DRAFT

BlueCross BlueShield of Alabama

Name of Policy:
Darzalex® (daratumumab)

Policy #: 670 Effective Date: November 19, 2018
Category: Pharmacology Latest Review Date: October 2018

Background/Definitions:

As a general rule, benefits are payable under Blue Cross and Blue Shield of Alabama health plans only in cases of medical necessity and only if services or supplies are not investigational, provided the customer group contracts have such coverage.

The following Association Technology Evaluation Criteria must be met for a service/supply to be considered for coverage:

1. *The technology must have final approval from the appropriate government regulatory bodies;*
2. *The scientific evidence must permit conclusions concerning the effect of the technology on health outcomes;*
3. *The technology must improve the net health outcome;*
4. *The technology must be as beneficial as any established alternatives;*
5. *The improvement must be attainable outside the investigational setting.*

Medical Necessity means that health care services (e.g., procedures, treatments, supplies, devices, equipment, facilities or drugs) that a physician, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury or disease or its symptoms, and that are:

1. *In accordance with generally accepted standards of medical practice; and*
2. *Clinically appropriate in terms of type, frequency, extent, site and duration and considered effective for the patient's illness, injury or disease; and*
3. *Not primarily for the convenience of the patient, physician or other health care provider; and*
4. *Not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient's illness, injury or disease.*

Description of Procedure or Service:

Darzalex® (daratumumab) is a human anti-CD38 monoclonal antibody (mAb) that targets the CD38 surface protein on myeloma cells. It inhibits the growth of CD38 expressing tumor cells by inducing apoptosis directly through Fc mediated cross linking as well as by immune-mediated tumor cell lysis through complement dependent cytotoxicity (CDC), antibody dependent cell mediated cytotoxicity (ADCC) and antibody dependent cellular phagocytosis (ADCP).

Policy:

Effective for dates of service on or after November 19, 2018

Darzalex® (daratumumab) meets Blue Cross and Blue Shield of Alabama's medical criteria for coverage for the treatment of individuals with **multiple myeloma**, including plasma-cell leukemia that has not received daratumumab or another anti-CD38 agent for **one** of following indications:

1. When used in **combination** with bortezomib, melphalan, and prednisone for newly diagnosed multiple myeloma who are ineligible for stem cell transplantation; **or**
2. When used as a **single agent** for relapsed or refractory disease following therapy with at least three prior lines of therapy including a proteasome inhibitor (PI) (e.g., bortezomib, carfilzomib, or ixazomib) and an immunomodulatory agent (e.g., thalidomide, lenalidomide, or pomalidomide); **or**
3. When used as **combination therapy** for relapsed or refractory disease following therapy with at least one prior line of therapy including a PI or an immunomodulatory agent when used with one of following:
    A. Bortezomib and dexamethasone; **or**
    B. Lenalidomide and dexamethasone.
4. When used in **combination** with pomalidomide and dexamethasone for relapsed or refractory disease following therapy with at least two prior lines of therapy including a PI and lenalidomide

Darzalex ® (daratumumab) does not meet Blue Cross Blue Shield of Alabama's medical criteria for coverage and is considered **investigational** when the above criteria are not met, and for all other conditions, including but not limited to **any** of the following:

- Presence of human immunodeficiency virus (HIV infection) or hepatitis B virus infection;
- The reason for the treatment is other than for a diagnosis of multiple myeloma, including plasma-cell leukemia.

Effective for dates of service June 30, 2017 through November 18, 2018

Darzalex® (daratumumab) meets Blue Cross and Blue Shield of Alabama's medical criteria for coverage for the treatment of individuals with **multiple myeloma**, including plasma-cell leukemia that has not received daratumumab or another anti-CD38 agent for **one** of following indications:

5. When used as a **single agent** for relapsed or refractory disease following therapy with at least three prior lines of therapy including a proteasome inhibitor (PI) (e.g., bortezomib, carfilzomib, or ixazomib) and an immunomodulatory agent (e.g., thalidomide, lenalidomide, or pomalidomide); **or**
6. When used as **combination therapy** for relapsed or refractory disease following therapy with at least one prior line of therapy including a PI or an immunomodulatory agent when used with one of following:
    A. Bortezomib and dexamethasone; **or**
    B. Lenalidomide and dexamethasone.

Blue Cross and Blue Shield of Alabama 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 Cross and Blue Shield of Alabama administers benefits based on the member's contract and corporate 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 (ACS) has estimated 30,770 new cases of multiple myeloma will be diagnosed in the United States in 2018, with an estimated 12,770 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%.

The FDA approval of daratumumab was based on the safety and efficacy demonstrated in two open-label, non-comparative phase II studies. Lokhorst and colleagues reported results on a two-part study, part 1 dose-escalation and part 2 the dose-expansion phase. Part 2 randomly assigned 30 participants to receive daratumumab monotherapy (8 mg per kilogram) and 42 participants to receive daratumumab monotherapy (16 mg per kilogram) administered once weekly for eight doses, twice monthly for eight doses, then monthly for up to 24 months. The study enrolled participants with relapsed multiple myeloma, or disease that was refractory (79%) to two or more different therapies (for example, PI, immunomodulatory agents, chemotherapy, or autologous stem-cell transplantation); participants enrolled had received a median of four prior treatments.

Subjects were at least 18 years of age, with a life expectancy greater than 3 months, ECOG performance status of 0-2, and a measurable level of M protein or free light chains. Pneumonia and thrombocytopenia were identified as the most common adverse events. Serious adverse events occurred in 40% of participants in the 8 mg per kilogram cohort and 33% in the 16 mg per kilogram cohort, with infection-related events the most common among both groups. Lokhorst and colleagues concluded:

> The overall response rate was 36% in the cohort that received 16 mg per kilogram (15 patients had a partial response or better, including 2 with a complete response and 2 with a very good partial response) and 10% in the cohort that received 8 mg per kilogram (3 had a partial response). In the cohort that received 16 mg per kilogram, the median progression-free survival was 5.6 months (95% confidence interval [CI], 4.2 to 8.1), and 65% (95% CI, 28 to 86) of the patients who had a response did not have progression at 12 months.

Lonial and colleagues reported preliminary results of an ongoing phase II open-label, multicenter study of 106 participants (18 years or older) that received daratumumab 16 mg per kilogram in parts 1 and 2; 80% (n=85) of participants had previously undergone autologous stem cell transplantation, 95% of participants (n=101) were refractory to most recent treatment (PI and immunomodulatory agent used), and 97% of participants (n=103) were refractory to last lines of therapy. Final results reported an overall response rate of 29% among participants (n=31) that experienced a complete or partial reduction in tumor burden, which lasted for an average of 7.4 months "(95% CI 5.5 not estimable) and progression-free survival was 3.7 months (95% CI 2.8-4.6). The 12-month overall survival was 64.8% (95% CI 51.2-75.5) and, at a subsequent cutoff, median overall survival was 17.5 months (95% CI 13.7- not estimable)." The most common adverse reactions (any grade) for daratumumab were fatigue (n=42; 40%) and anemia (n=35; 33%). Daratumumab was well tolerated, with no drug-related adverse events that led to discontinuation of treatment. Authors found daratumumab monotherapy an effective option for individuals with relapsed or refractory multiple myeloma for whom available treatments have been exhausted.

The National Comprehensive Cancer Network® (NCCN) Drugs and Biologics Compendium™ and the NCCN CPG for multiple myeloma included recommendations for off-label use of daratumumab for previously treated myeloma for disease relapse or for progressive or refractory disease. The panel offers a category 2A recommendation for use as a single agent in individuals that have received at least three prior therapies, including a PI and an immunomodulatory agent or who are double refractory to a PI and immunomodulatory agent. The panel included a category 1 recommendation for use of daratumumab when used in combination with bortezomib and dexamethasone or lenalidomide and dexamethasone. The NCCN off-label recommendations are based on interim analysis from a phase II study and two phase III studies hat evaluated the use of daratumumab in the treatment of multiple myeloma.

Palumbo and colleagues reported an interim analysis from the CASTOR study, a phase III randomized controlled study that enrolled 498 participants with relapsed or refractory multiple myeloma (RRMM). Subjects were randomly assigned to receive daratumumab in combination with standard of care bortezomib, and dexamethasone (DVd) (n=259) versus the control group

that received bortezomib and dexamethasone (Vd) (n=247), after receiving a partial response from one or more prior therapies (median of two previous lines of therapy). "The primary endpoint was progression-free survival, defined as the time from the date of randomization to the date of disease progression or death, whichever occurred first". Data from the clinical trial showed that daratumumab in combination with standard of care therapy demonstrated a 60.7% reduction in the risk of disease progression or death (PFS) at 12 months compared to 26.9% in the control group population with RRMM. The authors reported additional interim findings:

> After a median follow-up period of 7.4 months, the median progression-free survival was not reached in the daratumumab group and was 7.2 months in the control group (hazard ratio for progression or death with daratumumab vs. control, 0.39; 95% confidence interval, 0.28 to 0.53; P<0.001). The rate of overall response was higher in the daratumumab group than in the control group (82.9% vs. 63.2%, P<0.001), as were the rates of very good partial response or better (59.2% vs. 29.1%, P<0.001), as were the rates of very good partial response or better (59.2% vs. 29.1%, P<0.001) and complete response or better (19.2% vs. 9.0%, P=0.001).

The majority of participants in both groups reported at least one adverse event, with grade 3 or 4 adverse events observed in 76.1% of the daratumumab population and 62.4% of the control population. Commonly reported grade 3 or 4 adverse events among the daratumumab group and the control group were thrombocytopenia (45.3% vs/ 32.9%), anemia (14.4% vs. 16.0%), and neutropenia (12.8% vs. 4.2%). In the daratumumab group, 45.3% of subjects reported infusion-related reactions (majority grade 1 or 2), with 98.2% of infusion-related reactions occurring during the first daratumumab infusion. In conclusion, the authors reported that:

> Among patients with relapsed or relapsed and refractory multiple myeloma, daratumumab in combination with bortezomib and dexamethasone resulted in significantly longer progression-free survival than bortezomib and dexamethasone alone.

Dimopoulos and colleagues reported interim results from a randomized, open-label, multicenter phase III trial that enrolled 569 participants with relapsed or refractory multiple myeloma with one or more prior lines of therapy to receive lenalidomide and dexamethasone alone (control group) (n=283) or in combination with daratumumab (n=286). "The primary endpoint was progression-free survival, with progression determined with the use of a validated computer algorithm that combined laboratory results (e.g., M-protein level) and applicable imaging and generated the outcome according to IMWG criteria." Interim analysis was reported at 13.5 months (median follow-up); "169 events of disease progression or death were observed (in 53 of 286 patients [18.5%] in the daratumumab group vs. 116 of 283 [41.0%] in the control group; hazard ratio, 0.34; 95% confidence interval [CI], 0.27 to 0.52; P<0.001 by stratified log-rank test)." At 12 months the rate of progression-free survival was "83.2% (95% CI, 78.3 to 87.2) in the daratumumab group, as compared with 60.1% (95% CI, 54.0 to 65.7) in the control group". The overall response rate observed in the daratumumab group was 92.9% compared to 76.4% among the control group; the complete response was also higher in the daratumumab group, 43.1% versus a rate of 19.2% in the control group. Grade 3 or 4 adverse events commonly reported among the daratumumab group and the control group included neutropenia (51.9% vs 37.0%), thrombocytopenia (12.7% vs 13.5%) and anemia (12.4% vs. 19.6%). Infusion-related

reactions occurred in 47.7% of participants in the daratumumab group; the majority reported as grade 1 or 2 adverse events. The authors concluded that "the addition of daratumumab to lenalidomide and dexamethasone significantly lengthened progression-free survival among patients with relapsed or refractory multiple myeloma."

The FDA approval for expanded use of daratumumab in combination with pomalidomide and dexamethasone was based on unpublished data from a cohort of a phase 1 (MMY1001, EQUULEUS) study that investigated the safety and tolerability of daratumumab in combination with pomalidomide and dexamethasone in relapsed or refractory multiple myeloma. The phase 1, open-label study included 103 participants with multiple myeloma who received prior treatment with PI and an immunomodulatory agent. The overall response rate observed in the study was 59% (95% CI, 49.1%-68.8%) and partial response achieved in 28% of participants. The median duration of response reported was 13.6 months. Among participants that received treatment, grade 3 or 4 serious adverse events were reported in 5% of participants, including pneumonia, neutropenia, thrombocytopenia and anemia.

Mateos and colleagues (2017) reported interim analysis from a multicenter, randomized, open-label, phase 3 trial (NCT02195479) that enrolled participants with newly diagnosed multiple myeloma, ineligible for high-dose chemotherapy with stem-cell transplantation due to age greater than or equal to 65 years, or in participants less than 65 years of age with presence of comorbid conditions likely to have a negative impact on tolerability of high-dose chemotherapy with stem cell transplantation. A total of 700 participants received the assigned intervention, 346 participants in the daratumumab group (daratumumab in combination with bortezomib, melphalan, and prednisone) and 354 participants in the control group (bortezomib, melphalan, and prednisone alone). The primary endpoint was PFS, “defined as the time from randomization to either disease progression or death.” The authors reported interim findings:

> The 18-month progression-free survival rate was 71.6% (95% confidence interval [CI], 65.5 to 76.8) in the daratumumab group and 50.2% (95% CI, 43.2 to 56.7) in the control group (hazard ratio for disease progression or death, 0.50; 95% CI, 0.38 to 0.65; P<0.001). The overall response rate was 90.9% in the daratumumab group, compared with 73.9% in the control group (P<0.001), and the rate of complete response or better (including stringent complete response) was 42.6%, versus 24.4% (P<0.001).

The most common grade 3 or 4 adverse events reported among the daratumumab group and the control group included neutropenia (39.9% vs 38.7%), thrombocytopenia (34.4% vs 37.6%) and anemia (15.9% vs. 19.8%). Infusion-related reactions occurred in 47.7% of participants in the daratumumab group; the majority reported as grade 1 or 2 adverse events. The authors concluded that daratumumab combined with bortezomib, melphalan, and prednisone in individuals newly diagnosed with multiple myeloma who were ineligible for stem cell transplantation resulted in a lower risk of disease progression or death than treatment with bortezomib, melphalan and prednisone.

Daratumumab is also currently being studied in clinical trials for other uses including, but not limited to the treatment of acute myeloid leukemia (AML), relapsed/refractory mantle cell

lymphoma, diffuse large B-cell lymphoma, and follicular lymphoma. However, there is insufficient published evidence to support the use of daratumumab for such conditions.

Key Words:

Darzalex, daratumumab, multiple myeloma

Approved by Governing Bodies:

On November 16, 2015 daratumumab was the first human mAb to achieve accelerated approval and breakthrough therapy status by the U.S. Food and Drug Administration (FDA), because it provided an option for individuals with multiple myeloma who have received at least three prior lines of therapy, including a PI and an immunomodulatory agent, or who are double-refractory to a PI and an immunomodulatory agent. The FDA approved daratumumab injection for intravenous infusion to be used as a single agent for the treatment of relapsed or refractory disease

On November 21, 2016, daratumumab was FDA approved for use in combination with lenalidomide and dexamethasone, or bortezomib and dexamethasone, for the treatment of patients with multiple myeloma who have received at least one prior therapy.

Benefit Application:

Coverage is subject to member's specific benefits. Group specific policy will supersede this policy when applicable.
ITS: Home Policy provisions apply.
FEP: Special benefit consideration may apply. Refer to member's benefit plan. FEP does not consider investigational if FDA approved and will be reviewed for medical necessity.

Current Coding:

CPT Codes:

J9145	Injection, daratumumab, 10mg

References:

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Policy History:

Medical Policy Group, May 2017 (2): New policy created
Medical Policy Administration Committee, May 2017
Available for comment May 15, 2017 through June 29, 2017
Medical Policy Group, October 2018 (**2**): Updates to Key Points, Approved by Governing Bodies, and References; Policy section updated with criteria for combination therapy for newly diagnosed multiple myeloma and relapsed/refractory disease after at least two prior lines of therapy, also added investigational statement for HIV or hepatitis B vaccine.
Available for comment October 5, 2018 through November 19, 2018