, tumor cells may be released from the marrow and subsequently collected in the leukapheresis product. The effect of potential reinfusion of tumor cells has not been well-studied. Mozobil (plerixafor) may cause mobilization of leukemic cells and subsequent contamination of the apheresis product. Therefore, Mozobil (plerixafor) is not intended for HSC mobilization and harvest in patients with leukemia.

Advise patients of the signs and symptoms of potential systemic reactions such as urticaria, periorbital swelling, dyspnea, or hypoxia during and following Mozobil (plerixafor) injection.

Patients should inform a health care professional immediately if symptoms of vasovagal reactions such as orthostatic hypotension or syncope occur during or shortly after their Mozobil (plerixafor) injection.

Advise female patients with reproductive potential to use effective contraceptive methods during Mozobil (plerixafor) use.

Mozobil (plerixafor) should not be utilized in the following:

- Members with known hypersensitivity to plerixafor of any of the products constituents
- Members that are pregnant or nursing and have not been apprised of the risks associated with this therapy
- The safety and efficacy of Mozobil (plerixafor) in pediatric members less than 18 years old have not been established in controlled clinical studies.
Flomenberg and colleagues (2010) evaluated the safety and efficacy of plerixafor as a single agent when given subcutaneously and followed by apheresis 6 hours later for the mobilization of hematopoietic stem cells (HSC) for transplantation in 9 patients with MM. All patients mobilized enough cells for at least 1 transplant, and demonstrated prompt recovery of hematopoietic function. Median time to engraftment was 10.5 days for neutrophils and 21 days for platelets. Significant adverse events were not observed. Recovery of peripheral blood cell counts was durable in all surviving patients. Despite these successes, mobilization with plerixafor alone was modest. However, in clinical circumstances where G-CSF or chemotherapy based-mobilization should not be used, mobilization with plerixafor alone may be required and effective. The authors concluded that further research into single agent use should focus on alternate route of administration as well as adjustment of the timing of the apheresis to improve HSC yield.

Worel and colleagues (2012) stated that plerixafor with G-CSF has been shown to enhance stem cell mobilization in patients with multiple myeloma and lymphoma with previous mobilization failure. These investigators reported the experience in insufficiently mobilizing patients diagnosed with non-hematologic diseases. A total of 33 patients with germ cell tumor (n = 11), Ewing sarcoma (n = 6), Wiscott-Aldrich disease (n = 5), neuroblastoma (n = 4), and other non-hematologic diseases (n = 7) were included in the study. Plerixafor was limited to patients with previous or current stem cell mobilization failure and given after 4 days of G-CSF (n = 21) or after chemotherapy and G-CSF (n = 12) in patients who mobilized poorly. Overall, 28 (85 %) patients succeeded in collecting at least 2 × 10^6 /kg body weight (b.w.) CD34+ cells (median, 5.0 × 10^6 /kg b.w. CD34+ cells; range of 2.0 × 10^6 to 29.5 × 10^6 /kg b.w. CD34+ cells), and 5 (15 %) patients collected a median of 1.5 × 10^6 /kg b.w. CD34+ cells (range of 0.9 × 10^6 to 1.8 × 10^6 /kg b.w. CD34+ cells). Nineteen patients proceeded to transplantation. The median dose of CD34+ cells infused was 3.3 × 10^6/kg b.w. (range of 2.3 × 10^6 to 6.7 × 10^6 /kg b.w. CD34+ cells). The median numbers of days to neutrophil and platelet engraftment were 11 (range of 9 to 12) and 15 (range of 10 to 25) days, respectively. The authors concluded that these findings emphasized the role of plerixafor in combination with G-CSF or chemotherapy and G-CSF as an effective mobilization regimen with the potential of successful stem cell collection. Accordingly, plerixafor seems to be safe and effective in patients with non-hematologic diseases. However, they stated that larger prospective studies are needed to further evaluate its use in these patients.

The National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium (2019) for "Mozobil" includes the following recommendations:

- Hematopoietic Growth Factors - Management of neutropenia - used in hematopoietic cell transplant for -
- mobilization of hematopoietic progenitor cells in combination with filgrastim, filgrastim-aafi, filgrastim-sndz, or tbo-filgrastim in the autologous setting for patients with non-Hodgkin lymphoma or multiple myeloma (Category 2A)
- mobilization of donor hematopoietic progenitor cells in the allogeneic setting (Category 2B for mobilization of allogeneic donors)

**Myeloid Growth Factors - used in hematopoietic cell transplant for -**

- mobilization of hematopoietic progenitor cells in combination with filgrastim, filgrastim-sndz, or tbo-filgrastim in the autologous setting for patients with non-Hodgkin lymphoma or multiple myeloma (Category 2A)
- mobilization of donor hematopoietic progenitor cells in the allogeneic setting (Category 2B for mobilization of allogeneic donors).

**WHIM Syndrome**

WHIM (warts, hypogammaglobulinemia, infections, and myelokathexis) syndrome, a rare congenital immunodeficiency disorder characterized by chronic non-cyclic neutropenia, is caused by autosomal dominant mutations in the gene for the chemokine receptor, CXCR4, resulting in a carboxy-terminus truncation of the receptor of between ten and 19 residues. This condition is one of only a few diseases directly and primarily caused by an aberrant chemokine. Patients with WHIM syndrome exhibit increased susceptibility to bacterial and viral infections, especially from common serotype human papilloma virus, resulting in warts on the hands and feet starting in childhood. Myelokathexis refers to retention of neutrophils in the bone marrow. Furthermore, lymphocytes and gammaglobulins are often deficient.

Dale and colleagues (2011) stated that mutations in CXCR4 cause severe leukopenia in myelokathexis or WHIM syndrome. Plerixafor inhibits binding of CXCR4 to its ligand CXCL12. These researchers investigated the effects of plerixafor (0.04 to 0.24 mg/kg body weight) administered at 2 to 4 day intervals in 6 patients. Outcome measures were the patients' complete blood cell counts, CD34+ cell counts and lymphocyte subtypes compared with 5 normal subjects similarly treated with plerixafor. All patients showed prompt leukocytosis with maximum blood neutrophils and lymphocytes at 6 to 12 hrs. Blood neutrophils peaked at 6 to 12 hrs, increasing from a mean baseline of 0.4 +/- 0.1 x 10(9)/L, to mean peak of 4.5 +/- 0.78 x 10(9)/L. Lymphocytes also increased; the greatest increase was in B cells (CD19+ cells), a greater than 40-fold increase over baseline at the 0.08 mg/kg dose. None of the patients experienced any significant adverse effects. The authors concluded that plerixafor is a promising therapy for this condition.
McDermott et al (2014) noted that warts, hypogammaglobulinemia, infections, and myelokathexis (WHIM) syndrome is a rare immunodeficiency disorder caused by gain-of-function mutations in the G protein-coupled chemokine receptor CXCR4. The CXCR4 antagonist plerixafor, which is approved by the FDA for stem cell mobilization in cancer and administered for that indication at 0.24 mg/kg, has been shown in short-term (1- to 2-week) phase 1 dose-escalation studies to correct neutropenia and other cytopenias in WHIM syndrome. However, long-term safety and long-term hematologic and clinical efficacy data are lacking. In a phase I study, these investigators reported findings from the first long-term clinical trial of plerixafor in any disease, in which 3 adults with WHIM syndrome self-injected 0.01 to 0.02 mg/kg (4 % to 8 % of the FDA-approved dose) subcutaneously twice-daily for 6 months. Circulating leukocytes were durably increased throughout the trial in all patients, and this was associated with fewer infections and improvement in warts in combination with imiquimod; however, immunoglobulin levels and specific vaccine responses were not fully restored. No drug-associated side effects were observed. The authors concluded that these results provided preliminary evidence for the safety and clinical efficacy of long-term, low-dose plerixafor in WHIM syndrome and support its continued study as mechanism-based therapy in this disease.

An UpToDate review on “Combined immunodeficiencies” (Bonilla, 2014) states that “Immune globulin replacement therapy is effective for reducing bacterial infections in patients with WHIM syndrome. Therapy with either granulocyte colony-stimulating factor (G-CSF) or granulocyte macrophage colony-stimulating factor (GM-CSF) results in increases in peripheral blood neutrophils. Preliminary evidence suggests treatment with the CXCR4 antagonist and stem cell mobilizing agent plerixafor is effective in increasing circulating leukocytes and decreasing infection frequency and the size of some warts, which were also treated with imiquimod. However, improvement in immunoglobulin levels and vaccine responses was not seen in a six-month phase 1 trial with three patients”.

Lung Cancer

Burger and associates (2011) stated that despite advances in surgery, chemotherapy and radiotherapy over the last decades, the death rate from lung cancer has remained largely unchanged, which is mainly due to metastatic disease. Because of the overall poor prognosis, new treatment strategies for lung cancer patients are urgently needed, and targeting CXCR4 constitutes such a novel, attractive strategy. Tumor cell migration and metastasis share many similarities with leukocyte trafficking, which is critically regulated by chemokine receptors and adhesion molecules. Lung cancer cells express CXCR4 (CD184), a seven-transmembrane G-protein-coupled chemokine receptor. Stromal cells within the tumor microenvironment constitutively secrete stromal cell-derived factor-1 (SDF-1/CXCL12), the ligand for CXCR4. Activation of CXCR4 induces lung cancer cell migration and adhesion to stromal cells, which in
turn provides growth- and drug-resistance signals to the tumor cells. CXCR4 antagonists, such as plerixafor (AMD3100) and T140 analogs (TN14003/BKT140), can disrupt CXCR4-mediated tumor cell adhesion to stromal cells and sensitize lung cancer cells to cytotoxic drugs. Thus, targeting the CXCR4-CXCL12 axis is a novel, attractive therapeutic approach in small-cell lung cancer and non-small-cell lung cancer. The authors summarized data about the cellular and molecular microenvironment in small-cell lung cancer and non-small-cell lung cancer, as well as the role of CXCR4 in tumor-stroma cross-talk. In addition, they reviewed the current status of the pre-clinical and clinical development of CXCR4 antagonists.

Acute Myeloid Leukemia

Uy and colleagues (2012) stated that the interaction of acute myeloid leukemia (AML) blasts with the leukemic micro-environment is postulated to be an important mediator of resistance to chemotherapy and disease relapse. These investigators hypothesized that inhibition of the CXCR4/CXCL12 axis by plerixafor would disrupt the interaction of leukemic blasts with the environment and increase the sensitivity of AML blasts to chemotherapy. In a phase I/II study, 52 patients with relapsed or refractory AML were treated with plerixafor in combination with mitoxantrone, etoposide, and cytarabine. In phase I, plerixafor was escalated to a maximum of 0.24 mg/kg/day without any dose-limiting toxicities. In phase II, 46 patients were treated with plerixafor 0.24 mg/kg/day in combination with chemotherapy with an overall complete remission and complete remission with incomplete blood count recovery rate (CR + CRi) of 46 %.

Correlative studies demonstrated a 2-fold mobilization in leukemic blasts into the peripheral circulation. No evidence of symptomatic hyper-leukocytosis or delayed count recovery was observed with the addition of plerixafor. The authors concluded that the addition of plerixafor to cytotoxic chemotherapy is feasible in AML, and resulted in encouraging rates of remission with correlative studies demonstrating in-vivo evidence of disruption of the CXCR4/CXCL12 axis. These preliminary findings need to be validated by well-designed studies.

Chronic Lymphocytic Leukemia

Stamatopoulos and co-workers (2012) the ability of plerixafor (AMD3100), a CXCR4 antagonist, to sensitize chronic lymphocytic leukemia (CLL) cells to chemotherapy in a CLL/mesenchymal stromal cell based or nurse-like cell based micro-environment co-culture model. Plerixafor decreased CXCR4 expression signal (n = 15, p = 0.0078) and inhibited actin polymerization/migration in response to SDF-1α (n = 8, p < 0.01) and pseudo-emperipolesis (n = 10, p = 0.0010), suggesting that AMD3100 interferes with CLL cell trafficking. Plerixafo did not have a direct effect on apoptosis when CLL cells were cultured alone (n = 10, p = 0.8812). However, when they were cultured with SDF-1α, mesenchymal stromal cells or nurse-like cells (protecting them from apoptosis, p < 0.001), CLL cell pre-treatment with AMD3100 significantly
inhibited these protective effects (n = 8, p < 0.01) and decreased the expression of the anti-apoptotic proteins MCL-1 and FLIP. Furthermore, combining AMD3100 with various drugs (fludarabine, cladribine, valproic acid, bortezomib, flavopiridol, methylprednisolone) in the authors' mesenchymal stromal cell co-culture model enhanced drug-induced apoptosis (n = 8, p < 0.05) indicating that AMD3100 could mobilize CLL cells away from their protective micro-environment, making them more accessible to conventional therapies. The authors concluded that taken together, these data demonstrated that interfering with the SDF-1α/CXCR4 axis by using plerixafor inhibited CLL cell trafficking and micro-environment-mediated protective effects. They stated that combining plerixafor with other drugs may, therefore, represent a promising therapeutic approach to kill CLL cells.

Chronic Myeloid Leukemia

Agarwal and colleagues (2012) stated that sequestration in the bone marrow niche may allow leukemic stem cells (LSC) to evade exposure to drugs. Since the CXCR4/SDF-1 axis is an important mechanism of LSC interaction with marrow stroma, these researchers examined if plerixafor may dislodge chronic myeloid leukemia (CML) cells from the niche, sensitizing them to tyrosine kinase inhibitors (TKIs). They initially treated mice with retrovirally induced CML-like disease with imatinib plus plerixafor. Plerixafor mobilized CXCR4-positive cells, but no difference was observed in leukemia burden, possibly reflecting insufficient disease control by imatinib. In a 2nd series of experiments, these investigators tested the combination of plerixafor with dasatinib in the same as well as an attenuated CML model. Despite much improved leukemia control, plerixafor failed to reduce leukemia burden over dasatinib alone. Additionally mice receiving plerixafor had an increased incidence of neurological symptoms in association with central nervous system (CNS) infiltration by BCR-ABL expressing cells. The authors concluded that plerixafor is ineffective in reducing leukemia burden in this model, but promotes CNS infiltration.

Ewing Sarcoma

Vives et al (2012) noted that some malignant tumors in childhood require high-dose chemotherapy with stem cell support to achieve a cure. In patients heavily pre-treated with myelosuppressive chemotherapy or irradiation, G-CSF may fail to mobilize stem cells from the bone marrow. Based on the experience with lymphoma and myeloma patients in whom PBSC collection following mobilization with G-CSF failed, these researchers successfully employed plerixafor in a 14-year old female diagnosed with Ewing's sarcoma in early relapse treated with 3 lines of chemotherapy in whom PBSC could not be mobilized using either G-CSF alone or G-
CSF following chemotherapy. No side effects were observed. The authors stated that plerixafor may be an effective and safe agent for stem cell collection in pediatric patients with solid tumors, although new studies are needed to evaluate its safety and effectiveness.

Renal Ischemia

Zuk and colleagues (2014) examined if antagonism of the CXCR4 receptor ameliorates the loss of renal function following ischemia-reperfusion. CXCR4 is ubiquitously expressed on leukocytes, known mediators of renal injury, and on bone marrow HSC. Plerixafor (AMD3100, Mozobil) is a small molecule CXCR4 antagonist that mobilizes HSCs into the peripheral blood and also modulates the immune response in in-vivo rodent models of asthma and rheumatoid arthritis. Treatment with plerixafor before and after ischemic clamping ameliorated kidney injury in a rat model of bilateral renal ischemia-reperfusion. Serum creatinine and blood urea nitrogen were significantly reduced 24 hours after re-perfusion, as was tissue injury and cell death. Plerixafor prevented the renal increase in the pro-inflammatory chemokines CXCL1 and CXCL5 and the cytokine IL-6. Flow cytometry of kidney homogenates confirmed the presence of significantly fewer leukocytes with plerixafor treatment; additionally, myeloperoxidase activity was reduced. AMD3465, a monocyclam analog of AMD3100, was likewise reno-protective. Four weeks post-reperfusion, long-term effects included diminished fibrosis, inflammation and ongoing renal injury. The mechanism by which CXCR4 inhibition ameliorates acute kidney injury (AKI) is due to modulation of leukocyte infiltration and expression of pro-inflammatory chemokines/cytokines, rather than a HSC mediated effect. The authors concluded that these data suggested that CXCR4 antagonism with plerixafor may be a potential option to prevent AKI.

Acute Lymphoblastic Leukemia

van den Berk et al (2014) noted that malignant cells infiltrating the bone marrow (BM) interfere with normal cellular behavior of supporting cells, thereby creating a malignant niche. These researchers found that CXCR4-receptor expression was increased in pediatric precursor B-cell acute lymphoblastic leukemia (BCP-ALL) cells compared with normal mononuclear hematopoietic cells (p < 0·0001). Furthermore, high CXCR4-expression correlated with an unfavorable outcome in BCP-ALL (5-year cumulative incidence of relapse ± standard error: 38.4 % ± 6.9 % in CXCR4-high versus 12 % ± 4.6 % in CXCR4-low expressing cases, p < 0.0001). Interestingly, BM levels of the CXCR4-ligand (CXCL12) were 2.7-fold lower (p < 0.0001) in diagnostic BCP-ALL samples compared with non-leukemic controls. Induction chemotherapy restored CXCL12 levels to normal. Blocking the CXCR4-receptor with plerixafor showed that the lower CXCL12 serum levels at diagnosis could not be explained by consumption by the leukemic cells, nor did these investigators observed an altered CXCL12-production capacity of BM-mesenchymal stromal cells (BM-MSC) at this time-point. These researchers rather observed
that a very high density of leukemic cells negatively affected CXCL12-production by the BM-MSC while stimulating the secretion levels of G-CSF. The authors concluded that these results suggested that highly proliferative leukemic cells are able to down-regulate secretion of cytokines involved in homing (CXCL12), while simultaneously up-regulating those involved in hematopoietic mobilization (G-CSF). Therefore, interference with the CXCR4/CXCL12 axis may be an effective way to mobilize BCP-ALL cells.

Sison and colleagues (2014) noted that in spite of advances in the treatment of pediatric ALL, a significant number of children with ALL are not cured of their disease. The authors and others have shown that signaling from the bone marrow microenvironment confers therapeutic resistance, and that the interaction between CXCR4 and stromal cell-derived factor-1 (SDF-1 or CXCL12) is a key mediator of this effect. These researchers demonstrated that ALL cells that up-regulate surface CXCR4 in response to chemotherapy treatment are protected from chemotherapy-induced apoptosis when co-cultured with bone marrow stroma. Treatment with the CXCR4 inhibitor plerixafor diminishes stromal protection and confers chemosensitivity. Using xenograft models of high-risk pediatric ALL, plerixafor plus chemotherapy induces significantly decreased leukemic burden, compared to chemotherapy alone. Further, treatment with plerixafor and chemotherapy influences surface expression of CXCR4, VLA-4, and CXCR7 in surviving ALL blasts. Finally, prolonged exposure of ALL blasts to plerixafor leads to a persistent increase in surface CXCR4 expression, along with modulation of surface expression of additional adhesion molecules, and enhanced SDF-1α-induced chemotaxis, findings that may have implications for therapeutic resistance. The authors concluded that these findings suggested that while CXCR4 inhibition may prove useful in ALL, further study is needed to understand the full effects of targeting the leukemic microenvironment.

Post-Herpetic Neuralgia

Xie and colleagues (2015) stated that varicella-zoster virus (VZV) causes varicella (chicken pox) and establishes latency in ganglia. A re-activation of latent VZV leads to herpes zoster (shingles). Herpes zoster often causes herpetic pain that can last for months or years after the rash has healed. Prolonged herpetic pain is defined as post-herpetic neuralgia (PHN). There is an unmet need to explore novel therapeutic approaches for intractable PHN. Post-mortem studies have shown that VZV induces neuro-inflammation and damage to the ganglia and spinal cord. These pathological changes may be critical factors resulting in PHN. Available evidence suggests that stem cells may alleviate neuropathic pain in animal models through immunomodulatory actions and neuronal repair. Unfortunately, exogenous stem cell transplantation has limited clinical use due to safety concerns, immune rejection, and complications. Pharmacological mobilization of endogenous bone marrow stem cells may overcome these obstacles. The authors stated that plerixafor can stimulate the release of stem
cells from the bone marrow into blood circulation. They proposed a hypothesis that endogenous stem cells mobilized by plerixafor may relieve the symptoms of PHN. If so, it may represent a novel approach for the treatment of intractable PHN.

Sickle Cell Disease

Choi and colleagues (2016) stated that gene therapy for sickle cell disease (SCD) is currently in active trials. Collecting hematopoietic progenitor cells (HPCs) safely and effectively is challenging, however, because G-CSF, the drug used most commonly for mobilization, can cause life-threatening vaso-occlusion in patients with SCD, and bone marrow harvest requires general anesthesia and multiple hip bone punctures. Plerixafor is an inhibitor of the CXCR4 chemokine receptor on HPCs, blocking its binding to SDF-1 (CXCL12) on bone marrow stroma. In support of a clinical trial in patients with SCD of plerixafor mobilization (NCT02193191), these researchers administered plerixafor to sickle cell mice and found that it mobilized HPCs without evidence of concomitant cell activation or brain vaso-occlusion. The authors concluded that these pre-clinical data in sickle cell mice suggested that plerixafor may be safe and effective for HPC mobilization in SCD patients, and supported continuation of a clinical trial in SCD patients studying plerixafor mobilization (NCT02193191) for gene therapy. They noted that use of plerixafor alone in patients with SCD may allow for HPC mobilization for curative gene therapy without the vaso-occlusive side effects seen with G-CSF.

Furthermore, NCCN’s Drugs & Biologics Compendium (2017) does not list SCD as a recommended indication of plerixafor.

Antibody-Mediated Rejection in Lung Transplantation

Hulbert and colleagues (2018) noted that there is increasing recognition of the importance of antibody-mediated rejection (AMR) after lung transplantation. The development of donor-specific antibodies, a key feature of AMR, occurs in approximately 30% of lung transplant recipients and is associated with poor post-transplant outcomes. These investigators highlighted recently developed AMR diagnostic criteria in lung transplantation, potential mechanisms that mediate the development of AMR, and discussed current and emerging treatment strategies for this significant, graft-limiting complication. A major advance is the development of consensus guidelines to precisely define AMR amongst lung transplant. Regimens for the treatment of AMR continue to evolve with varying success reported with regards to antibody clearance and improving clinical outcomes. A multi-modality treatment approach is common, typically involving a combination of intravenous immune globulin, plasmapheresis, rituximab, and bortezomib or carfilzomib. Recent studies suggested several new agents including tocilizumab, belimumab, daratumumab, plerixafor, and C1 esterase inhibitor as potentially novel and effective therapies to
employ in AMR treatment. The authors concluded that despite advancements in the diagnosis of AMR through well-defined consensus guidelines, there is limited evidence to guide treatment. Current data suggested that conventional approaches are of sub-optimal efficacy, but emerging therapeutic agents with diverse biological mechanisms offer promise for improved AMR treatment.

Furthermore, an UpToDate review on “Evaluation and treatment of antibody-mediated lung transplant rejection” (Hachem, 2018) does not mention plerixafor as a therapeutic option.

Glioma

Lee and colleagues (2018) stated that although anti-angiogenic therapy for high-grade glioma (HGG) is promising, responses are not durable. Correlative clinical studies suggested that the SDF-1α/CXCR4 axis may mediate resistance to vascular endothelial growth factor receptor (VEGFR) inhibition. Pre-clinical data have demonstrated that plerixafor could inhibit glioma progression after anti-VEGF pathway inhibition. These researchers conducted a phase-I study to determine the safety of plerixafor and bevacizumab in recurrent HGG. Part 1 enrolled 23 patients with a 3x3 dose escalation design to a maximum tolerated dose (MTD) of plerixafor 320 µg/kg subcutaneously on days 1 to 21 and bevacizumab 10 mg/kg intravenously on days 1 and 15 of each 28-day cycle. Cerebrospinal fluid (CSF) and plasma samples were obtained for pharmacokinetic analyses. Plasma and cellular biomarkers were evaluated before and after treatment. Part 2 enrolled 3 patients and was a surgical study to determine plerixafor's penetration in tumor tissue. In Part 1, no dose-limiting toxicities (DLT) were seen at the MTD of plerixafor + bevacizumab. Treatment was well-tolerated. After plerixafor 320 µg/kg treatment, the average CSF drug concentration was 26.8 ± 19.6 ng/ml. Plerixafor concentration in resected tumor tissue from patients pre-treated with plerixafor was 10 to 12 µg/g. Circulating biomarker data indicated that plerixafor + bevacizumab induced rapid and persistent increases in plasma SDF1α and PIGF. Progression-free survival (PFS) correlated with pre-treatment plasma sMET and sVEGFR1, and overall survival (OS) with the change during treatment in CD34+ progenitor/stem cells and CD8-T cells. The authors concluded that plerixafor + bevacizumab was well-tolerated in HGG patients. Plerixafor distributed to both the CSF and brain tumor tissue, and treatment was associated with biomarker changes consistent with VEGF and CXCR4 inhibition. The clinical value of plerixafor for the treatment of HGG needs to be further investigated.

Malaria
Abiri (2018) noted that death by Plasmodium falciparum, the leading cause of malaria, is going to remain a major obstacle among the infectious diseases. Plasmepsin aspartic proteases are key proteins in the pathogenesis of plasmodium species that break down the hemoglobin (Hb) and exploit it as a source of amino acids. These enzymes are one of the favorite targeting agents for medicinal chemists to design new drugs. Plasmepsin proteins show a "flap" region in their N-terminal domain, predisposing them to a good "filler" drug with an exceptional affinity to this enzyme. Plerixafor (Mozobil), a CXCR4 antagonist with a bicyclam ring, historically discovered as an impurity in a mixture which had anti-HIV properties, is now a FDA-approved drug for mobilizing hematopoietic stem cells in cancer patients. In this hypothesis, these researchers focused on the similarity of the structure of plerixafor and its analogs with heme functional group of Hb, the main substrate of plasmepsin, and also with some other recent azamacrocyclic compounds demonstrating anti-malarial activity, to examine if these compounds are capable of exhibiting anti-malarial activity by inhibiting plasmepsin or not. A preliminary in-silico docking study was used to evaluate this hypothesis and docking results indicated that macrocyclic cyclams and cyclens can reliably act as potent lead drug or central pharmacophore in developing new plasmepsin inhibitors as compared with previously designed plasmepsin II inhibitors.

CPT Codes / HCPCS Codes / ICD-10 Codes

*Information in the [brackets] below has been added for clarification purposes.  Codes requiring a 7th character are represented by "+":*

<table>
<thead>
<tr>
<th>Code</th>
<th>Code Description</th>
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<tr>
<td>Other CPT codes related to the CPB:</td>
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<tr>
<td>38205</td>
<td>Blood-derived hematopoietic progenitor cell harvesting for transplantation, per collection; allogeneic</td>
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<td>38206</td>
<td>Blood-derived hematopoietic progenitor cell harvesting for transplantation, per collection; autologous</td>
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<td>38230</td>
<td>Bone marrow harvesting for transplantation; allogeneic</td>
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<tr>
<td>38232</td>
<td>autologous</td>
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<tr>
<td>38241</td>
<td>Hematopoietic progenitor cell (HPC); autologous transplantation</td>
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<tr>
<td>96372</td>
<td>Therapeutic, prophylactic, or diagnostic injection (specify substance or drug); subcutaneous or intramuscular</td>
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<td>HCPCS codes covered if selection criteria are met:</td>
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<tr>
<td>J2562</td>
<td>Injection, plerixafor, 1 mg [Mozobil]</td>
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<td>Other HCPCS codes related to the CPB:</td>
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<tr>
<td>J1442</td>
<td>Injection, filgrastim (G-CSF), excludes biosimilars, 1 microgram</td>
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<td>J1447</td>
<td>Injection, tbo-filgrastim, 1 microgram [Granix, Neutroval]</td>
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<td>J2505</td>
<td>Injection, pegfilgrastim, 6 mg</td>
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<td>J2820</td>
<td>Injection, sargramostim (GM-CSF), 50 mcg</td>
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<td>Q5110</td>
<td>Injection, filgrastim-aafi, biosimilar, (nivestym), 1 microgram</td>
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<td>Injection, Pegfilgrastim-cbqv, biosimilar, (udenyca), 0.5 mg</td>
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ICD-10 codes covered if selection criteria are met:

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<tr>
<td>C82.00 - C82.99</td>
<td>Other malignant neoplasms of lymphoid and histiocytic tissue</td>
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<td>C84.00 - C84.49</td>
<td>Lymphosarcoma and reticulosarcoma and other specified malignant tumors of lymphatic tissue</td>
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<td>C84.00 - C84.99</td>
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<td>C85.10 - C85.99</td>
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<td>C91.40 - C91.42</td>
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<td>C96.0 - C96.4</td>
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<td>C96.a - C96.9</td>
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<td>C83.00 - C83.99</td>
<td>Malignant immunoproliferative diseases and multiple myeloma and malignant plasma cell neoplasms</td>
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<td>C84.60 - C84.79</td>
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<td>C88.4</td>
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<td>C88.8 - C90.32</td>
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ICD-10 codes not covered for indications listed in the CPB:

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<tbody>
<tr>
<td>B02.21 - B02.29</td>
<td>Zoster with other nervous system involvement</td>
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<tr>
<td>B50.0 - B54</td>
<td>Malaria</td>
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<tr>
<td>C33 - C34</td>
<td>Malignant neoplasm of trachea, bronchus, and lung</td>
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<td>C71.0 - C71.9</td>
<td>Malignant neoplasm of brain.[glioma]</td>
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<tr>
<td>C72.0</td>
<td>Malignant neoplasm of spinal cord [glioma]</td>
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<tr>
<td>C91.00 - C91.02</td>
<td>Acute lymphoblastic leukemia [ALL]</td>
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<tr>
<td>C91.10 - C91.12</td>
<td>Chronic lymphocytic leukemia of B-cell type</td>
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<td>C92.0 - C92.92</td>
<td>Myeloid leukemia</td>
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<td>D57.00 - D57.819</td>
<td>Sickle-cell disorders</td>
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<td>D70.0 - D70.9</td>
<td>Neutropenia[treatment or prophylaxis]</td>
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<td>D84.9</td>
<td>Unspecified immunity deficiency [covered for WHIM syndrome]</td>
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<tr>
<td>Code</td>
<td>Code Description</td>
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<td>N17.0 - N17.9</td>
<td>Acute kidney failure</td>
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<td>Congenital falciparum malaria</td>
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<td>N97.4</td>
<td>Other congenital malaria</td>
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<tr>
<td>T86.810</td>
<td>Lung transplant rejection. [antibody-mediated rejection]</td>
</tr>
</tbody>
</table>

The above policy is based on the following references:


42. Bonilla FA. Combined immunodeficiencies. UpToDate [serial online]. Waltham, MA: UpToDate; reviewed July 2014.


Amendment to
Aetna Clinical Policy Bulletin Number: 0779
Plerixafor (Mozobil) Injection

Plerixafor used for mobilization of donor hematopoietic progenitor cells in the allogeneic setting is considered medically necessary in the Pennsylvania Medical Assistance plan.

Concomitant use of plerixafor injection with a granulocyte colony stimulating factor may be approved under the Pennsylvania Medical Assistance plan.