Effective for dates of service November 1, 2018, and after, refer to Palmetto Article A56141.

BlueCross BlueShield of Alabama

"Unless otherwise noted, coverage for specific indications is effective the date of the FDA approval of that indication."
"Please check Approved by Governing Bodies for FDA approval date."

Name of Blue Advantage Policy:
Empliciti (Elotuzumab)

Policy #:	671	Effective Date:	June 30, 2017
Category:	Pharmacology	Latest Review Date:	May 2017

Background:
Blue Advantage *medical policy does not conflict with Local Coverage Determinations (LCDs), Local Medical Review Policies (LMRPs) or National Coverage Determinations (NCDs) or with coverage provisions in Medicare manuals, instructions or operational policy letters. In order to be covered by Blue Advantage the service shall be reasonable and necessary under Title XVIII of the Social Security Act, Section 1862(a)(1)(A). The service is considered reasonable and necessary if it is determined that the service is:*

1. *Safe and effective;*
2. *Not experimental or investigational*;*
3. *Appropriate, including duration and frequency that is considered appropriate for the service, in terms of whether it is:*
   - *Furnished in accordance with accepted standards of medical practice for the diagnosis or treatment of the patient's condition or to improve the function of a malformed body member;*
   - *Furnished in a setting appropriate to the patient's medical needs and condition;*
   - *Ordered and furnished by qualified personnel;*
   - *One that meets, but does not exceed, the patient's medical need; and*
   - *At least as beneficial as an existing and available medically appropriate alternative.*

Routine costs of qualifying clinical trial services with dates of service on or after September 19, 2000 which meet the requirements of the Clinical Trials NCD are considered reasonable and necessary by Medicare. Providers should bill* ***Original Medicare* *for covered services that are related to* ***clinical trials*** *that meet Medicare requirements (Refer to Medicare National Coverage*

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Determinations Manual, Chapter 1, Section 310 and Medicare Claims Processing Manual Chapter 32, Sections 69.0-69.11).

Description of Procedure or Service:

Empliciti™ (elotuzumab) is a humanized IgG1 monoclonal antibody that targets the signaling lymphocytic active molecule (SLAM) family member F7 (SLAMF7) protein which is expressed on myeloma cells and natural killer cells. Elotuzumab directly activates natural killer cells through both the SLAMF7 pathway and Fc receptors .Elotuzumab also targets SLAMF7 on myeloma cells and facilitates the interaction with natural killer cells to mediate the killing of myeloma cells through antibody-dependent cellular cytotoxicity.

Policy:

Effective for dates of service on or after November 1, 2018 refer to Palmetto Article A56141

Effective for dates of service on and after June 30, 2017 and prior to November 1, 2018:
Blue Advantage will treat **Empliciti™ (elotuzumab)** as a **covered benefit** for the treatment of individuals with **multiple myeloma**, including plasma-cell leukemia, when all of the following criteria are met:

1. When used in combination with lenalidomide and dexamethasone for relapsed or refractory disease;**and**
2. Prior lines of therapy did not include elotuzumab.

Blue Advantage does not approve or deny procedures, services, testing, or equipment for our members. Our decisions concern coverage only. The decision of whether or not to have a certain test, treatment or procedure is one made between the physician and his/her patient. Blue Advantage administers benefits based on the members' contract and medical policies. Physicians should always exercise their best medical judgment in providing the care they feel is most appropriate for their patients. Needed care should not be delayed or refused because of a coverage determination.

Key Points:

Multiple myeloma is a systemic malignancy of plasma cells that accumulate in the bone marrow, leading to destruction of bone and failure of the bone marrow. Multiple myeloma is highly treatable but rarely curable. However, when it presents as a solitary plasmacytoma of bone or as an extramedullary plasmacytoma it is potentially curable. Multiple myeloma accounts for approximately 10% of all hematologic cancers. The American Cancer Society has estimated 30,280 new cases of multiple myeloma will be diagnosed in the United States in 2017, with an estimated 12,590 deaths. The stage of the disease at presentation is a strong determinant of survival, but has little influence on the choice of therapy since almost all individuals (except for

those with solitary bone tumors or extramedullary plasmacytomas) have generalized disease. Multiple myeloma affects mostly older individuals around 62 years of age. The age and general health of the individual, prior therapy and the presence of complications of the disease influence treatment selection. The median survival in the pre-chemotherapy era was about 7 months. Multiple myeloma has demonstrated chemosensitivity to initial treatment or treatment for relapsed disease. Improvements in newer treatments have resulted in an increase in 5-year survival which is currently around 50%.

Richardson and colleagues reported final phase II results of a randomized, multi-center, open-label, dose-escalation study of elotuzumab in combination with lenalidomide and dexamethasone. Between January 2010, and December 2010, a total of 73 participants were recruited and randomly assigned to elotuzumab (36 to 10 mg/kg, 37 to 20 mg/kg). Subjects were at least 18 years of age with relapsed multiple myeloma, Eastern Cooperative Oncology Group (ECOG) performance status of 0-2, and one to three previous therapies, excluding lenalidomide. Treatment consisted of 28 day cycles given until disease progression or unacceptable toxic side effects. At data cutoff in January 2014, 13 subjects continued on treatment (6 subjects on 10 mg/kg and 7 subjects on 20 mg/kg). A total of 61 subjects (84%) achieved an objective response (33 [92%] with 10 mg/kg, 28 [76%] with 20 mg/kg). Thirty-one subjects (42%) had a very good partial response (17 [47%] with 10 mg/kg, 14 [38%] with 20 mg/kg); and 20 (27%) a partial response (10 [28%] with 10 mg/kg, 10 [27%] with 20 mg/kg). Those most common adverse events were diarrhea, muscle spasms and fatigue. Grade 3–4 events occurred in 57 (78%), the most common of which were lymphopenia and neutropenia. Three deaths occurred; however, none were related to the study drugs. The authors concluded that elotuzumab combined with lenalidomide and dexamethasone in subjects with relapsed multiple myeloma showed acceptable safety and efficacy that seemed better than that previously noted with lenalidomide and dexamethasone only.

A single randomized phase III, controlled, open-label, multi-center trial (ELOQUENT-2) evaluated the effectiveness and safety of elotuzumab in individuals with relapsed or refractory multiple myeloma who had disease progression after one to three previous therapies. The median number of prior therapies was two, including stem cell transplant (55%), bortezomib (70%), melphalen (65%), thalidomide (48%), and lenalidomide (6%). Prior lines of therapy did not include elotuzumab. Previous treatment with lenalidomide was allowed, subject to restrictions. All subjects had a creatinine clearance of 30 ml per minute or higher. Coprimary end points were progression-free survival (PFS) and the overall response rate (partial response or better). A total of 646 subjects were randomized to receive elotuzumab (10 mg/kg) in combination with lenalidomide/ dexamethasone (E-Ld) (n=321) or lenalidomide/ dexamethasone alone (Ld) (n=325). The final analysis showed a statistically significant improvement in median PFS time of 4.5 months between Arm E-Ld (19.4 months) and Arm Ld (14.9 months) and overall response rates of 78.5 and 65.5%, respectively. PFS increased with increasing elotuzumab exposure. The most common adverse reactions were fatigue, diarrhea, pyrexia, constipation, cough, peripheral neuropathy, nasopharyngitis, upper respiratory tract infection, decreased appetite, and pneumonia. At the approved dose, 10% of subjects had grade 3 or lower infusion reactions and 1% discontinued elotuzumab due to infusion reactions. Individuals on elotuzumab had increased infections relative to those in the active control group. The rates of grade three or higher adverse

events or adverse events leading to discontinuations or deaths did not increase with increasing elotuzumab concentration.

The National Comprehensive Cancer Network (NCCN) Multiple Myeloma Clinical Practice Guideline (V3.2017) and the NCCN Drugs and Biologics Compendium indicate that elotuzumab is recommended in combination with lenalidomide and dexamethasone for the treatment of individuals with multiple myeloma who have received one to three prior therapies (category 1 recommendation).

Key Words:

Empliciti, elotuzumab, multiple myeloma

Approved by Governing Bodies:

On November 30, 2015, the U.S. Food and Drug Administration (FDA) granted approval to elotuzumab (Empliciti) injection in combination with lenalidomide and dexamethasone for the treatment of individuals with multiple myeloma who have received one to three prior therapies.

Benefit Application:

Coverage is subject to member's specific benefits. Group specific policy will supersede this policy when applicable.

Current Coding:

CPT Codes:

J9176	Injection, elotuzumab 1 mg

References:

1. EMPLICITI™ (elotuzumab). Highlights of prescribing information. Bristol-Myers Squibb Company, Princeton, NJ. Revised November 2015. Available at: www.packageinserts.bms/pi/pi_empliciti.pdf.
2. Lonial S, Dimopoulos M, Palumbo A, et al. Elotuzumab therapy for relapsed or refractory multiple myeloma. N Engl J Med. 2015; 373(7):621-631.
3. National Comprehensive Cancer Network®. NCCN Drugs & Biologic Compendium™ (electronic version). Available at: www.nccn.org.
4. NCCN Clinical Practice Guidelines in Oncology®. 2016 National Comprehensive Cancer Network, Inc. Multiple Myeloma (V.3.2017). Available at: www.nccn.org/index.asp.
5. Richardson PG, Jagannath S, Moreau P, et al; 1703 study investigators. Elotuzumab in combination with lenalidomide and dexamethasone in patients with relapsed multiple myeloma: final phase 2 results from the randomised, open-label, phase 1b-2 dose-escalation study. Lancet Haematol. 2015; 2(12):e516-527.

Policy History:

Adopted for Blue Advantage, June 2017
Available for comment May 15, 2017 through June 29, 2017
Medical Policy Group, November 2018

This medical policy is not an authorization, certification, explanation of benefits, or a contract. Eligibility and benefits are determined on a case-by-case basis according to the terms of the member's plan in effect as of the date services are rendered. All medical policies are based on (i) research of current medical literature and (ii) review of common medical practices in the treatment and diagnosis of disease as of the date hereof. Physicians and other providers are solely responsible for all aspects of medical care and treatment, including the type, quality, and levels of care and treatment.

This policy is intended to be used for adjudication of claims (including pre-admission certification, pre-determinations, and pre-procedure review) in Blue Cross and Blue Shield's administration of plan contracts.