09-J2000-50

Original Effective Date: 03/15/16

Reviewed: 06/12/19

Revised: 07/15/19

Subject: Elotuzumab (Empliciti®) Injection

THIS MEDICAL COVERAGE GUIDELINE IS NOT AN AUTHORIZATION, CERTIFICATION, EXPLANATION OF BENEFITS, OR A GUARANTEE OF PAYMENT, NOR DOES IT SUBSTITUTE FOR OR CONSTITUTE MEDICAL ADVICE. ALL MEDICAL DECISIONS ARE SOLELY THE RESPONSIBILITY OF THE PATIENT AND PHYSICIAN. BENEFITS ARE DETERMINED BY THE GROUP CONTRACT, MEMBER BENEFIT BOOKLET, AND/OR INDIVIDUAL SUBSCRIBER CERTIFICATE IN EFFECT AT THE TIME SERVICES WERE RENDERED. THIS MEDICAL COVERAGE GUIDELINE APPLIES TO ALL LINES OF BUSINESS UNLESS OTHERWISE NOTED IN THE PROGRAM EXCEPTIONS SECTION.

DESCRIPTION:

Elotuzumab (Empliciti) is a humanized IgG1 monoclonal antibody that specifically binds to the Signaling Lymphocytic Activation Molecule Family member 7 (SLAMF7) protein, a cell surface glycoprotein receptor present on myeloma cells and natural killer (NK) cells. Elotuzumab directly activates natural killer cells and facilitates the killing of myeloma cells through antibody-dependent cellular cytotoxicity. Elotuzumab was approved by the FDA in November 2015 for the treatment of patients with multiple myeloma (MM), in combination with lenalidomide and dexamethasone, who have received one to three prior therapies. Elotuzumab was previously granted orphan drug designation by the FDA in September 2011 for the treatment of MM. In November 2018, the FDA approved an additional indication of “in combination with pomalidomide and dexamethasone for the treatment of adult patients with multiple myeloma who have received at least two prior therapies including lenalidomide and a proteasome inhibitor.”

The efficacy and safety of elotuzumab in combination with lenalidomide and dexamethasone, leading to FDA-approval, were evaluated in a multicenter, randomized, open-label, phase III trial (n = 646; the ELOQUENT-2 trial) in patients with MM who had received one to three prior therapies. The median number of prior therapies was two (range of 1 to 4). Thirty-five percent (35%) of patients were refractory (progression during or within 60 days of last therapy) and 65% were relapsed. Prior therapies included stem cell transplant (55%), bortezomib (70%), melphalan (65%), thalidomide (48%), and lenalidomide (6%). During an interim analysis, at a median follow-up time of 24.5 months, the median progression-free survival (PFS) time was significantly improved with elotuzumab plus lenalidomide and dexamethasone (median duration of therapy, 17 months) vs. lenalidomide and dexamethasone alone (19.4 months vs. 14.9 months; hazard ratio = 0.7; 95% CI, 0.57 to 0.85). Progression free survival rates were 68% vs 57% at 1 year and 41% vs 27% at 2 years. Additionally, a significant improvement in the overall response rate was observed with elotuzumab (79% vs 66%). In a subset analysis of extended 3-year follow-up, median

duration of response reported with the 3-drug combination was 20.3 months vs. 16.6 months with lenalidomide + dexamethasone.

The National Comprehensive Cancer Network (NCCN) Guidelines for MM (Version 2.2019) list elotuzumab triplet therapy (elotuzumab + lenalidomide + dexamethasone) as a category 1 recommendation under "Preferred Regimens" for the treatment of previously treated MM. Two footnotes are included stating, "indicated in combination with lenalidomide and dexamethasone for the treatment of patients who have received one to three prior therapies (elotuzumab-specific footnote), and "clinical trials with these regimens primarily included patients who were lenalidomide-naïve or with lenalidomide-sensitive MM." There are numerous other category 1 preferred regimens listed by NCCN. The triplet therapy of elotuzumab + bortezomib + dexamethasone is listed as a category 2A recommendation under "Other Recommended Regimens" for the treatment of previously treated MM. The triplet therapy of elotuzumab + pomalidomide + dexamethasone is listed as a category 2A recommendation under "Other Recommended Regimens" for the treatment of previously treated MM. A footnote is included stating, "Indicated for the treatment of patients who have received at least two prior therapies including an immunomodulatory agent and a proteasome inhibitor."

POSITION STATEMENT:

Initiation of elotuzumab (Empliciti) **meets the definition of medical necessity** when **EITHER** of the following criteria are met ("1" or "2"):

1. The member has a diagnosis of relapsed or refractory multiple myeloma (MM), and **ALL** of the following ("a" to "d"):
    a. **EITHER** of the following ("i" or "ii"):
        i. **BOTH** of the following ("1" and "2"):
            1. Elotuzumab will be used as triplet therapy in combination with **BOTH** pomalidomide (Pomalyst) **AND** dexamethasone for treatment of the member's MM
            2. Member has received at least **TWO** prior therapies including an immunomodulatory agent [i.e., lenalidomide (Revlimid) or thalidomide (Thalomid)] **AND** a proteasome inhibitor [i.e., bortezomib, ixazomib (Ninlaro), or carfilzomib (Kyprolis)]
        ii. **BOTH** of the following ("1" and "2"):
            1. **EITHER** of the following ("a" or "b"):
                a. Elotuzumab will be used as triplet therapy in combination with **BOTH** lenalidomide (Revlimid) **AND** dexamethasone for treatment of the member's MM
                b. Elotuzumab will be used as triplet therapy in combination with **BOTH** bortezomib **AND** dexamethasone for treatment of the member's MM
            2. The member has previously received at least **ONE** prior line of therapy for their MM
    b. The member's MM was not previously refractory (i.e., disease progression on treatment or progression within 60 days after the last dose of a given therapy) to a elotuzumab-containing treatment regimen
    c. The dosage of elotuzumab does not exceed the following based on the regimen used:
        i. Elotuzumab + lenalidomide + dexamethasone regimen:
            1. Cycles 1 and 2 (4-week cycle): 10 mg/kg every week (e.g., day 1, 8, 15, and 22 of cycle)
            2. Cycle 3 until disease progression (4-week cycle): 10 mg/kg every 2 weeks (e.g., day 1 and 15 of cycle)

ii. Elotuzumab + bortezomib + dexamethasone regimen:

1. Cycles 1 and 2 (3-week cycle): 10 mg/kg every week (e.g., day 1, 8, and 15 of cycle)
2. Cycles 3 to 8 (3-week cycle): 10 mg/kg twice every cycle (e.g., day 1 and 11)
3. Cycle 9 until disease progression (4-week cycle): 10 mg/kg every 2 weeks (e.g., day 1 and 15 of cycle)

iii. Elotuzumab + pomalidomide + dexamethasone regimen:

1. Cycles 1 and 2 (4-week cycle): 10 mg/kg every week (e.g., day 1, 8, 15, and 22 of cycle)
2. Cycle 3 until disease progression (4-week cycle): 20 mg/kg every 4 weeks

d. The member's baseline (i.e., within 90 days prior to initiating treatment with elotuzumab) serum monoclonal protein (M-protein) level **AND** serum free light chain (SFLC) levels (kappa and lambda), as detected by serum protein electrophoresis (SPEP) and serum free light chain assay (SFLCA) respectively, is provided

2. Member has another FDA-approved or NCCN-supported diagnosis (not previously listed above), and **BOTH** of the following are met ("a" and "b"):

a. **EITHER** of the following ("i" or "ii"):

i. Member is diagnosed with a condition that is consistent with an indication listed in the product's FDA-approved prescribing information (or package insert) AND member meets any additional requirements listed in the "Indications and Usage" section of the FDA-approved prescribing information (or package insert)

ii. Indication **AND** usage is recognized in NCCN Drugs and Biologics Compendium as a Category 1 or 2A recommendation

b. The dosage of elotuzumab does not exceed the maximum recommended in the FDA-approved prescribing information or the maximum recommended by the applicable NCCN guidelines for the diagnosis

Approval duration: 6 months

Continuation of elotuzumab (Empliciti) **meets the definition of medical necessity** when **BOTH** of the following criteria are met ("1" and "2"):

1. An authorization or reauthorization for elotuzumab has been previously approved by Florida Blue or another health plan in the past 2 years for the treatment of multiple myeloma, or other FDA-approved or NCCN-supported diagnosis; **OR** the member previously met **ALL** indication-specific initiation criteria
2. **EITHER** of the following based on the indication for use ("a" or "b"):

a. Multiple myeloma, and **ALL** of the following ("i", "ii", and "iii"):

i. Elotuzumab is being used in combination with **ANY** of the following ("1", "2", or "3"):

1. lenalidomide + dexamethasone
2. bortezomib + dexamethasone
3. pomalidomide + dexamethasone

ii. The member's dosage of elotuzumab does not exceed the following based on the regimen used:

1. Elotuzumab + lenalidomide + dexamethasone regimen:

a. Cycles 1 and 2 (4-week cycle): 10 mg/kg every week (e.g., day 1, 8, 15, and 22 of cycle)

b. Cycle 3 until disease progression (4-week cycle): 10 mg/kg every 2 weeks (e.g., day 1 and 15 of cycle)

2. Elotuzumab + bortezomib + dexamethasone regimen:

a. Cycles 1 and 2 (3-week cycle): 10 mg/kg every week (e.g., day 1, 8, and 15 of cycle)

b. Cycles 3 to 8 (3-week cycle): 10 mg/kg twice every cycle (e.g., day 1 and 11)

c. Cycle 9 until disease progression (4-week cycle): 10 mg/kg every 2 weeks (e.g., day 1 and 15 of cycle)

3. Elotuzumab + pomalidomide + dexamethasone regimen:

a. Cycles 1 and 2 (4-week cycle): 10 mg/kg every week (e.g., day 1, 8, 15, and 22 of cycle)

b. Cycle 3 until disease progression (4-week cycle): 20 mg/kg every 4 weeks

iii. Member meets **EITHER** of the following ("1" or "2"):

1. If less than 18 months of treatment - a serum M-protein value decrease of 25% or more* compared to baseline, or M-protein is undetectable; **AND** no increase in the size or number of lytic bone lesions after at least two cycles of treatment with elotuzumab[#]

2. 18 months or more of treatment - provider attestation that the member has not had disease progression during elotuzumab treatment

**Elotuzumab can interfere with assays used to monitor M-protein. If a 25% reduction is not achieved or if the M-protein was undetectable by SPEP at baseline, and a baseline SFLC level is available, a decrease of 25% or more in the difference between the light chain produced by the myeloma cells (lambda or kappa) and the other light chain must be achieved*

*#An exception is permitted if a baseline M-protein level **AND** SFLC level are unavailable. In these cases the physician may provide an attestation of a beneficial clinical response which must include no increase in the size or number of lytic bone lesions.*

b. Other FDA-approved or NCCN-supported diagnosis, and **ALL** of the following ("i", "ii", and "iii"):

i. The dosage of elotuzumab does not exceed the maximum recommended in the FDA-approved prescribing information or the maximum recommended by the applicable NCCN guidelines for the diagnosis

ii. Elotuzumab is used in a treatment regimen in accordance with the FDA-approved prescribing information or applicable NCCN guideline recommendation for the diagnosis

iii. The member has had a beneficial response to treatment with elotuzumab

Approval duration: 1 year

DOSAGE/ADMINISTRATION:

THIS INFORMATION IS PROVIDED FOR INFORMATIONAL PURPOSES ONLY AND SHOULD NOT BE USED AS A SOURCE FOR MAKING PRESCRIBING OR OTHER MEDICAL DETERMINATIONS. PROVIDERS SHOULD REFER TO THE MANUFACTURER'S FULL PRESCRIBING INFORMATION FOR DOSAGE GUIDELINES AND OTHER INFORMATION RELATED TO THIS MEDICATION BEFORE MAKING ANY CLINICAL DECISIONS REGARDING ITS USAGE.

FDA-approved

- Elotuzumab is indicated in combination with lenalidomide and dexamethasone for the treatment of patients with multiple myeloma who have received one to three prior therapies.
    - The recommended dosage is 10 mg/kg IV once weekly on 28-day cycles 1 and 2 (on days 1, 8, 15, and 22), then 10 mg/kg every 2 weeks (on days 1 and 15) thereafter until disease progression or unacceptable toxicity.
    - Administer in combination with lenalidomide 25 mg orally daily on days 1 through 21 and dexamethasone 28 mg orally (taken 3 to 24 hours prior to elotuzumab) on days 1, 8, 15, and 22 on cycles 1 and 2 and on days 1 and 15 of subsequent cycles; give dexamethasone 40 mg orally on days 8 and 22 of cycles 3 and beyond.
- Elotuzumab is indicated in combination with pomalidomide and dexamethasone for the treatment of adult patients with multiple myeloma who have received at least two prior therapies including lenalidomide and a proteasome inhibitor.
    - The recommended dosage is 10 mg/kg IV once weekly on 28-day cycles 1 and 2 (on days 1, 8, 15, and 22), then 20 mg/kg every 4weeks thereafter until disease progression or unacceptable toxicity.
    - Administer in combination with pomalidomide 4 mg orally daily on days 1 through 21 and dexamethasone at a dose of 28 mg orally (if 75 years of age or less) or 8 mg orally (if over 75 years of age) (taken 3 to 24 hours prior to elotuzumab) on days 1, 8, 15, and 22 on cycles 1 and 2 and on day 1 of subsequent cycles; give dexamethasone at a dose of 40 mg orally (if 75 years of age or less) or 20 mg orally (if over 75 years of age) on days 8, 15 and 22 of cycles 3 and beyond.
- Initial infusion rates differ for first, second, and subsequent infusions. The initial infusion rate is 0.5 mL/minute and the maximum infusion rate is 5 mL/minute. Elotuzumab should be given with an infusion set and a sterile, non-pyrogenic, low-protein-binding filter (with a pore size of 0.2 to 1.2 micrometer) using an automated infusion pump. See the package insert for additional information.
- Administer the following premedications 45 to 90 minutes prior to each elotuzumab infusion: acetaminophen 650 to 1,000 mg PO, diphenhydramine 25 to 50 mg PO or IV (or equivalent), ranitidine 50 mg IV or 150 mg PO (or equivalent), and dexamethasone 8 mg IV.
- Hold elotuzumab if a grade 2 or higher infusion-related reaction occurs. An infusion rate reduction or therapy discontinuation may be necessary depending on the severity of the reaction. See the package insert for additional information.

Dose Adjustments

- **Renal impairment:** no dosage adjustment is necessary based on data from a pharmacokinetic population analysis
- **Hepatic impairment:** no dosage adjustment is necessary in patients with mild hepatic impairment based on data from a pharmacokinetic population analysis. Elotuzumab has not been studied in patients with moderate or severe hepatic impairment.

Drug Availability

- 300 mg and 400 mg powder for injection in a single-dose vial for reconstitution
- Store under refrigeration at 2 to 8 degrees C (36 to 46 degrees F). Protect from light by storing in the original package until time of use. Do not freeze or shake.

PRECAUTIONS:

Boxed Warning

- None

Contraindications

- None

Precautions/Warnings

- **Infusion reactions**: Infusion reactions were reported in approximately 10% of patients (1% Grade 3, no Grade 4) in the ELOQUENT-2 trial and 3.3% in the ELOQUENT-3 trial. The most common symptoms of an infusion reaction included fever, chills, and hypertension. Bradycardia and hypotension also developed during infusions. Premedication is required. Interrupt elotuzumab for Grade 2 or higher and permanently discontinue for severe infusion reaction.
- **Infections**: Infections (including bacterial, fungal, and viral) are more common when elotuzumab is added to treatment. Monitor for fever and other signs of infection and treat promptly.
- **Second Primary Malignancies (SPM)**: Higher incidences of SPM were observed in a controlled clinical trial of patients with multiple myeloma receiving elotuzumab. Monitor patients for the development SPM.
- **Hepatotoxicity:** Monitor liver function and stop elotuzumab if hepatotoxicity is suspected.
- **Interference with determination of complete response**: Elotuzumab can interfere with assays used to monitor M-protein. This interference can impact the determination of complete response.
- **Pregnancy:** There are no studies with elotuzumab with pregnant women to inform any drug associated risks, and animal reproduction studies have not been conducted. However, elotuzumab is administered in combination with lenalidomide and dexamethasone. Lenalidomide can cause embryo-fetal harm and is contraindicated for use in pregnancy.

BILLING/CODING INFORMATION:

The following codes may be used to describe:

HCPCS Coding

J9176	Injection, elotuzumab, 1 mg

ICD-10 Diagnosis Codes That Support Medical Necessity

C90.00	Multiple myeloma not having achieved remission
C90.02	Multiple myeloma in relapse
C90.10	Plasma cell leukemia not having achieved remission
C90.12	Plasma cell leukemia in relapse
C90.20	Extramedullary plasmacytoma not having achieved remission
C90.22	Extramedullary plasmacytoma in relapse
C90.30	Solitary plasmacytoma not having achieved remission
C90.32	Solitary plasmacytoma in relapse

REIMBURSEMENT INFORMATION:

Refer to section entitled **POSITION STATEMENT**.

PROGRAM EXCEPTIONS:

Federal Employee Program (FEP): Follow FEP guidelines.

State Account Organization (SAO): Follow SAO guidelines.

Medicare Part D: BCBSF has delegated to Prime Therapeutics authority to make coverage determinations for the Medicare Part D services referenced in this guideline.

Medicare Advantage: No National Coverage Determination (NCD) and/or Local Coverage Determination (LCD) were found at the time of the last guideline review date.

DEFINITIONS:

Heavy chain – the larger component of an immunoglobulin. There are five types: IgG, IgA, IgM, IgD, and IgE.

Immunoglobulins (a.k.a., antibodies) – proteins made by normal plasma cells that have an important role in fighting infection as part of the humoral immune response. Antibodies are composed of two heavy chains and two light chains that form a larger complex. Each plasma cell produces only one type of heavy chain and one type of light chain.

Light chain – the smaller component of an immunoglobulin. There are two types: kappa and lambda.

Minimal response (MR) (according to the Revised Uniform Response Criteria by the International Myeloma Working Group) – **ALL** of the following:

- ≥25% but ≤49% reduction of serum M-protein
- Reduction in 24-hour urine M-protein by 50% to 89%
- In addition, if present at baseline, 25% to 49% reduction in size of soft tissue plasmacytomas is also required
- No increase in size or number of lytic bone lesions (development of compression fractures dose not exclude response).

Myeloma Protein (M-Protein) – a nonfunctional immunoglobulin protein or protein fragment produced by malignant plasma cells (or myeloma cells). Since myeloma cells are monoclonal, the M-proteins for a given patient are structurally identical. Both portions of an immunoglobulin (the heavy chain and light chain) can be found in the serum, while only light chains can be found in the urine.

Plasma cell - a fully differentiated B lymphocyte (a type of white blood cell) that is specialized for immunoglobulin production and is found primarily in bone marrow.

Primary refractory MM - patients who never achieve at least a MR to initial induction therapy and progress while on therapy

Progressive MM - at least a 25% increase from nadir in the serum M-protein (absolute increase must be ≥0.5 g/dL) or urine M-protein (absolute increase must be ≥200mg/24 hours), or in the difference between involved and uninvolved serum-free light-chain (FLC) levels (with an abnormal FLC ratio and FLC difference >100 mg/L).

Relapsed and refractory MM - patients who never achieve at least a MR or who progress within 60 days of their last therapy

Serum free light chain assay (SFLCA) – a test that detects the amount of unbound or free light chains (i.e., not attached to a heavy chain) in the serum. Normal values - kappa: 3.3 to 19.4 mg/L, lambda: 5.71 to 26.3 mg/L, kappa/lambda ratio: 0.26–1.65 (0.37–3.1 if renal impairment).

Serum Protein Electrophoresis (SPEP) – a test that detects and quantifies the amount of M-protein in the serum. An serum M-protein of greater than 30 g/L is consistent with a diagnosis of MM.

Smoldering (Asymptomatic) myeloma: defined as M-protein in serum of 30 g/dL or more and/or bone marrow clonal plasma cells of 10% or more, but no related organ or tissue impairment (no end organ damage, including bone lesions) or symptoms.

RELATED GUIDELINES:

Allogeneic Bone Marrow and Stem Cell Transplantation, 02-38240-01

Bortezomib (Velcade) IV, 09-J0000-92

Carfilzomib (Kyprolis) IV, 09-J1000-81

Daratumumab (Darzalex) IV, 09-J2000-49

Doxorubicin HCl Liposome (Doxil) IV, 09-J0000-91

Ixazomib (Ninlaro), 09-J2000-51

Lenalidomide (Revlimid), 09-J0000-80

Panobinostat (Farydak), 09-J2000-37

Pomalidomide (Pomalyst) Capsule, 09-J1000-95

Thalidomide (Thalomid) Capsules, 09-J1000-56

OTHER:

None

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9. National Comprehensive Cancer Network. Cancer Guidelines. Cancer Guidelines and Drugs and Biologics Compendium. Accessed 5/24/19.
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COMMITTEE APPROVAL:

This Medical Coverage Guideline (MCG) was approved by the Florida Blue Pharmacy Policy Committee on 6/12/19.

GUIDELINE UPDATE INFORMATION:

03/15/16	New Medical Coverage Guideline.
04/15/16	Revision to guideline consisting of clarifying the position statement.
07/01/16	Revision to guideline consisting of updating HCPCS codes.
12/15/16	Revision to guideline consisting of updating the position statement with a new triplet regimen and updating the lab documentation requirements.
01/01/17	Revision: added HCPCS code J9176.
02/16/17	Revision: Update to Position Statement.
07/15/17	Review and revision to guidelines consisting of updating the description section, position statement, dosage/administration section, and references.
07/15/18	Review and revision to guidelines consisting of updating the description section, position statement, billing/coding information, definitions, and references.
01/15/19	Revision to guideline consisting of updating the description section, position statement, dosage/administration section, and references based on a new FDA-approved indication and NCCN Guidelines update.
07/15/19	Review and revision to guidelines consisting of updating the description section, position statement, and references.