Effective November 1, 2018, 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:
Lartruvo™ (olaratumab)

Policy #: 677
Category: Pharmacology
Effective Date: April 1, 2018
Last Review Date: February 2018

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

Description of Procedure or Service:

Olaratumab is a human IgG1 antibody that binds platelet-derived growth factor receptor alpha (PDGFR-α). PDGFR-α is a receptor tyrosine kinase expressed on cells of mesenchymal origin. Signaling through this receptor plays a role in cell growth, chemotaxis, and mesenchymal stem cell differentiation. The receptor has also been detected on some tumor and stromal cells, including sarcomas, where signaling can contribute to cancer cell proliferation, metastasis, and maintenance of the tumor microenvironment. The interaction between olaratumab and PDGFR-α prevents binding of the receptor by the PDGF-AA and -BB ligands as well as PDGF-AA, -BB, and -CC-induced receptor activation and downstream PDGFR-α pathway signaling. Olaratumab exhibits in vitro and in vivo anti-tumor activity against selected sarcoma cell lines and disrupted the PDGFR-α signaling pathway in in vivo tumor implant models.

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 April 1, 2018 and prior to November 1, 2018:

Blue Advantage will treat **Lartruvo™ (olaratumab)** as a **covered benefit** for the treatment of **soft tissue sarcoma** when **all** of the following criteria are met:

- Individual has a histologically confirmed diagnosis of late stage soft tissue sarcoma (locally advanced or metastatic) not previously treated with an anthracycline; **and**
- Radiotherapy or surgery is not a curative treatment option; **and**
- Individual's current Eastern Cooperative Oncology Group (ECOG) performance status is 0-2; **and**
- If the individual is less than 18 years of age, olaratumab is not used as first-line chemotherapy; **and**
- Olaratumab is used in combination with doxorubicin and, after at least 8 cycles with doxorubicin or earlier discontinuation of doxorubicin due to toxicity, and then if so chosen, continuing olaratumab as monotherapy in the absence of unacceptable toxicities until disease progression.

Blue Advantage will treat **Lartruvo™ (olaratumab)** as a **non-covered benefit** and as **investigational** when the above criteria are not met and for all other indications.

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:

Sarcomas are a diverse group of rare solid tumors of mesenchymal cell origin with distinct clinical and pathologic features, usually divided into two broad categories: sarcomas of soft tissues (including fat, muscle, nerve and nerve sheath, blood vessels, and other connective tissues), and sarcomas of bone.

Collectively, sarcomas account for approximately 1% of all adult malignancies and 15% of pediatric malignancies. In 2017, the American Cancer Society estimates 12,390 people will be diagnosed with soft tissue sarcoma in the United States and approximately 4990 deaths will occur as a result of the disease. More than 50 different histologic subtypes of soft tissue sarcoma have been identified; the most common are undifferentiated pleomorphic sarcoma, gastrointestinal stromal tumors (GISTs), liposarcoma, leiomyosarcoma, synovial sarcoma, and malignant peripheral nerve sheath tumors (MPNSTs). Metastasis most commonly occurs in the lungs; liver and peritoneum. Rhabdomyosarcoma is the most common soft tissue sarcoma of children and adolescents.

Surgical resection is the standard primary treatment for most individuals with soft tissue sarcoma. Radiation therapy with or without chemotherapy may be used prior to surgery to downstage large high-grade tumors to enable effective surgical resection. Radiation therapy may also be administered either as primary, preoperative, or postoperative treatment. For individuals with advanced, unresectable, or metastatic disease, chemotherapy with single agents or combination regimens have typically been used.

Historically, little progress has been made in improving the median overall survival (OS) of individuals with advanced soft-tissue sarcoma. Traditional treatment has consisted of regimens of doxorubicin alone or doxorubicin in combination with ifosfamide. The prognosis for those with metastatic disease has been poor because of the limited efficacy of traditional regimens.

Tap and colleagues (2016) performed an open-label phase 1b and randomized phase 2 study of doxorubicin plus olaratumab for the treatment of unresectable or metastatic soft-tissue sarcoma at 16 U.S. clinical sites. The phase 1b primary endpoint was safety and the phase 2 primary endpoint was progression-free survival (PFS). For both the phase 1b and phase 2 parts of the study, eligible subjects were at least 18 years of age or older and had a histologically confirmed diagnosis of locally advanced or metastatic soft-tissue sarcoma not previously treated with an anthracycline, an Eastern Cooperative Oncology Group (ECOG) performance status of 0–2, and available tumor tissue to determine PDGFRα expression by immunohistochemistry. In the phase Ib study, 15 subjects were treated with olaratumab (15 mg/kg) intravenously on day 1 and day 8 plus doxorubicin (75 mg/m2) on day 1 of each 21-day cycle up to a maximum of eight cycles. After eight cycles of the combination drug therapy, in the absence of unacceptable toxicities or disease progression subjects were given olaratumab monotherapy until disease progressed. The FDA approval of olaratumab (Lartruvo) was based on the phase 2 part of the study in which 133 subjects were randomized in a 1:1 ratio to receive either olaratumab (15 mg/kg) intravenously on day 1 and day 8 plus doxorubicin (75 mg/m^2) or doxorubicin alone (75 mg/m^2) on day 1 of each 21-day cycle for up to eight cycles. After completion of eight cycles of doxorubicin, individuals in the olaratumab plus doxorubicin group could receive olaratumab monotherapy until disease progression and those is the doxorubicin group could receive olaratumab monotherapy after

documented disease progression. A total of 129 subjects (97%) received at least one dose of study treatment (64 received olaratumab plus doxorubicin, 65 received doxorubicin). Median progression-free survival (PFS) in phase 2 was 6.6 months with olaratumab plus doxorubicin and 4.1 months with doxorubicin. Median OS was 26.5 months with olaratumab plus doxorubicin and 14.7 months with doxorubicin. The objective response rate was 18.2% with olaratumab plus doxorubicin and 11.9% with doxorubicin. Steady state olaratumab serum concentrations were reached during the third cycle. Results were not separately reported for the doxorubicin group that received olaratumab monotherapy after documented disease progression. Adverse events that were more frequent with olaratumab plus doxorubicin versus doxorubicin alone included neutropenia (37 [58%] vs 23 [35%]), mucositis (34 [53%] vs 23 [35%]), nausea (47 [73%] vs 34 [52%]), vomiting (29 [45%] vs 12 [18%]), and diarrhea (22 [34%] vs 15 [23%]). Febrile neutropenia of grade 3 or higher was similar in both groups (olaratumab plus doxorubicin: 8 [13%] of 64 subjects vs doxorubicin: 9 [14%] of 65 subjects).

Two other completed clinical trials involving olaratumab are available in the published literature. Both small phase 1 studies evaluated the safety and acceptable dosing of olaratumab for future clinical trials. The Chiorean trial consisted of 19 subjects with advanced solid tumors divided across five cohorts. The authors indicated that olaratumab was well tolerated and showed preliminary antitumor activity at the recommended phase II doses of 16 mg/kg weekly and 20 mg/kg biweekly. The Doi trial consisted of 16 Japanese subjects with advanced/refractory solid malignancies divided across three cohorts. No dose-limiting toxicities occurred; therefore, the maximum tolerated dose was not reached. The authors reported that olaratumab had an acceptable safety profile. Additionally noted was that single and multiple doses of olaratumab at 15 mg⁄kg on days 1 and 8 every 3 weeks (cohort 3) and multiple doses at 20 mg⁄kg every 2 weeks (cohort 2) could represent an acceptable schedule for future trials of Japanese subjects.

A randomized, double-blind, placebo-controlled, phase III trial of doxorubicin plus olaratumab vs doxorubicin plus placebo in individuals with advanced or metastatic soft tissue sarcoma is currently ongoing (ANNOUNCE trial). It was designed to evaluate the effectiveness of olaratumab across multiple subtypes of soft tissue sarcoma and study results are not currently available in the published literature.

Other Proposed Uses
Additional uses of olaratumab under investigation per clinical trials.gov include glioblastoma, non-small cell lung cancer, prostate cancer and ovarian cancer. However, at this time there is a lack of published evidence to support the use of olaratumab for any indication other than for the treatment of late stage soft tissue sarcoma when specific criteria are met.

Key Words:

Lartruvo, olaratumab, soft tissue sarcoma

Approved by Governing Bodies:

On October 19, 2016, the U.S. Food and Drug Administration (FDA) granted accelerated approval of olaratumab (Lartruvo), in combination with doxorubicin, for the treatment of adults with soft tissue sarcoma with a histologic subtype for which an anthracycline-containing regimen is appropriate and which is not amenable to curative treatment with radiotherapy or surgery. Continued approval for this indication may be contingent upon verification and description of clinical benefit in the confirmatory trial.

Benefit Application:

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

Current Coding:

CPT Codes:

J9285 Injection, olaratumab, 10 mg [Lartruvo]

References:

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Policy History:

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Medical Policy Group, November 2018