I. PURPOSE

To define and describe the accepted indications for Darzalex (daratumumab) usage in the treatment of cancer.

II. DEFINITIONS

**Darzalex (daratumumab):** is an IgG1κ human monoclonal antibody directed against CD38. CD38 is a cell surface glycoprotein which is highly expressed on myeloma cells, yet is expressed at low levels on normal lymphoid and myeloid cells. Daratumumab binds to CD38 inhibiting its growth and expresses tumor cells by inducing apoptosis directly through Fc mediated cross linking as well as by immune-mediated tumor cell lysis through complement dependent cytotoxicity, antibody dependent cell mediated cytotoxicity, and antibody dependent cellular phagocytosis.

Darzalex (daratumumab) is FDA approved for the treatment of patients with multiple myeloma who have received at least three prior lines of therapy including a proteasome inhibitor (PI) and an immunomodulatory agent or who are double-refractory to a PI and an immunomodulatory agent OR 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. It is also approved in combination with pomalidomide and dexamethasone for the treatment of patients with multiple myeloma who have received at least two prior therapies including lenalidomide and a proteasome inhibitor or in combination with bortezomib, melphalan and prednisone for the treatment of patients with newly diagnosed multiple myeloma who are ineligible for autologous stem cell transplant.

Darzalex (daratumumab) is available in 100 mg/5 mL (5 mL) IV solution and 400 mg/20 mL (20 mL) IV solution.

III. POLICY

New Century is responsible for processing all medication requests from network ordering providers. Medications not authorized by New Century may be deemed as not approvable and therefore not reimbursable. Treatment request outside the approved FDA manufacturer labeling or CMS approved compendia must be supported by, at minimum, two peer reviewed citations. If references are not produced, delays may occur to the processing of such request.

**Inclusion Criteria:** Darzalex (daratumumab) may be considered medically necessary when any of the following selection criteria is met:

1. **Multiple Myeloma**
   a. Darzalex (daratumumab) is being used as a single agent all of the following:
i. Member has disease progression to at least 3 prior therapies AND

ii. Prior therapies include a proteasome Inhibitor (i.e. bortezomib, ixazomib, or carfilzomib) AND an immunomodulatory agent (i.e. thalidomide, lenalidomide, or pomalidomide) OR

iii. Member is double refractory to a proteasome inhibitor AND an immunomodulatory agent for relapse or for progressive or refractory disease. OR

b. Darzalex (daratumumab) is being used in combination with bortezomib, melphalan, and prednisone for non-transplant candidates OR

c. Darzalex (daratumumab) is being used in combination with bortezomib and dexamethasone OR in combination with lenalidomide and dexamethasone OR

d. Darzalex (daratumumab) is being used in combination with pomalidomide and dexamethasone in patients who have received at least two prior therapies including an immunomodulatory agent and a proteasome inhibitor and who have demonstrated disease progression on or within 60 days of completion of the last therapy.

Exclusion Criteria: Darzalex (daratumumab) is not considered medically necessary when any of the following selection criteria is met:

1. Disease progression while taking Darzalex (daratumumab).
2. Dosing exceeds single dose limit of 16 mg/kg body weight.
3. Indications not supported by CMS recognized compendia or acceptable peer reviewed literature may be deemed as not approvable and therefore not reimbursable.

IV. PROCEDURE

Requests for Darzalex (daratumumab) shall be reviewed for appropriateness per FDA approved product labeling, the National Comprehensive Cancer Network (NCCN) and American Society of Clinical Oncology (ASCO) clinical guidelines, or CMS approved compendia.

1. Dosage and Administration:

   a. Monotherapy and in combination with lenalidomide or pomalidomide and low-dose dexamethasone: 16 mg/kg weekly for weeks 1-8, every two weeks for weeks 9-24, and then every 4 weeks from week 25 until disease progression.

b. In combination with bortezomib and dexamethasone: 16 mg/kg weekly for weeks 1-9, every 3 weeks for weeks 10-24, and then every 4 weeks for week 25 until disease progression.
c. In combination with Bortezomib, Melphalan and Prednisone (6-week cycle regimen) for Patients Ineligible for Autologous Stem Cell Transplant: 16 mg/kg (actual body weight) IV weekly on weeks 1 to 6 (6 doses), 16 mg/kg IV every 3 weeks on weeks 7 to 54 (16 doses), and then 16 mg/kg IV every 4 weeks starting on week 55 until disease progression.

The following medications is infused approximately 1 hour prior to administration of Darzalex (daratumumab) to reduce the risk of an infusion reaction:
- Intravenous corticosteroid (methylprednisolone 100 mg, or equivalent dose of an intermediate-acting or long-acting corticosteroid), plus
- oral antipyretics (acetaminophen 650 to 1000 mg), plus
- oral or intravenous antihistamine (diphenhydramine 25 to 50 mg or equivalent).

Following the second infusion, the dose of corticosteroid may be reduced (methylprednisolone 60 mg intravenously).
- oral corticosteroid (20 mg methylprednisolone or equivalent dose of a corticosteroid in accordance with local standards) on the first and second day after all infusions must be administered to reduce the risk of delayed infusion reaction to all members.
- Infusion should be completed within 15 hours.

2. Dosage Adjustments:
   a. For infusion reactions of any grade/severity, immediately interrupt the Darzalex (daratumumab) infusion and manage symptoms. Management of infusion reactions may further require reduction in the rate of infusion, or treatment discontinuation of Darzalex (daratumumab).
   b. Grade 1-2 (mild to moderate): Once reaction symptoms resolve, resume the infusion at no more than half the rate at which the reaction occurred. If the patient does not experience any further reaction symptoms, infusion rate escalation may resume at increments and intervals as appropriate.
   c. Grade 3 (severe): If the intensity of the reaction decreases to Grade 2 or lower, consider restarting the infusion at no more than half the rate at which the reaction occurred. If the patient does not experience additional symptoms, resume infusion rate escalation at increments and intervals as outlined in Table 2. Repeat the procedure above in the event of recurrence of Grade 3 symptoms. Permanently discontinue Darzalex (daratumumab) upon the third occurrence of a Grade 3 or greater infusion reaction.
   e. Members with a history of obstructive pulmonary disorder should be prescribed post-infusion medications such as short and long-acting bronchodilators, and inhaled corticosteroids for only the first four infusions in case of a reaction.

3. Monitoring
   a. Coombs test, serum protein electrophoresis (SPE) and immunofixation (IFE) to monitor endogenous M-protein.
b. Infusion reactions: Interrupt infusion for infusion reactions of any severity. Permanently
discontinue the infusion in case of life-threatening infusion reactions.

c. Interference with cross-matching and red blood cell antibody screening: Type and screen
patients prior to starting treatment. Inform blood banks that a patient has received Darzalex.

d. Neutropenia: Monitor complete blood cell counts periodically during treatment. Monitor
patients with neutropenia for signs of infection. Dose delay may be required to allow
recovery of neutrophils.

e. Thrombocytopenia: Monitor complete blood cell counts periodically during treatment. Dose
delay may be required to allow recovery of platelets.

V. ATTACHMENTS

VII. REFERENCES

1. PI prescribing information accessed on 1/8/19: http://www.accessdata.fda.gov/drugsatfda_docs/label/2016/208434s000lbl.pdf
   2019.
5. AHFS Drug Information. American Society of Health-Systems Pharmacists or Wolters Kluwer Lexi-Drugs.
   Bethesda, MD. 2019.