Mozobil (plerixafor)

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Policy
Blue Cross and Blue Shield of Kansas City (Blue KC) will provide coverage for Mozobil when it is determined to be medically necessary because the following criteria have been met.

When Policy Topic is covered
Plerixafor injection is considered medically necessary in combination with granulocyte colony stimulating factor (G-CSF) to mobilize autologous hematopoietic stem cells in adults (greater than or equal to 18 years of age) when the following criteria are met (A, B and C):

A. The individual has a diagnosis of (Hodgkin or non-Hodgkin) lymphoma, multiple myeloma or testicular carcinoma; and

B. After stem cell mobilization and collection, a subsequent autologous hematopoietic stem cell transplant is anticipated; and

C. A maximum of up to four consecutive doses of plerixafor injections per cycle for up to 2 cycles.

DOSING:
Adult FDA-approved uses: see FDA labeling
Pediatric: Safety and effectiveness have not been established
Drug must be sourced from an approved specialty infusion provider.

When Policy Topic is not covered
Plerixafor injection is considered investigational for all other indications, including but not limited to the following:

A. As a mobilizing agent for an allogeneic stem cell donor;

B. As a mobilizer of leukemic cells;

C. As a component of a conditioning regimen prior to an allogeneic hematopoietic stem cell transplant.

Considerations
Mozobil requires prior authorization through the Clinical Pharmacy Department.

This Blue Cross and Blue Shield of Kansas City policy Statement was developed using available resources such as, but not limited to: Food and Drug Administration (FDA) approvals, Facts and Comparisons, National specialty guidelines, Local medical policies of other health plans, Medicare (CMS), Local providers.
**Description of Procedure or Service**

**Background**

Collecting sufficient CD34+ autologous stem cells could enable eligible individuals with specific malignancies to proceed to autologous HSCT.

Plerixafor injection is recommended at 0.24 mg/kg of body weight and is initiated after the individual has received G-CSF once daily for 4 days. The SQ injection is typically given approximately 11 hours prior to initiation of each session of apheresis for up to 4 consecutive days (Product Information Label, 2013).

Plerixafor is primarily excreted through the kidneys and clinical studies showed a correlation between renal function and plerixafor clearance. Recommended dosing is reduced by one-third to 0.16 mg/kg for individuals with moderate to severe renal impairment, defined as creatinine clearance (CL_{CR}) less than or equal to 50 mL/min. For maximum dosing, the Product Information Label (2013) notes:

> There is limited experience with the 0.24 mg/kg dose of plerixafor in patients weighing above 160 kg. Therefore the dose should not exceed that of a 160 kg patient, (i.e., 40 mg/day if the estimated creatinine clearance (CL_{CR}) is > 50 mL/min and 27 mg/day if CL_{CR} is ≤ 50 mL/min).

**Adverse Events and Warnings:**

The Product Information Label (2013) for plerixafor includes the following warnings and precautions:

*Anaphylactic shock and Hypersensitivity reactions*

Serious hypersensitivity reactions, including anaphylactic-type reactions, some of which have been life-threatening with clinically significant hypotension and shock, have occurred in patients receiving Mozobil. Observe patients for signs and symptoms of hypersensitivity during and after Mozobil administration for at least 30 minutes and until clinically stable following completion of each administration. Only administer Mozobil when personnel and therapies are immediately available for the treatment of anaphylaxis and other hypersensitivity reactions.

*Tumor Cell Mobilization in Leukemia Patients*

Mozobil may cause mobilization of leukemic cells and subsequent contamination of the apheresis product. Therefore, Mozobil is not intended for HSC mobilization and harvest in patients with leukemia.

*Leukocytosis*

Administration of Mozobil in conjunction with G-CSF increases circulating leukocytes as well as HSC populations. Monitor white blood cell counts during Mozobil use.

*Thrombocytopenia*

Thrombocytopenia has been observed in patients receiving Mozobil. Monitor platelet counts in all patients who receive Mozobil and then undergo apheresis.

*Potential for Tumor Cell Mobilization*

When Mozobil is used in combination with G-CSF for HSC mobilization, 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.

*Splenic Enlargement and Potential for Rupture*

Higher absolute and relative spleen weights associated with extramedullary hematopoiesis were observed following prolonged (2 to 4 weeks) daily plerixafor SC administration in rats at doses approximately 4-fold higher than the recommended human dose based on body surface area. The effect of Mozobil on spleen size in patients was not specifically evaluated in clinical studies. Evaluate individuals receiving Mozobil in combination with G-CSF who report left upper abdominal pain and/or scapular or shoulder pain for splenic integrity.
**Embryo-fetal Toxicity**

Mozobil may cause fetal harm when administered to a pregnant woman. Plerixafor is teratogenic in animals. There are no adequate and well-controlled studies in pregnant women using Mozobil. Advise women of childbearing potential to avoid becoming pregnant while receiving treatment with Mozobil. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus.

**Rationale**

Plerixafor injection is a hematopoietic stem cell mobilizer that is given SQ with granulocyte colony stimulating factor (G-CSF). Also known as AMD3100 in early clinical studies, plerixafor injection is the first agent in a class of small molecules that reversibly inhibits the CXCR4 chemokine receptor and blocks binding of the stromal cell-derived factor-1α (SDF-1α). CXCR4 and SDF-1α play a role in homing of human HSCs to the bone marrow (DiPersio, 2009b; Product Information Label, 2013). HSC binding is inhibited with plerixafor injection which releases (mobilizes) CD34+ stem cells from the marrow into the bloodstream where they can be collected through apheresis for subsequent autologous HSCT to treat individuals with multiple myeloma (MM) or non-Hodgkin lymphoma (NHL) (Giralt, 2009).

The U.S. Food and Drug Administration (FDA) approved Mozobil (plerixafor injection) in 2008 to mobilize autologous HSCs in individuals with MM and NHL who were anticipating an autologous HSCT. There were two phase III randomized, placebo-controlled trials that studied the use of plerixafor injection in adults with NHL and MM. In both trials, the use of plerixafor injection resulted in a statistically significant increase in the number of CD34+ cells collected and it was accomplished in fewer number of apheresis sessions compared to the placebo groups (DiPersio, 2009a, 2009b; Product Information Label, 2015).

DiPersio (2009a) reported 59.3% of 150 individuals assigned to the plerixafor injection group achieved the primary endpoint by collecting $\geq 5 \times 10^6$ CD34+ cells/kg in $\leq 4$ apheresis days versus 19% of individuals in the placebo group who achieved the primary endpoint ($p<0.001$). The time to collecting $\geq 5 \times 10^6$ CD34+ cells was significantly shorter in the plerixafor injection group compared to the placebo group ($p<0.001$). The median number of CD34+ cells collected for the plerixafor injection group was 5.69 X $10^6$ cells/kg (range, 0.03 to 29.22) versus 1.98 X $10^6$ cells/kg (range, 0.06 to 15.00) for the placebo group. In the NHL trial, 90% (135/150 participants) in the plerixafor treatment cohort and 55% (82/148 participants) in the placebo cohort had an HSCT after mobilization. There was no significant difference in the median time to engraftment between the cohorts. Participants who failed to collect sufficient CD34+ cells ($\geq 0.8 \times 10^6$ CD34+ cells/kg) after 2 apheresis days or $\geq 2 \times 10^6$ CD34+ cells/kg in $\leq 4$ apheresis days were eligible to enter an open-label rescue procedure. The rescue procedure with G-CSF and plerixafor 240 µg/kg was initiated after a minimum 7-day rest period. The rescue group consisted of 52 placebo-treated individuals and 10 plerixafor-treated individuals. Thirty-seven (59.7%) of rescue participants were able to collect sufficient CD34+ cells in $\leq 4$ apheresis days with the plerixafor rescue regimen. A total of 52 (84%) participants in the rescue cohort proceeded to transplantation. Fifty-three (85.5%) of 62 rescue participants were alive at 12 months of follow-up. The authors concluded plerixafor and G-CSF resulted in significantly higher proportions of individuals who achieved "Optimal CD34+ cell target for transplantation in fewer apheresis days compared with C-CSF alone."

The primary endpoint for the phase III MM trial (DiPersio, 2009b) was the percentage of individuals who collected $\geq 6 \times 10^6$ CD34+cells/kg in $\leq 2$ apheresis. The group treated with plerixafor and G-CSF had significantly more individuals who met the primary endpoint, with 71.6% (106/148 participants) compared to the placebo group 34.4% (53/154 participants) ($p<0.001$). Fifty-four percent of the individuals in the treatment group achieved the targeted collection cell dose in 1 day of apheresis. Fifty-six percent of the placebo group required four apheresis sessions to achieve the targeted cell dose.

The two phase III RCTs reported similar overall incidence of adverse events with most being mild to moderate in severity. The most common adverse event for plerixafor injection was gastrointestinal disorders and reactions at the injection site.
Additional published literature support the use of plerixafor and G-CSF mobilization to collect sufficient CD34+ cells for autologous HSCT for individuals with Hodgkin lymphoma and testicular cancer (Calandra, 2008; Cashen, 2008; De Blasio, 2013; Shaughnessy, 2013).

The product information label (2013) notes tumor cells may be released during mobilization with plerixafor injection and G-CSF. The label warns against utilizing plerixafor injection in individuals with leukemia. Additionally, the label states "The safety and efficacy of Mozobil in pediatric patients has not been established in controlled clinical studies."

Chambon and colleagues (2013) reported results from a phase IIA study of 1-day mobilization of autologous stem cells with plerixafor injection in children (age 0-18 years) with solid tumors. A single dose of 240 µg/kg of plerixafor injection was given at zero hour (h0) which was scheduled at 8 a.m. Circulating CD34+ cells were monitored at h0 and then hourly from h3 thru h11. Apheresis was initiated at h5 if CD34+ cells were at least 10 X 10^6/L. If the threshold was not met, apheresis was postponed and if by h10, the threshold was not met, the child was considered a non-responder. The primary endpoint was the percentage of children with optimal mobilization of at least 5 X 10^6 CD34+/kg during the single apheresis with less than three blood volumes processed (BVP). All 5 children met the CD34+ threshold after the plerixafor injection and proceeded to apheresis. However, the median number of CD34+ cells/child collected was 1.62 X 10^6 (0.47-3.5) and none of the participants met the criterion of 5 X 10^6 CD34+ cells/kg during the standard apheresis. Therefore, the stopping criteria for the trial were met. The authors noted this was the first study of single-agent plerixafor injection as a mobilizing agent in children and the:

Data on the use of plerixafor in children remains scarce... CD34+ blood cell content decreased very early after the start of apheresis and collection efficiency was very poor in every child. The data suggest that mobilization was no longer sustained after h5. The use of plerixafor in children should be optimized by further studies addressing dose-effect and Plerixafor-induced mobilization kinetics during hematological recovery.

According to the National Comprehensive Cancer Network® (NCCN) Drugs & Biologic Compendium™ plerixafor (2016) is given the following recommendations for use in hematopoietic cell transplant for:

- Mobilization of hematopoietic progenitor cells in combination with filgrastim, filgrastim-sndz, or tbo-filgrastim in the autologous setting in select patients with non-Hodgkin's lymphoma or multiple myeloma (Category 2A);
- Mobilization of donor hematopoietic progenitor cells in the allogeneic setting (Category 2B).

The NCCN Clinical Practice Guidelines in Oncology™ for multiple myeloma provide the following:

There are data indicating successful stem cell harvest with the addition of plerixafor when conventional mobilization methods fail (NCCN, 2016).

There are multiple ongoing clinical trials investigating the use of plerixafor injection in combination with other drugs and as a component of treatment regimens for other malignancies, such as breast cancer, leukemia and myelodysplastic syndromes. Additional trials are investigating the use of plerixafor in various dosing schedules, including use beyond the FDA approved use of 4 consecutive days. At the present time, the data on safety, efficacy and long-term effects of plerixafor as a treatment of other malignancies have not been published from prospective clinical trials sufficiently powered to definitively determine that plerixafor injection is as beneficial as established mobilization therapy.

There is an ongoing phase I/II randomized trial that is investigating plerixafor injection as part of a mobilization regimen for children with solid tumors. The estimated completion date for the trial is 2017-2018. There is a paucity of trials investigating the use of plerixafor in the pediatric population.

References:


Government Agency, Medical Society, and Other Authoritative Publications:


Billing Coding/Physician Documentation Information

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State and Federal mandates and health plan contract language, including specific provisions/exclusions, take precedence over Medical Policy and must be considered first in determining eligibility for coverage. The medical policies contained herein are for informational purposes. The medical policies do not constitute medical advice or medical care. Treating health care providers are independent contractors and are neither employees nor agents Blue KC and are solely responsible for diagnosis, treatment and medical advice. No part of this publication may be reproduced, stored in a retrieval system or transmitted, in any form or by any means, electronic, photocopying, or otherwise, without permission from Blue KC.