Introduction

When the body detects something that can cause disease, like a virus or bacteria or a cancer cell, the immune system sends out specific cells to try to destroy the invader. Antibodies connect to harmful molecules. The antibodies act as flags for other immune system cells to attack the harmful molecule. Monoclonal antibodies are made in a lab and are engineered to attach to very specific targets on cancer cells. On some monoclonal antibodies, tiny particles of radiation can be attached. When this radiation-enhanced monoclonal antibody enters the body, it seeks out and links to its target to deliver the radiation. This treatment is known as radioimmunotherapy. This policy describes when radioimmunotherapy 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.
<table>
<thead>
<tr>
<th>Drug</th>
<th>Medical Necessity</th>
</tr>
</thead>
</table>
| Zevalin® (ibritumomab tiuxetan) | The use of Zevalin® (ibritumomab tiuxetan) may be considered medically necessary for:  
|                             | • The initial treatment of follicular lymphoma in patients who are unable to tolerate standard chemotherapy, eg, elderly or frail patients  
|                             | • Consolidation after chemotherapy for previously untreated CD20-positive follicular non-Hodgkin lymphoma patients who achieve a partial or complete response to first line chemotherapy  
|                             | • A single course of ibritumomab tiuxetan (Zevalin®) for the treatment of relapsed or refractory CD20-positive low-grade or follicular B-cell non-Hodgkin lymphoma, including patients with rituximab refractory non-Hodgkin lymphoma |

<table>
<thead>
<tr>
<th>Drug</th>
<th>Investigational</th>
</tr>
</thead>
</table>
| Zevalin® (ibritumomab tiuxetan) | The use of Zevalin® (ibritumomab tiuxetan) is considered investigational for:  
|                             | • Consolidation of a first remission following chemotherapy for de novo aggressive B-cell NHL  
|                             | • Use as part of a preparatory regimen before autologous or allogeneic hematopoietic stem-cell transplantation in patients with non-Hodgkin lymphoma |

**Note:** Because of the hematologic effects associated with the use of these agents (ie, cytopenias), it is recommended that they not be used in patients with more than 25% bone-marrow involvement by lymphoma and/or in patients with impaired bone-marrow reserve (ie, a platelet count less than 100,000/mm3 or a neutrophil count less than 1,500/mm3).

**Documentation Requirements**  
The patient’s medical records submitted for review for all conditions should document that medical necessity criteria are met. The record should include office visit notes that contain the relevant history and physical supporting any of the following:
### Documentation Requirements

- Initial treatment for patient with follicular lymphoma who is unable to tolerate standard chemotherapy (for example, an elderly or frail patient)
- Patient has partially or completely responded to the initial chemotherapy for CD20-positive follicular non-Hodgkin lymphoma and needs additional treatment
- To be used as a single course for a patient with relapsed or refractory CD20-positive low-grade or follicular B-cell non-Hodgkin lymphoma, including patients with rituximab refractory non-Hodgkin lymphoma

### Coding

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>CPT</td>
<td></td>
</tr>
<tr>
<td>79403</td>
<td>Radiopharmaceutical therapy, radiolabeled monoclonal antibody by intravenous infusion</td>
</tr>
<tr>
<td>HCPCS</td>
<td></td>
</tr>
<tr>
<td>A9542</td>
<td>Indium In-111 ibritumomab tiuxetan, diagnostic, per study dose, up to 5 millicuries</td>
</tr>
<tr>
<td>A9543</td>
<td>Yttrium Y-90 ibritumomab tiuxetan, therapeutic, per treatment dose, up to 40 millicuries (Zevalin)</td>
</tr>
</tbody>
</table>

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### Related Information

N/A

### Evidence Review
Description

Radioimmunotherapy (RIT) involves the administration of an antibody linked to a radioisotope, targeted to a specific cell type. Zevalin® (ibritumomab tiuxetan) is a radioimmunoconjugate that targets cell-surface CD20 found on normal B lymphocytes and more than 90% of B-cell non-Hodgkin lymphomas (NHL).

Background

CD20-based radioimmunotherapy (RIT) for non-Hodgkin lymphoma (NHL) is similar to the anti-CD20 monoclonal antibody rituximab, which is widely used against B-cell malignancies; however, 90Y-ibritumomab tiuxetan uses a monoclonal anti-CD20 antibody to deliver beta-emitting yttrium-90.¹

RIT offers several advantages over external beam irradiation in the treatment of NHL, a relatively radiosensitive disease.¹ RIT is given intravenously and, therefore, normal tissues overlying the tumor are spared significant radiation exposure. RIT provides radiation to known, as well as unsuspected tumor cells and nearby normal cells, producing a “bystander effect” because the radiation emitted from the isotopes is deposited over several cell diameters with poorly perfused or non-antigen-expressing nearby cells within a tumor mass suffering cytotoxic radiation effect.

B-cell and other NHLs can be subdivided into major subcategories as indolent and aggressive. Indolent B-cell lymphomas eg, follicular lymphoma or small cell lymphocytic lymphoma (SLL) usually present with advanced stage disease (stage IV) and are not considered curable in that stage with current treatments, including chemotherapy or radiotherapy. The disease course is usually prolonged, with a median survival of 7 to 10 years, characterized by initial response to chemotherapy, multiple relapses, and increasing resistance to treatment. In addition, approximately 60% of patients may eventually transform to a more aggressive type of lymphoma. Diffuse large B-cell lymphoma (DLBCL) is the most common aggressive B-cell lymphoma. Although rituximab is widely used in the treatment of B-cell NHL, not all patients respond, and a certain number of patients eventually develop resistance to the drug, necessitating additional treatments after rituximab.

Review articles published in 2010 and 2012 summarized various uses of RIT in NHL, include newly diagnosed disease, recurrent B-cell lymphoma, in combination with chemotherapy or other monoclonal antibodies, as preparative regimen for hematopoietic stem-cell transplant.²³
Summary of Evidence

For individuals with relapsed or refractory low-grade or follicular B-cell non-Hodgkin lymphomas (NHL) who receive ibritumomab tiuxetan, the evidence includes a randomized controlled trial (RCT) and 2 single-arm studies. Relevant outcomes are overall survival (OS), disease-specific survival, change in disease status, morbid events, quality of life, and treatment-related mortality and morbidity. The RCT showed that ibritumomab tiuxetan resulted in a significantly higher overall response rate of 80% compared with 56% with rituximab alone. Single-arm trials have also demonstrated response rates of 74% to 89% in previously treated disease. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who receive initial treatment of follicular B-cell NHL who receive ibritumomab tiuxetan, the evidence includes 3 single-arm studies. Relevant outcomes are OS, disease-specific survival, change in disease status, morbid events, quality of life, and treatment-related mortality and morbidity. The 3 studies have reported high overall response rates ranging from 87% to 94%. However, the median progression-free survival was less than that observed with first-line chemotherapy regimens plus rituximab in other studies. Although RCTs are needed, the current evidence has suggested that ibritumomab may be of clinical value as an initial treatment of indolent NHL, particularly in older, frail patients and that it provides long remissions and results equivalent to multicycle rituximab and chemotherapy combinations. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals with untreated follicular B-cell NHL who receive ibritumomab tiuxetan as consolidation treatment after remission, the evidence includes a pivotal RCT, a meta-analysis, and 2 single-arm studies. Relevant outcomes are OS, disease-specific survival, change in disease status, morbid events, quality of life, and treatment-related mortality and morbidity. The pivotal RCT demonstrated that consolidation with ibritumomab tiuxetan significantly prolonged median progression-free survival by 23.2 months regardless of partial or complete response after a median follow-up of 3.5 years. The number of patients who died was too small to permit a reliable comparison of survival. Results of the single-arm studies and meta-analysis were directionally consistent with the progression-free survival benefit. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals with untreated follicular B-cell NHL who receive ibritumomab tiuxetan as consolidation treatment after remission, the evidence includes a pivotal RCT, a meta-analysis, and 2 single-arm studies. Relevant outcomes are OS, disease-specific survival, change in disease status, morbid events, quality of life, and treatment-related mortality and morbidity. Several studies, published from 2007 to 2010, have focused on elderly patients ineligible for stem cell transplantation as
postremission therapy. These studies have shown 5-year OS estimates ranging from 83% to 94%. However, whether ibritumomab tiuxetan adds survival benefit over current standard rituximab-containing chemotherapy regimens cannot be determined from these studies. Further, the small samples and lack of data for direct comparison with outcomes of alternative treatments in similar patients preclude firm conclusions. The evidence is insufficient to determine the effects of the technology on health outcomes, therefore this is considered investigational.

For individuals with chemotherapy-sensitive, relapsed NHL who require hematopoietic cell transplantation and who receive ibritumomab tiuxetan as part of the conditioning regimen, the evidence includes small cohort studies or case series with heterogeneous patient populations and a meta-analysis. Relevant outcomes are OS, disease-specific survival, change in disease status, morbid events, quality of life, and treatment-related mortality and morbidity. Data are promising but evolving; preliminary data have suggested there may be a role for ibritumomab tiuxetan, particularly in patients unable to tolerate potentially curative high-dose chemotherapy and/or total body irradiation because of the risk of excessive treatment-related mortality and morbidity. However, currently, the available data do not support the superiority of conditioning regimens containing ibritumomab tiuxetan over alternative conditioning regimens before hematopoietic cell transplant. RCTs comparing the efficacy and safety of conditioning regimens containing ibritumomab tiuxetan are required. The evidence is insufficient to determine the effects of the technology on health outcomes, therefore this is considered investigational.

Clinical Input Received from Physician Specialty Societies and Academic Medical Centers

While the various physician specialty societies and academic medical centers may collaborate with and make recommendations during this process, through the provision of appropriate reviewers, input received does not represent an endorsement or position statement by the physician specialty societies or academic medical centers, unless otherwise noted.

2014 Input

In response to requests, input was received from 2 physician specialty societies, 1 academic medical center, and 3 Blue Distinction Centers for Transplant when this policy was under review in 2014. Reviewers unanimously agreed that tositumomab and ibritumomab tiuxetan were
investigational as part of a preparatory regimen before autologous or allogeneic hematopoietic cell transplantation in patients with non-Hodgkin lymphoma (NHL).

**2010 Input**

In response to requests, input was received from 1 specialty medical society and 1 academic medical center and while this policy was under review in 2010. Both reviewers agreed that tositumomab was medically necessary for relapsed or rituximab-refractory follicular lymphoma and that use of ibritumomab tiuxetan would be medically necessary for relapsed or refractory NHL, although 1 reviewer questioned the use of ibritumomab tiuxetan in lymphoma transformed to diffuse large B-cell lymphoma. Both reviewers indicated that there is a role for radioimmunotherapy in the initial treatment of indolent NHL, particularly in older, frail patients and that it provides long remissions and results equivalent to multicycle rituximab and chemotherapy combinations. Both reviewers indicated that radioimmunotherapy is medically necessary as consolidation therapy, and both agreed that there conditioning regimens are beneficial role before hematopoietic cell transplantation.

**Practice Guidelines and Position Statements**

**National Comprehensive Cancer Network (NCCN)**

NCCN practice guidelines (V. 4.2018)\textsuperscript{1} make the following recommendations for radioimmunotherapy (RIT) in non-Hodgkin lymphoma (NHL):

- Follicular lymphoma (These guidelines apply to patients with histological grade 1 or 2 follicular lymphoma; grade 3 follicular lymphoma is commonly treated like diffuse large B-cell lymphoma.)
  - As first-line therapy for elderly or infirm if other first-line therapies are not tolerable (category 2B)
  - As first-line consolidation after induction with chemotherapy or chemoimmunotherapy (category 2B)

- For histologic transformation of follicular lymphoma to diffuse large B-cell lymphoma, either after multiple prior therapies, or after minimal or no prior chemotherapy if initial treatment for transformed disease yields only partial response, no response, or progressive disease RIT (category 2A)
• Primary Cutaneous Diffuse Large B-Cell Lymphoma, leg type
  
  o As secondary therapy for generalized (skin-only) disease (stage T3) that either has relapsed or only partially responded to initial therapy (category 2A).

National Comprehensive Cancer Network guidelines do not list RIT among its recommended primary or secondary treatments for any other type of B-cell NHL (eg, de novo diffuse large B-cell or mantle cell lymphomas).\textsuperscript{51}

Ongoing and Unpublished Clinical Trials

Some currently unpublished trials that might influence this review are listed in Table 1.

Table 1. Summary of Key Trials

<table>
<thead>
<tr>
<th>NCT No.</th>
<th>Trial Name</th>
<th>Planned Enrollment</th>
<th>Completion Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ongoing</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NCT01827605</td>
<td>A Phase III Multicenter, Randomized Study Comparing Consolidation With 90yttrium-Labeled Ibritumomab Tiuxetan (Zevalin®) Radioimmunotherapy Versus Autologous Stem Cell Transplantation (ASCT) in Patients With Relapsed Follicular Lymphoma (FL)</td>
<td>265</td>
<td>Jan 2018</td>
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<tr>
<td>NCT02063685</td>
<td>A Multicenter, Phase III, Randomized Study to Evaluate the Efficacy of Response-adapted Strategy to Define Maintenance After Standard Chemoimmunotherapy in Patients With Advanced-stage Follicular Lymphoma</td>
<td>602</td>
<td>Jul 2019</td>
</tr>
<tr>
<td>NCT02320292</td>
<td>The Asymptomatic Follicular Lymphoma (AFL) Trial: A Phase III Study of Single-Agent Rituximab Immunotherapy Versus Zevalin Radioimmunotherapy for Patients With New, Untreated Follicular Lymphoma Who Are Candidates for Observation</td>
<td>128</td>
<td>Jan 2026</td>
</tr>
</tbody>
</table>

NCT: national clinical trial.
Medicare National Coverage

There is no national coverage determination. In the absence of a national coverage determination, coverage decisions are left to the discretion of local Medicare carriers.

Regulatory Status

In 2002, ibritumomab tiuxetan (Zevalin®) was granted accelerated approval by the U.S. Food and Drug Administration (FDA) for the treatment of patients with relapsed or refractory low-grade, follicular or transformed B-cell NHL, including patients with rituximab-refractory follicular NHL. In March 2008, the indication for transformed B-cell NHL was removed. In 2009, FDA approved ibritumomab tiuxetan (Zevalin®) for consolidation therapy in previously untreated follicular NHL in patients who achieve a partial or complete response to first-line chemotherapy. Current FDA-approved indications are (1) relapsed or refractory, low-grade or follicular B-cell NHL and (2) previously untreated follicular NHL in patients who achieve a partial or complete response to first-line chemotherapy.

In 2003, tositumomab (Bexxar®) was approved by FDA for rituximab-refractory follicular NHL. In February 2014, GlaxoSmithKline discontinued the manufacture and sale of tositumomab (Bexxar®).

References


### Date | Comments
--- | ---
07/14/15 | Annual Review. Policy updated with literature search; no change to policy statement. References updated.
10/13/15 | Annual Review. Policy updated with literature review; no change in policy statements.
12/01/16 | Annual Review, approved November 8, 2016. No changes to policy statement.
10/01/17 | Annual Review, approved September 5, 2017. Policy updated with literature review through June 2, 2017; references 9 and 19 added; no change in policy statements.
10/01/18 | Annual Review, approved September 20, 2018. No changes to policy statement.

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Email AppealsDepartmentInquiries@Premera.com

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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 https://ocrportal.hhs.gov/ocr/portal/lobby.jsf, or by mail or phone at:
U.S. Department of Health and Human Services
200 Independence Avenue SW, Room 509F, HHH Building
Washington, D.C. 20201, 1-800-368-1019, 800-537-7697 (TDD)

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Call 800-722-1471 (TTY: 800-842-5357).

Oromo (Cushite):
Lakkoofsa biiibilaa 800-722-1471 (TTY: 800-842-5357) ti biiibilaa.

French (French):
Appelez le 800-722-1471 (TTY: 800-842-5357).

Kreyòl ayisyen (Creole):
Avi sila a gen Enfòmasyon Enpòtan ladan. Avi sila a kapab genyen enfòmasyon enpòtan konséjann aplikasyon w an oswa ko enpòt an kouvèti asirans lan atrav Ste Premera Blue Cross. Kapab genyen dat ki enpòtan nan avi sila a. Ou ka gen pou prin kék aksyon aven se tran ki pou ka tenbe kouvèti asirans sante w la oswa pou yo ka ede w ak demens yo. Se dwa w pou resevwa enfòmasyon sa a ak asirans lan lang ou pale a, san ou pa gen pou peu pou sa. Rate nan 800-722-1471 (TTY: 800-842-5357).

Deutsche (German):

Hmoob (Hmong):
Tsab ntawv tsjaj xo no muaj cov ntsiab lus tseem ceeb. Tej zaum tsab ntawv tsjaj xo no muaj cov ntsiab lus tseem ceeb bote kog diaw ntawv thov kev pav loy kog koy kev lac pw cim los ntawm Premera Blue Cross. Tej zaum muaj cov hnuv tseem ceeb los rau hauv daim ntawm no. Tej zaum kog juay tuu uae qee um yeem uab kog kog tus piv dahau cov caj nyong tus teev rau hauv daim ntawm no mas kog tajjjuay tuu baaj kev pav lac kwu kho mob los koy kev keb lac paij kog juay tuu baaj kev pav lac kwu kho mel los koy kev keb lac paij kog juay tuu baaj kev pav lac kwu kho mob.

Illok (Illocano):
Daytoy a Pakdaar ket naglaon iti Napateg nga Impormasion. Daytoy a pakdaar mabalini nga adda ket naglaon iti napateg nga impormasion maipanggep iti aplikasyonno wynno coverage babaen iti Premera Blue Cross. Daytoy ket mabalini dagiti importante a pelsa iti daytoy a pakdaar. Mabalini nga adda rumbeng nga aramidenyo nga adda sakkay dagiti partikular a naa naituding nga ardampay nga adda.tapong tapo tapungayadio nga coverage ti salному yowo tungol kadagit gastos. Adda karbanganyo a mangila iti daytoy nga impormasion ken tungol iti bukodyo a pasaga ng awan ti bayadanyo. Tumawag ti numero nga 800-722-1471 (TTY: 800-842-5357).

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Questo avviso contiene informazioni importanti. Questo avviso può contenere informazioni importanti sulla tua domanda o copertura attraverso Premera Blue Cross. Potrebbero esserci date chiave in questo avviso. Potrebbe essere necessario un tuo intervento entro una scadenza determinata per consentirti di mantenere la tua copertura o sovvenzione. Hai il diritto di ottenere queste informazioni e assistenza nella tua lingua gratuitamente.
Chiamai 800-722-1471 (TTY: 800-842-5357).
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