Introduction

Phosphoinositide 3-kinase inhibitors (PI3K inhibitors) block one or more enzymes, which are part of an important signaling pathway inside cells, essentially working to turn the cell growth to the “off” position. This policy describes when this specific form of chemotherapy may be considered medically necessary.

Note: The Introduction section is for your general knowledge and is not to be taken as policy coverage criteria. The rest of the policy uses specific words and concepts familiar to medical professionals. It is intended for providers. A provider can be a person, such as a doctor, nurse, psychologist, or dentist. A provider also can be a place where medical care is given, like a hospital, clinic, or lab. This policy informs them about when a service may be covered.

Policy Coverage Criteria

<table>
<thead>
<tr>
<th>Drug</th>
<th>Medical Necessity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aliqopa™ (copanlisib) (IV infusion)</td>
<td>Aliqopa™ (copanlisib) or Copiktra™ (duvelisib) may be considered medically necessary for patients with Chronic Lymphocytic Leukemia (CLL)/Small Lymphocytic Lymphoma (SLL) or Follicular Lymphoma (FL) when the following criteria are met:</td>
</tr>
<tr>
<td>Copiktra™ (duvelisib) (oral)</td>
<td></td>
</tr>
<tr>
<td>Drug</td>
<td>Medical Necessity</td>
</tr>
<tr>
<td>------------------------------------------------</td>
<td>----------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>• Patient is at least 18 years of age,</td>
<td></td>
</tr>
<tr>
<td><strong>AND</strong></td>
<td></td>
</tr>
<tr>
<td>• Patient has had at least two prior systemic</td>
<td></td>
</tr>
<tr>
<td>therapies</td>
<td></td>
</tr>
</tbody>
</table>

**Zydelig® (idelalisib) (oral)**

*Zydelig® (idelalisib) may be considered medically necessary for the treatment of patients with ANY of the following:*

- Relapsed chronic lymphocytic leukemia (CLL), in combination with rituximab, in patients for whom rituximab alone would be considered appropriate therapy due to other co-morbidities
- Relapsed follicular B-cell non-Hodgkin lymphoma (FL) in patients who have received at least two prior systemic therapies
- Relapsed small lymphocytic lymphoma (SLL) in patients who have received at least two prior systemic therapies

**Note:** Zydelig is not indicated and is not recommended for first-line treatment of any patient.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Investigational</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>All drugs in this policy</strong></td>
<td>All other uses of drugs in this policy for conditions not outlined in the policy are considered investigational.</td>
</tr>
</tbody>
</table>

**Length of Approval**

<table>
<thead>
<tr>
<th>Approval</th>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial Approval</td>
<td>Initial approval for three months, according to the medical necessity criteria specified for each drug.</td>
</tr>
<tr>
<td>Reauthorization</td>
<td>Continued therapy will be approved for periods of up to one year as long as the drug-specific conditions are met, and the patient has shown and continues to show clinical benefit.</td>
</tr>
</tbody>
</table>
| Documentation     | **Initial:**  
|                   | • Chart notes demonstrating that the patient meets the stated criteria for medical necessity.  
|                   | • Test results showing the presence of any markers specified in the criteria must be included.  
|                   | **Reauthorization:**  
|                   | • Chart notes demonstrating that the patient continues to show clinical benefit. |
Coding

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>HCPC</td>
<td></td>
</tr>
<tr>
<td>J9057</td>
<td>Injection, copanlisib (Aliqopa™), 1 mg (new code effective 1/1/19)</td>
</tr>
</tbody>
</table>

Note: CPT codes, descriptions and materials are copyrighted by the American Medical Association (AMA). HCPCS codes, descriptions and materials are copyrighted by Centers for Medicare Services (CMS).

Related Information

Consideration of Age

Age limits specified in this policy are determined according to FDA-approved indications, where applicable.

Benefit Application

The drugs in this policy that are administered orally (Copiktra™ and Zydelig®) are managed through the Pharmacy benefit. Drugs administered via IV infusion (Aliqopa™) are managed through the Medical benefit.

Evidence Review
Description

Chronic Lymphocytic Leukemia (CLL)/Small Lymphocytic Lymphoma (SLL) and Follicular Lymphoma (FL)

CLL and SLL are different manifestations of the same lymphocytic malignancy and are subtypes of Non-Hodgkin Lymphoma. The primary difference between these conditions is that a majority of leukemic B-cells circulate in the blood in CLL, whereas they are found in lymphoid tissue in SLL. FL is another B-cell lymphoproliferative disorder and subtype of NHL.

Disease Burden

Approximately 7% of newly diagnosed NHL cases are CLL/SLL. In the US in 2018, the incidence of CLL is estimated to be 21,000 and approximately 4500 people will die of the disease. CLL is the most prevalent adult leukemia in Western countries. CLL is mainly diagnosed in older adults (median 72 years of age). Between 1998 and 2011, FL comprised 17% of all NHL diagnosed in the US. It is the second most common form of NHL and the most common form of indolent NHL.

Pathophysiology

CLL/SLL is characterized by a progressive accumulation of mature lymphocytes in the blood, bone marrow, and lymphoid tissues. These conditions typically proceed through a couple of different phases consisting of an early indolent phase where cells are small in size, proliferation is low, and there is prolonged cell survival and a transformation phase characterized by an increase in large immature cells and extramedullary proliferation. Unfavorable prognostic indicators include unmutated immunoglobulin heavy-chain variable (IGHV) status, TP53 mutation, the presence of cytogenic abnormalities (del[13q] or del[11q]), higher levels of flow-cytometry based prognostic markers (CD38, CD49d, and ZAP-70), and serum markers (eg, thymidine kinase and beta-2 microglobulin).

Patients with low-grade indolent disease without signs or symptoms for initiating treatment usually receive supportive care and watchful waiting as therapy, given active treatment has not been shown to prolong survival. Signs and symptoms for initiating active treatment include severe fatigue, weight loss, night sweats, fever (without infection), progressive bulky disease (enlarged spleen and/or lymph nodes), progressive anemia or thrombocytopenia, autoimmune anemia, thrombocytopenia unresponsive to corticosteroids, and threatened end-organ function.
FL is caused by a translocation between chromosome 14 and 18 that results in overexpression of the bcl-2 gene. This gene produces a protein that prevents apoptosis. Consequently, cells that overexpress the bcl-2 protein are basically immortal. Other translocations may also be involved. FL tumors are composed of centrocytes and centroblasts, and the volume of these cell types determines World Health Organization morphological grade.

Patients with asymptomatic disease usually receive supportive care and watchful waiting as therapy. When patients are symptomatic active treatment is initiated, with consideration to age, stage, and International Prognostic Index score.

**Treatment Alternatives**

*NCCN recommended first-line treatment alternatives include:*

**CLL/SLL patients w/o del(17p)/TP53 mutation** – chlorambucil + obinutuzumab; ibrutinib; chlorambucil + ofatumumab; chlorambucil + rituximab; FCR (fludarabine + cyclophosphamide + rituximab) (patients <65 yrs of age w/o significant comorbidities only); bendamustine + CD20 monoclonal antibody (rituximab, obinutuzumab, ofatumumab) (patients <65 yrs of age w/o significant comorbidities only)

**CLL/SLL patients w/ del(17p)/TP53 mutation** – ibrutinib

**Post first-line CLL/SLL maintenance therapy:** lenalidomide (high-risk patients only). In patients with histologically transformed disease, see other appropriate NCCN guidelines.

**FLL (grade 1-2):** bendamustine + obinutuzumab; bendamustine + rituximab; CHOP (cyclophosphamide + doxorubicin + vincristine + prednisone) + obinutuzumab; RCHOP (rituximab + CHOP); CVP (cyclophosphamide + vincristine + prednisone) + obinutuzumab; RCVP (rituximab + CVP); elderly patients or infirm – rituximab

**First-line FLL (grade 1-2) consolidation or extended dosing:** rituximab; obinutuzumab; ibrutinumab tiuxetan

**Preferred Existing Therapy**

**R/R CLL/SLL:** patients w/o del(17p)/TP53 mutation - ibrutinib; idelalisib + rituximab; venetoclax + rituximab
**R/R CLL/SLL:** patients w/ del(17p)/TP53 mutation - ibritinib; idelalisib + rituximab; venetoclax + rituximab; venetoclax. In patients with histologically transformed disease, see other appropriate NCCN guidelines.

**R/R FLL (grade 1-2):** bendamustine or CHOP or CVP + obinutuzumab or rituximab; rituximab; lenalidomide + rituximab; elderly patients or infirm – rituximab

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**Other Therapeutic Alternatives**

**First-line CLL/SLL: patients w/o del(17p)/TP53 mutation** – high-dose methylprednisone (HDMP) + rituximab; obinutuzumab; chlorambucil; rituximab; FR (fludarabine + rituximab) (patients <65 yrs of age w/o significant comorbidities only); PCR (pentostatin + cyclophosphamide + rituximab) (patients <65 yrs of age w/o significant comorbidities only)

**First-line CLL/SLL: patients w/ del(17p)/TP53 mutation** – alemtuzumab ± rituximab; HDMP + rituximab; obinutuzumab

**First-line FL (grade 1-2):** lenalidomide + rituximab; rituximab; elderly patients or infirm – chlorambucil + rituximab; cyclophosphamide + rituximab; chlorambucil; cyclophosphamide; ibrutomomab tiuxetan

**R/R CLL/SLL: patients w/o del(17p)/TP53 mutation** – acalabrutinib; alemtuzumab ± rituximab; chlorambucil + rituximab; reduced-dose FCR; HDMP + rituximab; obinutuzumab; ofatumumab; PCR; venetoclax; dose-dense rituximab; bendamustine, rituximab + ibrutinib or idelalisib; bendamustine + rituximab (patients <65 yrs of age w/o significant comorbidities only); FC + ofatumumab (patients <65 yrs of age w/o significant comorbidities only); FCR (patients <65 yrs of age w/o significant comorbidities only); idelalisib (patients <65 yrs of age w/o significant comorbidities only); lenalidomide ± rituximab (patients <65 yrs of age w/o significant comorbidities only)

**R/R CLL/SLL: patients w/ del(17p)/TP53 mutation** – acalabrutinib; alemtuzumab ± rituximab; HDMP + rituximab; idelalisib; lenalidomide ± rituximab; ofatumumab

**Post second-line CLL/SLL maintenance therapy:** lenalidomide; ofatumumab. In patients with histologically transformed disease, see other appropriate NCCN guidelines.

**R/R FLL (grade 1-2):** ibrutumomab tiuxetan; idelalisib; copanlisib; elderly patients or infirm – chlorambucil or cyclophosphamide + rituximab; chlorambucil; cyclophosphamide; ibrutumomab tiuxetan
Second-line FLL consolidation or extended dosing: rituximab; obinutuzumab; high-dose therapy with autologous stem cell rescue; allogeneic hematopoietic stem cell transplant (HSCT) (highly selected patients only)

PI3K Inhibitors

Idelalisib, Copanlisib and Duvelisib are oral selective small molecule inhibitors of one or more of the phosphoinositide 3-kinase enzymes, which are part of the PI3K/AKT/mTOR pathway, an important signaling pathway for many cellular functions such as growth control, metabolism and translation initiation. Within this pathway there are many components, inhibition of which may result in tumor suppression.

There are a number of different classes and isoforms of PI3Ks. Class 1 PI3Ks have a catalytic subunit known as p110, with four types (isoforms) – p110 alpha, p110 beta, p110 gamma and p110 delta. The inhibitors being studied inhibit one or more isoforms of the class I PI3Ks. They are being actively investigated for treatment of various cancers. PI3K signaling is believed to play a role in the proliferation of malignant B- and T-cells and in the formation and maintenance of a supportive tumor microenvironment. The currently approved agents have the following target profiles:

- Idelalisib: targets delta
- Copanlisib: targets alpha and delta
- Duvalisib: targets gamma and delta

Summary of Evidence

Aliqopa™ (copanlisib)

The efficacy of Aliqopa™ (copanlisib) was evaluated in a single-arm, multicenter, phase 2 clinical trial, CHRONOS-1 in a total of 142 subjects, which included 104 subjects with follicular B-cell non-Hodgkin lymphoma who had relapsed disease following at least two prior treatments. Patients must have received rituximab and an alkylating agent. The most common prior systemic therapies were chemotherapy in combination with anti-CD20 immunotherapy (89%), chemotherapy alone (41%), and anti-CD20 immunotherapy alone (37%). In CHRONOS-1, 34% of patients received two prior lines of therapy and 36% received three prior lines of therapy.
One hundred forty-two patients received 60 mg Aliqopa; 130 patients received fixed dose 60 mg Aliqopa and 12 patients received 0.8 mg/kg equivalent Aliqopa administered as a 1-hour intravenous infusion on Days 1, 8, and 15 of a 28-day treatment cycle on an intermittent schedule (three weeks on and one week off). Treatment continued until disease progression or unacceptable toxicity. Tumor response was assessed according to the International Working Group response criteria for malignant lymphoma. Efficacy based on overall response rate (ORR) was assessed by an Independent Review Committee. Overall Response Rate (ORR) was 59% (61 patients, 95% CI (49, 68). Of these, 15 patients achieved a Complete Response. Median Duration of Response was 12.2 months (range 0+, 22.6 months).

Copiktra™ (duvelisib)

One moderate quality phase 3, randomized open-label, active-controlled clinical trial (DUO) demonstrates statistically significant incremental improvements in progression-free survival (PFS) of 3.4 months, objective response rate (ORR) of 28.5%, and lymph node response rate (LNRR) of 69% with duvelisib vs ofatumumab in patients with R/R CLL or SLL. One fair quality phase 2, open-label, single arm study (DYNAMO) of duvelisib monotherapy in adults with double-refractory iNHL showed an overall ORR of 46%, a median DoR of 9.9 months, a LNRR of 83%, a median PFS of 8.4 months, and a median OS of 18.4 months. Response appeared better in patients with SLL than in those with FL. Other potentially supportive studies of duvelisib monotherapy in patients with CLL or iNHL and off-label studies in patients with R/R peripheral T-cell lymphoma (PTCL) and for use in combination with chemoimmunotherapy are ongoing.

Zydelig® (idelalisib)

Zydelig® (idelalisib) is the first selective and reversible inhibitor of PI3K to receive FDA approval. It was approved on the basis of one multicenter, randomized, double-blind, Phase 3 study. The patients were randomly assigned to receive rituximab with either idelalisib or placebo. The patients in the placebo group who had disease progression were able to crossover to receive idelalisib. Patients in the idelalisib group who had disease progression could receive an increased dose.

The addition of idelalisib to rituximab therapy resulted in improved overall response rate (81% with idelalisib vs 13% with placebo). There were no complete responses. A higher proportion of patients with a reduction of lymphadenopathy of 50% or greater was observed with idelalisib (93% vs 4%). Improved progression-free survival (93% vs 46%) was also seen at 24 weeks with
idelalisib; PFS median was not reached with idelalisib vs 5.5 months with placebo. (HR 0.15; 95% CI 0.08–0.28). Overall survival rate at 12 months was (92% vs 80%; HR 0.28; 95% CI 0.09–0.86).

Idelalisib for treatment of relapsed FL and SLL is shown in the DELTA study, which is an open-label, single arm, Phase 2 study. Phase 3 trials are ongoing, and need to be assessed given the estimated primary completion date (December 2015) and estimated study completion date (April 2016) to establish whether there is an improvement in duration of response, and disease-related symptoms. In comparison, a phase 1b-2 multicenter study assessing ibrutinib as treatment for relapsed CLL in a similar population showed that at 26 months, the estimated progression-free survival rate was 75% and the rate of overall survival was 83%.

More than 90% of the patients were reported with having at least one adverse event. The common adverse events included pyrexia, fatigue, nausea, chills, and diarrhea. Serious adverse events included pneumonia, pyrexia, and febrile neutropenia. Adverse events leading to study-drug discontinuation were reported in 8%. Gastrointestinal and skin disorders lead to 6 discontinuations in the idelalisib group.

In March 2016, the FDA released a safety alert stating that 6 clinical trials studying first-line CLL and early-line iNHL have been terminated due to concerns of decreased overall survival and increased risk of serious adverse events (mostly infections including PCP pneumonia and CMV that could lead to sepsis and death). Health care authorities (FDA, Health Canada) reiterated that idelalisib is only indicated for relapsed CLL, relapsed SLL, and relapsed FL. NCCN CLL/SLL 1.2017 guidelines and NCCN NHL 3.2016 guidelines list idelalisib as a treatment option for these indications. It now carries a black box warning for “fatal and serious toxicities: hepatic, severe diarrhea, colitis, pneumonitis, infections, and intestinal perforation.”

References


**History**

<table>
<thead>
<tr>
<th>Date</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>12/01/18</td>
<td>New policy approved November 13, 2018. Add to Prescription Drug section. Aliqopa (copanlisib), Copiktra (duvelisib), or Zydelig (idelalisib) may be considered medically necessary when criteria are met. They are considered investigational for all other uses.</td>
</tr>
<tr>
<td>01/01/19</td>
<td>Coding update, added new HCPCS code J9057 (new code effective 1/1/19). Removed HCPCS code J9999.</td>
</tr>
</tbody>
</table>
Disclaimer: This medical policy is a guide in evaluating the medical necessity of a particular service or treatment. The Company adopts policies after careful review of published peer-reviewed scientific literature, national guidelines and local standards of practice. Since medical technology is constantly changing, the Company reserves the right to review and update policies as appropriate. Member contracts differ in their benefits. Always consult the member benefit booklet or contact a member service representative to determine coverage for a specific medical service or supply. CPT codes, descriptions and materials are copyrighted by the American Medical Association (AMA). ©2019 Premera All Rights Reserved.

Scope: Medical policies are systematically developed guidelines that serve as a resource for Company staff when determining coverage for specific medical procedures, drugs or devices. Coverage for medical services is subject to the limits and conditions of the member benefit plan. Members and their providers should consult the member benefit booklet or contact a customer service representative to determine whether there are any benefit limitations applicable to this service or supply. This medical policy does not apply to Medicare Advantage.
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  - Qualified sign language interpreters
  - Written information in other formats (large print, audio, accessible electronic formats, other formats)
- Provides free language services to people whose primary language is not English, such as:
  - Qualified interpreters
  - Information written in other languages

If you need these services, contact the Civil Rights Coordinator.

If you believe that Premera has failed to provide these services or discriminated in another way on the basis of race, color, national origin, age, disability, or sex, you can file a grievance with:
Civil Rights Coordinator - Complaints and Appeals
PO Box 91102, Seattle, WA 98111
Toll free 855-332-4535, Fax 425-918-5592, TTY 800-842-5357
Email AppealsDepartmentInquiries@Premera.com

You can file a grievance in person or by mail, fax, or email. If you need help filing a grievance, the Civil Rights Coordinator is available to help you.

You can also file a civil rights complaint with the U.S. Department of Health and Human Services, Office for Civil Rights, electronically through the Office for Civil Rights Complaint Portal, available at:

Getting Help in Other Languages

This Notice has Important Information. This notice may have important information about your application or coverage through Premera Blue Cross. There may be key dates in this notice. You may need to take action by certain deadlines to keep your health coverage or help with costs. You have the right to get this information and help in your language at no cost. Call 800-722-1471 (TTY: 800-842-5357).

Arabic (Arabic):
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本通知有重要的訊息。本通知可能有關於您透過 Premera Blue Cross 提交的申請或保險的重要訊息。本通知可能有重要日期，您可能需要在截止日期之前採取行動，以保留您的健康保險或者費用補貼。您有權利免費以您的母語得到本訊息和幫助。請接電話 800-722-1471 (TTY: 800-842-5357).

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Italiano (Italian):
Premera Blue Cross.

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Este aviso contém informações importantes. Este aviso poderá conter informações importantes a respeito de sua aplicação ou cobertura por meio do Premera Blue Cross. Poderão existir dados importantes neste aviso. Talvez seja necessário que você tome providências dentro de determinados prazos para manter sua cobertura de saúde e ajuda de custos. Você tem o direito de obter esta informação e ajuda em seu idioma e sem custos. Ligue para 800-722-1471 (TTY: 800-842-5357).

Română (Romanian):

Русский (Russian):
Настоящее уведомление содержит важную информацию. Это уведомление может содержать важную информацию о вашем заявлении или страховом покрытии через Premera Blue Cross. В настоящем уведомлении могут быть указаны ключевые даты. Вам, возможно, потребуется принять меры к определенным предельным срокам для сохранения страхового покрытия или помощи с расходами. Вы имеете право на бесплатное получение этой информации и помощь на вашем языке. Звоните по телефону 800-722-1471 (TTY: 800-842-5357).

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Este Aviso contiene información importante. Es posible que este aviso contenga información importante acerca de su solicitud o cobertura a través de Premera Blue Cross. Es posible que haya fechas claves en este aviso. Es posible que deba tomar alguna medida antes de determinadas fechas para mantener su cobertura médica o ayuda con los costos. Usted tiene derecho a recibir esta información y ayuda en su idioma sin costo alguno. Llame al 800-722-1471 (TTY: 800-842-5357).

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ประกาศนี้มีข้อมูลสําคัญ คุณมีสิทธิที่จะได้รับข้อมูลและความช่วยเหลือนี้ในภาษาของคุณโดยไม่มีค่าใช้จ่าย โปรดทราบถึงวันที่ที่มีผลกระทบต่อสิทธิของคุณที่ปรากฏในประกาศนี้.

Tagalog (Tagalog):
Ang Paunawa na ito ay naglalaman ng mahalagang impormasyon. Ang paunawa na ito ay maaring nagagamitin ng mahalagang impormasyon tungkol sa iyong aplikasyon o pagsakop sa pamamagitan ng Premera Blue Cross. Maaaring may mga mahalagang petsa dito sa paunawa. Maaring mangailangan ka na nagmagasa ng habang sa ilang mga itinakdang panahon upang mapanatili ang iyong pagsakop sa kalusugan o tulong na walang gastos. May karapatan ka na makakuha ng ganitong impormasyon at tulong sa iyong wika ng walang gastos. Turnaw sa 800-722-1471 (TTY: 800-842-5357).

Polski (Polish):

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Este aviso contém informações importantes. Este aviso poderá conter informações importantes a respeito de sua aplicação ou cobertura por meio do Premera Blue Cross. Poderão existir dados importantes neste aviso. Talvez seja necessário que você tome providências dentro de determinados prazos para manter sua cobertura de saúde e ajuda de custos. Você tem o direito de obter esta informação e ajuda em seu idioma e sem custos. Ligue para 800-722-1471 (TTY: 800-842-5357).

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Tiếng Việt (Vietnamese):