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:
Arzerra® (ofatumumab) and Gazyva® (obinutuzumab)

Policy #:	653	Effective Date:	April 21, 2018
Category:	Pharmacology	Latest Review Date:	March 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:

Monoclonal antibodies targeted to cancer-associated antigens have been approved by the U.S. Food and Drug Administration (FDA) for various uses in oncology. In some cases, these agents are used in settings outside of the FDA-approved label, (i.e., off-label use).

C20-Directed Cytolytic Antibodies

CD20 is a cell surface antigen expressed on pre B- and mature B-lymphocytes. More than 90% of malignant B-cells in non-Hodgkin lymphoma (NHL) express CD20. CD20-directed cytolytic antibodies mediate cell lysis by: (1) antibody-dependent cell-mediated cytotoxicity, (2) complement-dependent cytotoxicity, and (3) induction of intracellular death signaling pathways (apoptosis). All CD20-directed cytolytic antibodies carry black box warnings for hepatitis B virus reactivation and progressive multifocal leukoencephalopathy.

- Arzerra® (ofatumumab) is a fully human monoclonal antibody produced in a recombinant murine cell line. Ofatumumab targets an epitope that differs from the binding location of rituximab. In chronic lymphocytic leukemia (CLL), B cells underexpress CD20; unlike rituximab, which depends on CD20 expression for complement-dependent cytotoxicity, ofatumumab does not appear to depend on antigen intensity.

- Gazyva® (obinutuzumab) is a humanized monoclonal antibody produced in Chinese hamster ovary cell culture. In addition to the cytolytic mechanisms described earlier, obinutuzumab induces antibody-dependent cellular phagocytosis.

Policy:

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

Effective for dates of service on or after April 21, 2018 and prior to November 1, 2018:
Blue Advantage will treat **Arzerra (ofatumumab)** as a **covered benefit** for **ANY** one of the following indications:

- When used in combination with chlorambucil in previously untreated patients with **chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL)** for whom fludarabine-based therapy is considered inappropriate; **OR**
- When used for the treatment of **relapsed or refractory CLL/SLL** as a single agent and only in one line of therapy; **OR**
- When used for the treatment **of relapsed or refractory Waldenström's macroglobulinemia/Lymphoplasmacytic lymphoma** in patients intolerant of or refractory to rituximab; **OR**
- When used as maintenance treatment for **relapsed or progressive chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL)** for up to 24 months when a

complete or partial response has been achieved and it is following at least two lines of therapy.

Blue Advantage will treat **Arzerra (ofatumumab)** as a **non-covered benefit** and as **investigational** when the above criteria are not met.

Blue Advantage will treat **Gazyva (obinutuzumab)** as a **covered benefit** for **ANY** one of the following indications:

- When used in combination with chlorambucil in previously untreated patients with **chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL), without del (17p)** for whom fludarabine-based therapy is considered inappropriate; **OR**
- When used as a single agent for the treatment of **relapsed or refractory CLL/SLL** without del (17p) mutation.
- When used for the treatment of **follicular lymphoma**, when used as component of one of the following combination regimens and as monotherapy, for up to 24 months or until disease progression, following the listed combination therapy regimens:
    - Cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP regimen); **or**
    - Cyclophosphamide, vincristine, and prednisone (CVP regimen); **or**
    - Bendamustine

Blue Advantage will treat **Gazyva (obinutuzumab)** as a **non-covered benefit** and as **investigational** when the above criteria are not met.

Effective for dates of service on or after December 27, 2016 through April 20, 2018:

Blue Advantage will treat **Arzerra (ofatumumab)** as a **covered benefit** for **ANY** one of the following indications:

- The agent will be used in combination with chlorambucil in previously untreated patients with **chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL)** for whom fludarabine-based therapy is considered inappropriate; **OR**
- The agent will be used as a single agent and in a single line of therapy for the treatment **of relapsed or refractory CLL/SLL**; **OR**
- The agent will be used for the treatment **of relapsed or refractory Waldenström's macroglobulinemia/Lymphoplasmacytic lymphoma** in patients intolerant of or refractory to rituximab
- When used as maintenance treatment for **relapsed or progressive chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL)** for up to 24 months when a complete or partial response has been achieved and it is following at least two lines of therapy.

Blue Advantage will treat **Arzerra (ofatumumab)** as a **non-covered benefit** and as **investigational** when the above criteria are not met.

Blue Advantage will treat **Gazyva (obinutuzumab)** as a **covered benefit** for **ANY** one of the following indications:

- The agent will be used in combination with chlorambucil in previously untreated patients with **chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL)** for whom fludarabine-based therapy is considered inappropriate; **OR**
- When used as a single agent for the treatment of **relapsed or refractory CLL/SLL** without del (17p) mutation.
- When used for the treatment of **follicular lymphoma**, in combination with bendamustine followed by Gazyva monotherapy in individuals who have relapsed after or are refractory to a rituximab-containing regimen.

Blue Advantage will treat **Gazyva (obinutuzumab)** as a **non-covered benefit** and as **investigational** when the above criteria are not met.

Effective for dates of service September 1, 2015 through December 26, 2016:

Blue Advantage will treat **Arzerra (ofatumumab)** as a **covered benefit** for **ANY** one of the following indications:

- The agent will be used in combination with chlorambucil in previously untreated patients with **chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL)** for whom fludarabine-based therapy is considered inappropriate; **OR**
- The agent will be used as a single agent and in a single line of therapy for the treatment **of relapsed or refractory CLL/SLL**; **OR**
- The agent will be used for the treatment **of relapsed or refractory Waldenström's macroglobulinemia/Lymphoplasmacytic lymphoma** in patients intolerant of or refractory to rituximab

Blue Advantage will treat **Arzerra (ofatumumab)** as a **non-covered benefit** and as **investigational** when used as maintenance therapy in patients with CLL/SLL.

Blue Advantage will treat **Gazyva (obinutuzumab)** as a **covered benefit** for **ANY** one of the following indications:

- The agent will be used in combination with chlorambucil in previously untreated patients with **chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL)** for whom fludarabine-based therapy is considered inappropriate; **OR**
- The agent will be used as a single agent and in only one line of therapy for the treatment of **relapsed or refractory CLL/SLL**

Blue Advantage will treat **Gazyva (obinutuzumab)** as a **non-covered benefit** and as **investigational** when used as maintenance therapy in patients with CLL/SLL.

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:

Arzerra® (ofatumumab)

Newly Diagnosed Chronic Lymphocytic Leukemia (CLL)/Small Lymphocytic Lymphoma (SLL)

FDA-approval of ofatumumab in combination with chlorambucil, for previously untreated CLL was based on the results of the COMPLEMENT 1 randomized study that compared chlorambucil with and without ofatumumab in 447 subjects with comorbidities that resulted in intolerances to fludarabine. Treatment duration was a minimum of 3 cycles, until best response to a maximum of 12 cycles. The primary outcome was progression-free survival (PFS), which was significantly longer in the ofatumumab arm (22.4 months) compared to the chlorambucil arm (13.1 months, $p<0.001$). Complete remission (or response; CR) was also significantly higher in the ofatumumab arm (12% vs. 1%). The authors concluded that intravenous (IV) ofatumumab added to chlorambucil demonstrated clinically important improvements with a manageable side effect profile in those with CLL who are considered inappropriate candidates for fludarabine-based therapy.

Relapsed or Refractory CLL

Ofatumumab was approved by the FDA with a breakthrough therapy designation for the treatment of CLL refractory to alemtuzumab and fludarabine. The pivotal trial consisted of a single-arm clinical study (n=138; mean age, 64 years, range 41-86) enrolling adults with relapsed or refractory CLL (fludarabine-refractory disease and alemtuzumab-refractory disease [n=59] or fludarabine-refractory CLL with bulky lymphadenopathy [n=79]) Ofatumumab as a single agent was administered IV for a total of 8 weekly infusions, followed by 4 monthly infusions over a 24-week period (300 mg for dose 1; 2000 mg for doses 2-12). Individuals were considered drug refractory if they failed to achieve partial or full response to the last dose of fludarabine or alemtuzumab, or experienced disease progression within 6 months of the last dose of fludarabine or alemtuzumab. The primary outcome measure of a planned interim analysis was the overall response rate (ORR), reported in 58% and 47% in the fludarabine- and alemtuzumab-refractory and bulky lymphadenopathy groups, respectively. The median PFS ranged from 5.7 to 5.9 months in these 2 groups. The most common adverse events were grade 1 or 2 infusion-related reactions in 64% of individuals with refractory disease. A total of 4 deaths (7%) occurred in the fludarabine-refractory group and 2 (3%) in the lymphadenopathy group. This interim analysis focused on the more limited outcome of ORR, rather than the more mature outcome of PFS. However, based on the ORR, the authors concluded that ofatumumab provided meaningful improvements in heavily pretreated subjects refractory to both fludarabine and alemtuzumab, or in subjects with bulky lymphadenopathy considered poor candidates for alemtuzumab. For example, the drug was associated with resolution of constitutional symptoms and improvements in performance standards.

A randomized, open-label, phase III clinical trial was conducted by Byrd and colleagues, assessing the efficacy and safety of ofatumumab versus ibrutinib in 391 individuals with relapsed or refractory CLL/SLL. The primary outcome of interest was the duration of PFS, while overall survival and ORR were secondary endpoints. At a median follow-up of 9.4 months, ibrutinib arm (n=195) had not yet achieved median duration of survival. Therefore, ibrutinib was found to significantly improve PFS compared to the ofatumumab arm's (n=196) median PFS which was 8.1 months (hazard ration [HR] for PFS with ibrutinib was 0.22; 95% confidence interval [CI], 0.15-0.32; p<0.001). The ORR was significantly higher in the ibrutinib arm (42.6% vs. 4.1%, p<0.001). The efficacy of ibrutinib was not affected by baseline characteristics or molecular variations in disease. The safety profile of ibrutinib was acceptable, especially considering the duration of treatment, on average, exceeded that of the ofatumumab arm.

On August 31, 2016, the FDA expanded the PI label for ofatumumab to include treatment of relapsed CLL in combination with fludarabine and cyclophosphamide. Approval was based on the Phase III COMPLEMENT 2 clinical trial in which 365 individuals diagnosed with relapsed CLL were randomized 1:1 to receive either ofatumumab, fludarabine and cyclophosphamide (OFC) or fludarabine and cyclophosphamide (FC) alone. The primary endpoint was PFS and secondary outcomes included ORR and overall survival (OS). The median duration of treatment for both study arms was six cycles. At study-end, PFS was assessed by independent-review and determined to be significantly longer in the OFC arm versus the FC arm (28.9 months vs 18.8 months; HR=0.67 [95% CI, 0.51-0.89]; p=0.0036). Similarly, the ORR was 84% for the OFC arm and 68% for the FC arm (p=0.0004). Median OS (follow-up at 34 months) however, was not significantly different between the two arms. Furthermore, the comparator group for this trial was not the ideal choice for demonstration of superiority over best available treatments.

According to the National Comprehensive Cancer Network® (NCCN®) Clinical Practice Guidelines (CPG) for CLL/SLL (2018), ofatumumab is a category 2A recommended single-agent treatment for individuals with relapsed/refractory chronic CLL/SLL, with and without a del(17p)/TP53 mutation and in combination with fludarabine and cyclophosphamide in individuals without a del(17p)/TP53 mutation.

There are no standard and well-defined treatments for refractory or relapsed disease. Currently available salvage treatments include purine analogs, such as fludarabine or pentostatin; alkylating agents, such as chlorambucil, cyclophosphamide, or bendamustine; and chemoimmunotherapy, such as fludarabine, cyclophosphamide, and rituximab. However, these treatments, alone or in combination, often have low response rates, short time to treatment failure (median, 2-3 months) and poor survival outcomes (median, 6 months). As a result, new effective treatments are needed for refractory or relapsed disease.

Maintenance Therapy for CLL/SLL

The FDA approved ofatumumab for the extended treatment of individuals with recurrent or progressive CLL who have achieved a complete or partial response (PR) following at least two lines of therapy. This label expansion was based on the open-label, phase III PROLONG trial in which 474 individuals who had achieved either a PR or complete remission, after either second- or third-line therapy, were randomized to receive ofatumumab (n=238) or observation (n=236) across 24 countries. Eligible participants had a performance status of 2 or better, did not have

refractory disease (per a response assessment within the 3 months previous to enrollment), and had never received maintenance therapy or a stem cell transplant. Once enrolled, study participants in the treatment arm received ofatumumab every 8 weeks for up to 2 years or until withdrawal from the study for a variety of reasons (for example, withdrawn consent, disease progression or intolerable side-effects). The study arms were well matched demographically and with respect to prior therapies and disease severity. At the time of study end, the median duration of follow-up was 19.1 months. PFS, the primary outcome, was significantly longer in the ofatumumab group (29.4 months) compared with those assigned to the observation arm (15.2 months; HR=0.50; 95% CI, 0.38-0.66, p<0.0001). There was no difference in overall survival between the two study groups (HR=0.85, p=0.4877). The most frequently reported grade 3 and 4 adverse events were related to neutropenia and infection and were significantly higher in the ofatumumab group. A total of two treatment related deaths occurred in the ofatumumab arm and five deaths occurred in the observation arm; no deaths were attributable to the study drug. Limitations of this study include the open-label design, lack of effect on overall survival, and study funding and data analyses were administered by the drug manufacturer. The NCCN has given ofatumumab a category 2B recommendation for use of ofatumumab as a maintenance therapy for CLL.

Waldenström's Macroglobulinemia (WM)/Lymphoplasmacytic Lymphoma (LPL)
Many patients inevitably experience relapse after initial therapy and require further treatment. Administering the same regimen used for primary treatment is reasonable as therapy for relapsed disease if a patient achieved a response that lasted for at least twelve months or more. Otherwise, use of an alternative single agent or combination is recommended.

Two studies have addressed the role of ofatumumab in patients with WM, including patients who were intolerant to rituximab. These studies demonstrated that ofatumumab could be successfully administered, either as single-agent or as combination therapy, in patients with WM who were intolerant to rituximab, and were associated with responses. Therefore, according to the NCCN Panel, ofatumumab may be considered in patients who are intolerant to rituximab, either as single agent or combination therapy.

Other Uses
Ofatumumab has also been investigated as a component of a chemoimmunotherapy regimen, specifically as an alternative to rituximab. Wierda investigated ofatumumab combined with fludarabine and cyclophosphamide in previously untreated individuals. A total of 61 participants were randomized to receive either 500 mg (n=31) or 1000 mg (n=30) of ofatumumab combined with fludarabine and cyclophosphamide (O-FC) administered every 4 weeks for a total of 6 courses of treatment. CR rate was 32% in the 500 mg group compared to 50% in the 1000 mg group. The authors concluded that a chemoimmunotherapy regimen incorporating ofatumumab is active in individuals with newly diagnosed CLL.

Shanafelt conducted an uncontrolled study to evaluate ofatumumab combined with pentostatin and cyclophosphamide in 48 previously untreated individuals with CLL. A total of 13 individuals (27%) had grade 3+ hematologic toxicity and 23% had grade 3+ nonhematologic activity. The ORR was 96% (46/48) and the CR rate was 46% (22/48). After a median follow-up of 24 months, 21% experienced disease progression and 17% required additional treatment.

When compared with historical controls, time to retreatment appeared to be longer for ofatumumab-based chemoimmunotherapy. Study investigators suggested that well-designed randomized controlled trials are needed to compare ofatumumab-based chemoimmunotherapy with other standard treatments.

Cortelezzi and colleagues conducted a non-comparative, phase II trial investigating the safety and efficacy of ofatumumab in combination with bendamustine in 47 relapsed/refractory CLL subjects. Most of the study population had failed treatment with fludarabine (75%) or previously received rituximab (55%), and over one-third were 70 years of age or older. The median follow-up was 23.6 months (range, 1.3-33.3 months), and the primary outcome of the study, ORR, was 72.3% (95% CI, 57-84%), with 17% achieving a CR. The most common toxicity was myelosuppression. Grade 3 or higher neutropenia was observed in 61.7% of participants, and grade 3 or higher infections occurred in 6%. Authors concluded that ofatumumab in combination with bendamustine may be a feasible treatment option for relapsed/refractory CLL in a high-risk population. Larger randomized controlled trials are warranted.

Similarly, Flinn and colleagues conducted a non-comparative, slightly larger phase II trial (n=97) investigating the safety and efficacy of ofatumumab and bendamustine in treatment naïve (n=44) and relapsed individuals (n=53) with CLL. After 29 months of follow-up, the ORR was 95% (43% CR for the previously untreated, and 74% (11% CR) for the relapsed population). Grade 3 and grade 4 events occurred in 57% of previously untreated, and 72% of relapsed patients. An additional study conducted in this setting was stopped early due to toxicities). Although the NCCN has given a 2A recommendation for the treatment of relapsed CLL in the first-line setting a rationale is not provided; additional study is warranted.

Gazyva (obinutuzumab)

Previously Untreated CLL

The U.S. Food and Drug Administration (FDA) approved Gazyva (obinutuzumab) as the first drug with breakthrough therapy designation. Obinutuzumab received FDA approval in combination with chlorambucil as a treatment of individuals with previously untreated chronic lymphocytic leukemia (CLL). The basis of this approval was a pivotal randomized, multicenter, open-label, phase III trial which consisted of three arms: Arm 1 (active control arm) received chlorambucil alone (Clb); Arm 2 received obinutuzumab in combination with Clb (G-Clb); and those on Arm 3 were treated with rituximab in combination with Clb (R-Clb). All enrolled participants had clinically meaningful burden of coexisting conditions as represented by scores of 6 or higher on the Cumulative Illness Rating Scale (CIRS) (range 0-56) or a creatinine clearance of 30 to 69 ml per minute. The primary endpoint of the study was progression-free survival (PFS). Enrollment included a total of 781 participants, with 118 in Arm 1 (Clb), 333 in Arm 2 (G-Clb) and 330 in Arm 3 (R-Clb). The median age was 73 years, the median creatinine clearance was 62 ml/minute and the median baseline CIRS score was 8. The authors reported significant improvement in the median PFS was observed with G-Clb or R-Clb, as compared with Clb alone (26.7 months with G-Clb vs. 11.1 months with Clb alone; hazard ratio for progression or death, 0.18; 95% confidence interval [CI], 0.13 to 0.24; P<0.001; and 16.3 months with R-Clb vs. 11.1 months with Clb alone; hazard ratio, 0.44; 95% CI, 0.34 to 0.57; P<0.001).

At 3 months, complete responses (CR) were significantly improved in the antibody groups (G-Clb [20.7%], R-Clb [7.0%]) compared to no cases of CR noted in the Clb alone cohort. Adverse events were more frequent in the G-Clb and R-Clb groups compared to Clb alone with the most frequent serious adverse events reported as infections, infusion-related reactions and neoplasms. Grade 3 or 4 infusion-related reactions occurred during the first infusion of obinutuzumab in 20% of the participants, but there were no deaths associated with the reactions. Death due to adverse events was lowest in the G-Clb group (4%) compared to R-Clb (6%) and Clb alone (9%). The investigators noted the addition of antibodies to Clb increased the efficacy and the toxicity of the treatment. Longer follow-up is needed to determine if the improved disease-free survival (DFS) and higher response rate with G-Clb compared to R-Clb will result in improved overall survival benefit. Data from this pivotal trial resulted in the FDA approval for obinutuzumab treatment as first-line treatment of individuals with CLL.

The National Comprehensive Cancer Network® (NCCN®) Clinical Practice Guidelines (CPG) for CLL/SLL (2018) considers "CLL and SLL as different manifestations of the same disease and are managed in much the same way." In CLL, significant numbers of abnormal lymphocytes are found in the bone marrow while in SLL, the lymphocytes are found primarily in the lymph nodes. The NCCN notes obinutuzumab in combination with chlorambucil is indicated as first-line therapy for individuals with stage II-IV CLL/small lymphocytic lymphoma (SLL), especially those who are considered 'frail' as a result of advanced age or comorbidities. Based on a subset analysis of the pivotal clinical trial, the NCCN CPGs for CLL/SLL (V3.2018) had given a Category 3 recommendation for the treatment of CLL/SLL with del (17P) disease with obinutuzumab and chlorambucil in the first-line setting, due to a lack evidence of a clinical benefit in this subpopulation. However, based on consensus, and lack of other treatment options, this recommendation has been changed to a Category 2A for obinutuzumab as monotherapy in the first-line setting for the treatment of CLL/SLL with del (17P).

The NCCN also gives obinutuzumab a Category 2A recommendation for single-agent treatment of relapsed/refractory CLL/SLL with the exception of del (17p) disease. This recommendation is based on the GAUGUIN study, a Phase I and II dose-finding clinical trial that included 33 participants, of which 26 completed the study. A total of 62% (8) of 13 participants achieved a partial response (PR) in phase I and 15% (3) of 20 in phase II, while none achieved a CR. Overall response rate (ORR) was 30% with a median PFS of 10.7 months and duration of response of 8.9 months. The NCCN also cites the results of the CLL11 study which were published only in abstract form and not listed in the National Library of Medicine's PubMed database. This report included 30 subjects who received chlorambucil alone as initial treatment and developed progressive disease and were placed on combined obinutuzumab-chlorambucil therapy. Clinical response was reported in 87% of subjects with a partial response in 77%, complete response in 7%, and no response in 3%. Despite the lack of more robust evidence of efficacy of obinutuzumab in individuals with refractory or relapsed CLL, the NCCN consensus position was that in this difficult-to-treat population this therapy provides significant clinical benefits where no other options exist.

<u>Relapsed or Refractory NHL</u>

The FDA granted Gazyva (obinutuzumab) an additional approval for use in combination with bendamustine followed by obinutuzumab monotherapy for the treatment of individuals with

follicular lymphoma (FL) who relapse after, or are refractory to, a rituximab-containing regimen. This approval was based on results of an unpublished open-label, multicenter RCT demonstrating improvement in PFS in 321 subjects with follicular lymphoma with no response to or who have progressed during or within 6 months of a rituximab-containing regimen. The trial compared 6 cycles of bendamustine therapy alone (n=166) vs. 6 cycles of obinutuzumab plus bendamustine combination therapy followed by continued obinutuzumab monotherapy (n=155) for up to 2 years. Subjects had received a median of 2 prior therapies (range 1-10). The independent review-assessed median PFS was 13.8 months in the bendamustine arm while the median PFS was not reached in the obinutuzumab plus bendamustine arm (hazard ratio [HR]=0.48, log-rank test p<0.0001). This trial also enrolled 46 subjects with marginal zone lymphoma and 28 subjects with small lymphocytic lymphoma who were included in the safety analysis. The most common adverse reactions (greater than or equal to 10%) in the safety population treated with obinutuzumab plus bendamustine followed by obinutuzumab monotherapy were infusion reactions, neutropenia, nausea, fatigue, cough, diarrhea, constipation, pyrexia, thrombocytopenia, vomiting, upper respiratory tract infection, decreased appetite, arthralgia, sinusitis, anemia, asthenia and urinary tract infection. Serious adverse reactions were reported in 38% of subjects treated with obinutuzumab plus bendamustine followed by obinutuzumab monotherapy. The most common serious adverse reactions (greater than 2%) were febrile neutropenia, neutropenia, infusion related reactions, sepsis, pneumonia and pyrexia.

Sehn and others reported on the results of a randomized controlled trial (RCT) comparing obinutuzumab to rituximab in 149 subjects with relapsed CD20+ indolent follicular lymphoma. Subjects were randomly assigned in a 1:1 fashion to four once-per-week infusions of either obinutuzumab (1000 mg, n=74) or rituximab (375 mg/m^2, n=75). Subjects without evidence of disease progression after induction therapy received obinutuzumab or rituximab maintenance therapy every 2 months for up to 2 years (n=70 in each arm). The final analysis included 37 obinutuzumab subjects and 35 rituximab subjects (48.3% of the original study population). Following induction, blinded independent review reported that obinutuzumab subjects had a higher ORR than rituximab subjects (44.6% vs. 26.7%, p=0.01), but no significant differences in complete response (CR) rates (p=0.34). Independent reviewer-assessed best overall response (BOR) was higher in obinutuzumab subjects vs. rituximab subjects (63.5% vs. 49.3%, p=0.04); however, there were no significant differences in CR rates (p=0.07). This study also included a small population of 26 subjects with non-follicular B-cell lymphoma who also were randomized to receive obinutuzumab or rituximab. In this group the median follow-up was 32 months, with no differences between groups noted for progression-free survival (HR=1.44). Both follicular and non-follicular subjects together comprise the safety population. Only infusion reactions (74% vs. 51%) and cough (24% vs. 9%) were significantly more frequent adverse events in the obinutuzumab group (p=0.003 and p=0.013, respectively). The authors concluded that these findings warrant further investigation in a phase III trial.

The NCCN CPGs for B-cell Lymphomas (V3.2017) include 2A recommendations for the use of obinutuzumab maintenance for multiple types of refractory NHLs (gastric MALT lymphoma, nodal marginal zone lymphoma, nongastric MALT lymphoma, primary cutaneous B-Cell lymphoma and splenic marginal zone lymphoma), as well as 2A recommendation for its use a component of any of the following combination regiments for the aforementioned types of NHL: (1) cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP regimen), (2)

Cyclophosphamide, vincristine, and prednisone (CVP regimen) or (3) Bendamustine. The rationale cited for the above 2A indications is from an interim analysis (n=1202) of an open-label, randomized (1:1) phase III trial comparing the efficacy and safety of rituximab to obinutuzumab as both induction and maintenance therapy in indolent NHLs. Although participants with untreated follicular lymphoma and marginal lymphoma were enrolled, only data for follicular lymphoma was presented. Participants received CHOP, CVP or bendamustine in combination with either rituximab or obinutuzumab. After a median follow-up of 34.5 months, the relative risk reduction for progression or death was 34% (HR=0.66; 95% CI, 0.51, 0.85; p=0.001. Grade 3-5 adverse events were higher in the obinutuzumab arm (74.6%) relative to the rituximab arm (67.8%).

Key Words:

Chronic lymphocytic leukemia (CLL), Small lymphocytic lymphoma (SLL), Waldenström's macroglobulinemia, Lymphoplasmacytic lymphoma (LPL), Arzerra, ofatumumab, Gazyva, Obinutuzumab, Follicular Lymphoma (FL), Non-Hodgkin Lymphoma

Approved by Governing Bodies

On October 26, 2009, ofatumumab (Arzerra®; Novartis) was approved by the FDA through accelerated approval process for treatment of patients with CLL refractory to fludarabine and alemtuzumab.

On April 17, 2014, the FDA approved ofatumumab (Arzerra; GlaxoSmithKline) in combination with chlorambucil, for the treatment of previously untreated patients with chronic lymphocytic leukemia (CLL), for whom fludarabine-based therapy is considered inappropriate.

On January 19, 2016, the U.S. Food and Drug Administration approved ofatumumab (Arzerra Injection, Novartis) for extended treatment of patients who are in complete or partial response after at least two lines of therapy for recurrent or progressive chronic lymphocytic leukemia (CLL).

On November 11, 2013, obinutuzumab (Gazyva™; Genentech) was approved by FDA through breakthrough therapy designation process for treatment of patients with previously untreated CLL in combination with chlorambucil.

On February 26, 2016, obinutuzumab (Gazyva™, Genentech) was approved for use in combination with bendamustine followed by obinutuzumab monotherapy for the treatment of patients with follicular lymphoma who relapsed after, or are refractory to, a rituximab-containing regimen.

On November 16, 2017 the Food and Drug Administration granted regular approval to obinutuzumab (Gazyva, Genentech, Inc.) in combination with chemotherapy, followed by obinutuzumab monotherapy in patients achieving at least a partial remission, for the treatment of adult patients with previously untreated stage II bulky, III, or IV follicular lymphoma (FL).

Benefit Application:

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

Current Coding:

CPT Codes:

J9301	Injection, obinutuzumab, 10 mg
J9302	Injection, ofatumumab, 10 mg

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Policy History:

Medical Policy Group, September 1, 2015.
Medical Policy Group, July 2016

Medical Policy Group, December 2016
Medical Policy Group, March 2018
Available for comment March 6, 2018 to April 20, 2018
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.