Ibritumomab Tiuxetan (Zevalin)

**Policy**

*Please see amendment for Pennsylvania Medicaid at the end of this CPB.*

I. Aetna considers radioimmunotherapy with ibritumomab tiuxetan (Zevalin) medically necessary for the following types of B-cell non-Hodgkin's lymphoma:

A. Follicular lymphoma as:

1. Second-line or subsequent therapy for refractory or progressive disease in persons who are not elderly or infirm; or
2. Treatment of histologic transformation to diffuse large B-cell lymphoma (DLBCL) in members who have received the following:

   a. minimal or no chemotherapy prior to histologic transformation to DLBCL (without translocations of MYC and BCL2 and/or BCL6) and have partial response, no response, or progressive disease after chemoimmunotherapy; or
   b. multiple prior therapies including 2 or more lines of chemoimmunotherapy for indolent or transformed disease; or
B. Histologic transformation of marginal zone lymphoma to diffuse large B-cell lymphoma (DLBCL) as treatment of members who have received the following:

1. minimal or no chemotherapy prior to histologic transformation to DLBCL and have partial response, no response, or progressive disease after chemoimmunochemistry; or
2. multiple prior therapies including 2 or more lines of chemoimmunochemistry for indolent or transformed disease; or

C. Primary cutaneous B-cell lymphoma as:

1. Second-line or subsequent therapy for relapsed or refractory primary cutaneous diffuse large B-cell lymphoma, leg type; or

II. A single course of treatment with Zevalin therapeutic regimen is considered medically necessary. The U.S. Food and Drug Administration (FDA) has stated that the safety of multiple courses of the Zevalin therapeutic regimen, or combination of this regimen with other forms of irradiation, has not been evaluated.

III. Aetna considers the Zevalin therapeutic regimen experimental and investigational for all other indications (not an all-inclusive list) because its effectiveness for these indications has not been established.

A. Burkitt lymphoma
B. Chronic lymphocytic leukemia
C. Gastric MALT lymphoma
D. Hepatocellular carcinoma
E. Mantle cell lymphoma
F. Nodal marginal zone lymphoma
G. Nongastric MALT lymphoma
H. Post-transplantation lymphoproliferative disorders
I. Splenic marginal zone lymphoma.
Background

This policy is consistent with the Food and Drug Administration (FDA)-approved indications for ibritumomab tiuxetan (Zevalin) (IDEC Pharmaceuticals, San Diego, CA) and is adapted from the National Comprehensive Cancer Network (NCCN) Drugs & Biologics Compendium.

Ibritumomab Tiuxetan (Zevalin)

Ibritumomab tiuxetan (Zevalin) (IDEC Pharmaceuticals, San Diego, CA) consists of a monoclonal antibody linked to the radioactive isotope yttrium-90. After infusion into a patient, the monoclonal antibody targets the CD20 antigen, which is found on the surface of mature B cells and B-cell tumors. The CD20 antigen is expressed on more than 90% of B-cell non-Hodgkin's lymphomas. In this manner, cytotoxic radiation is delivered directly to malignant cells.

Zevalin (ibritumomab tiuxetan) is the immunoconjugate resulting from a stable thiourea covalent bond between the monoclonal antibody ibritumomab and the linker-chelator tiuxetan [N-{2-bis(carboxymethyl)amino}-3-(pisothiocyanatophenyl)-propyl]-[N-{2-bis(carboxymethyl)amino}-2-(methyl)-ethyl] glycine. This linker-chelator provides a high affinity, conformationally restricted chelation site for Indium-111 or Yttrium-90. The antibody moiety of Zevalin is ibritumomab, a murine IgG1 kappa monoclonal antibody directed against the CD20 antigen. Regions of ibritumomab bind to the CD20 antigen on B lymphocytes and induce apoptosis (programmed cell death) in CD20+ B-cell lines in vitro. Tiuxetan (chelator) tightly binds In-111 or Y-90. The chelator complex covalently links to the amino acids of exposed lysines and arginines contained within the antibody (ibritumomab). Beta emission from Y-90 induces cellular damage by the formation of free radicals in the target and neighboring cells.

Ibritumomab tiuxetan must be used along with rituximab (Rituxan), another monoclonal antibody that targets malignant B-lymphocytes and has been approved for treatment of low-grade B-cell NHL. Ibritumomab tiuxetan is approved by the FDA for patients who have not responded to standard chemotherapy treatments or to the use of rituximab alone.
Zevalin (ibrutinomab tiuxetan) is FDA approved for: patients with relapsed or refractory, low-grade or follicular B-cell non-Hodgkin' lymphoma (NHL); and patients with previously untreated follicular NHL who achieve a partial or complete response to first-line chemotherapy.

The Zevalin therapeutic regimen is administered in 2 parts. Patients first receive acetaminophen and rituximab (day 1). On day 7, 8, or 9, patients receive acetaminophen and rituximab again with a form of Zevalin that has a different radioactive chemical, Yttrium-90, that can provide a treatment benefit.

The FDA-approved prescribing information for Zevalin has the following recommendations regarding dosage and administration:

- Day 1: Administer rituximab 250 mg/m2 intravenous.
- Day 7, 8, or 9: Administer rituximab 250 mg/m2 intravenous infusion.

  - If platelets ≥ 150,000/mm3: Within 4 hours after rituximab infusion, administer 0.4 mCi/kg (14.8 MBq per kg) Y-90 Zevalin intravenous.
  - If platelets ≥ 100,000 but ≤ 149,000/mm3 in relapsed or refractory patients: Within 4 hours after rituximab infusion, administer 0.3 mCi/kg (11.1 MBq per kg) Y-90 Zevalin intravenous.

Otte (2008) noted that treatment of follicular NHL with yttrium-90 labeled Zevalin has become an efficacious asset in standard treatment concepts of this disease. The author stated that a pre-diagnostic imaging or dosimetry is not necessary as an additional mandatory safety measure to confirm the expected biodistribution.

Two multi-center trials were conducted to demonstrate the safety and effectiveness of the Zevalin therapeutic regimen. In the first trial, 54 patients who were no longer responding to chemotherapy or rituximab received the Zevalin therapeutic regimen. The overall response rate was 74 %.

The second study was a randomized, controlled phase III trial that included 143 subjects with relapsed or refractory, low-grade or follicular NHL or transformed B-cell NHL. An overall response rate of 80 % was obtained in subjects receiving the Zevalin therapeutic regimen (73 subjects), compared to 56 % for the subjects receiving rituximab alone (70 subjects). Thirty percent of Zevalin-treated subjects
experienced a complete response, compared to a 16% complete response rate for rituximab-treated subjects. The duration of response was approximately 2 months longer with the Zevalin therapeutic regimen, although it has not been determined whether Zevalin improves overall survival.

The Zevalin treatment regimen is more toxic than treatment with rituximab. More than 50% of the patients in the clinical trials experienced serious leukopenia or thromocytopenia lasting for 3 to 4 weeks. Hemorrhages, some fatal, and life-threatening infections occurred in a small number of patients. Because of these concerns, the Zevalin therapeutic regimen is only approved by the FDA for patients who have failed other treatments. In addition, the development of myeloid malignancies and dysplasias have been reported with Zevalin.

The FDA-approved labeling of Zevalin states that it should not be administered to patients with 25% or more lymphoma marrow involvement or impaired bone marrow reserve, e.g., prior myeloablative therapies; platelet count less than 100,000 cells/mm3; neutrophil count less than 1,500 cells/mm3; hypocellular bone marrow.

The NCCN Drugs and Biologics Compendium (2019) lists the following indications for ibritumomab tiuxetan (Zevalin):

- Follicular Lymphoma (grade 1-2) - Radioimmunotherapy as (Category 2A for second-line or subsequent therapy in patients who are not elderly or infirm; 2B for all others)
  
  • First-line therapy alone in elderly or infirm patients for stage I (≥7 cm), contiguous stage II (≥7 cm), non-contiguous stage II disease, or for patients with indications for treatment with stage III or IV disease
  • Optional first-line consolidation therapy or extended dosing
  • Second-line or subsequent therapy (if not previously given as first-line) for refractory or progressive disease in elderly or infirm patients with indications for treatment.

- Follicular lymphoma (grade 1-2) - Radioimmunotherapy as:
• Treatment of histologic transformation to diffuse large B-cell lymphoma (DLBCL) in patients who have received: (Category 2A)
  ◦ minimal or no chemotherapy prior to histologic transformation to DLBCL (without translocations of MYC and BCL2 and/or BCL6) and have partial response, no response, or progressive disease after chemoimmunotherapy
  ◦ multiple prior therapies including ≥2 lines of chemoimmunotherapy for indolent or transformed disease.

• Maintenance therapy for patients with histologic transformation to diffuse large B-cell lymphoma that is coexisting with extensive follicular lymphoma who achieve a complete response to chemoimmunotherapy (Category 2B).

  ▪ Gastric MALT Lymphoma -- Radioimmunotherapy in patients with indications for treatment as (Category 2B):
    • First-line therapy for stage IIE, or II2, or stage IV disease (distant nodal or advanced stage)
    • Additional therapy for stage I1, or I2, or stage II1 H. pylori positive disease if repeat endoscopy shows no response or recurrence after antibiotic therapy and involved site radiation therapy (ISRT)
    • additional therapy after ISRT or rituximab alone for stage I1, or I2, or stage II1 disease that is lymphoma positive after restaging with endoscopy
    • Second-line or subsequent therapy for recurrent or progressive disease

  ▪ Histologic Transformation of Marginal Zone Lymphoma to DLBCL - Radioimmunotherapy as (Category 2A):
    • Treatment of patients who have received
      ◦ minimal or no chemotherapy prior to histologic transformation to DLBCL and have partial response, no response, or progressive disease after chemoimmunotherapy
multiple prior therapies including ≥2 lines of chemoimmunotherapy for indolent or transformed disease

- Nodal Marginal Zone Lymphoma - Radioimmunotherapy as (Category 2B):
  - First-line therapy for stage I (≥7 cm), contiguous stage II (≥7 cm), non-contiguous stage II, or stage III, IV disease
  - Second-line and subsequent therapy

- Nongastric MALT Lymphoma - Radioimmunotherapy as (Category 2B):
  - First-line therapy for stage IV disease or recurrent stage I-II disease in patients with indications for treatment
  - Second-line and subsequent therapy

- Primary Cutaneous B-Cell Lymphoma - Radioimmunotherapy as (Category 2A):
  - Second-line or subsequent therapy for relapsed or refractory primary cutaneous diffuse large B-cell lymphoma, leg type.

- Splenic Marginal Zone Lymphoma - Radioimmunotherapy as (Category 2B):
  - First-line therapy for progressive disease following initial treatment for splenomegaly
  - Second-line (if prior treatment with rituximab) or subsequent therapy

Zevalin (ibritumomab tiuxetan) should not be utilized in the following:

- Pediatric members <18 years old
- Women who are pregnant (FDA category D) or breast feeding and have not been apprised of the risks of therapy
- Prior hypersensitivity to ibritumomab tiuxetan or any component of the product
- Do not administer Y-90 Zevalin (ibritumomab tiuxetan) to members with altered biodistribution
- Do not exceed 32 mCi (1184 MBq) of Y-90 Zevalin (ibritumomab tiuxetan)
- Do not administer Zevalin (ibritumomab tiuxetan) to members with \( \geq 25\% \)
  lymphoma marrow involvement or impaired bone marrow reserve
- Members with platelet counts \(<100,000\ \text{cells/mm}^3\) or neutrophil counts
  \(<1,500\ \text{cells/mm}^3\)

In a phase-II clinical trial, Krishnan and colleagues (2008) assessed the safety and
effectiveness of combining yttrium-90 (90Y) Zevalin with high-dose carmustine,
cytarabine, etoposide, and melphalan (BEAM) and autologous stem-cell
transplantation (ASCT) in patients with NHL who were ineligible for total-body
irradiation because of older age or prior radiotherapy. A total of 41 patients with
received standard-dose 90Y Zevalin (14.8 MBq/kg [0.4 mCi/kg]) followed by high-
dose BEAM. The median age was 60 years (range of 19 to 78 years), and the
median number of previous therapies was 2 (range of 1 to 6). Disease histologies
were diffuse large B-cell \((n = 20)\), mantle cell \((n = 13)\), follicular \((n = 4)\), and
transformed lymphoma \((n = 4)\). With a median follow-up of 18.4 months (range of
5.5 to 53.3 months), the estimated 2-year overall survival (OS) and progression-
free survival (PFS) were 88.9 % (95 % confidence interval [CI]: 75.3 % to 95.2 %)
and 69.8 % (95 % CI: 56.4 % to 79.7 %), respectively. The median time to white
blood cell engraftment was 11 days (range of 9 to 26 days) and time to platelet
engraftment was 12 days (range of 3 to 107 days). Adverse events were similar to
those seen historically with high-dose BEAM alone, and included grade 3 or 4
pulmonary toxicity in 10 patients. The authors concluded that adding 90Y Zevalin
to high-dose BEAM with ASCT is feasible and has a toxicity and tolerability profile
similar to that observed with BEAM alone. They noted that rates of PFS seen in
these patients are promising and warrant additional study.

Allogeneic SCT is an effective therapy for lymphoma. Reduced-intensity
conditioning (RIC) reduces non-relapse mortality associated with myeloablative
conditioning but relapse rates are high when performed in active disease. Shimoni
et al (2008) examined the safety and outcome of Zevalin combined with RIC in
patients with advanced lymphoma. The study included 12 patients, median age 54
years (37 to 62), with a median of 4 prior treatments (2 to 6) and active disease
documented on positron emission tomography-computed tomography (PET-CT).
Zevalin 0.4 mCi/kg was given on day-14 and fludarabine combined with busulfan \((n
= 6)\) or melphalan \((n = 6)\) was started on day-6. Graft-versus-host disease (GVHD)
prevention was tapered 3 months after SCT to augment the graft-versus-lymphoma
effect. All patients engrafted at a median of 14 days after SCT. Eighty-three
percent achieved complete response/partial response. With a median follow-up of
21 months (12 to 37), 2-year PFS was 33 %. Only 3 patients relapsed; cumulative incidence was 25 %. Non-relapse mortality was 42 %, predominantly due to acute GVHD. Zevalin-RIC is feasible with consistent engraftment, acceptable organ toxicity, but high rates of acute GVHD. The low incidence of relapse suggested augmented anti-lymphoma effect. The authors stated that Zevalin-RIC merits further study. Better results may be achieved in patients earlier in disease course and with longer duration of immune-suppression.

In a pilot study, Maza et al (2008) evaluated the outcome and assessed complications of (90)Y ibritumomab tiuxetan (IT) therapy in patients with primary cutaneous B-cell lymphomas (PCBCL). A total of 10 patients, all but 1, with relapsed PCBCL were included and treated with rituximab (250 mg m(-2)/body surface) on days 1 and 8 followed by a single dose of (90)Y IT (11-15 MBq kg(-1)). The overall response rate was 100 %. The complete response rate was 100 %. The median time to relapse was 12 months. Ongoing remissions were achieved in 4 patients (median follow-up of 19 months). Transient and reversible myelosuppression (grade 3 to 4) was the most frequent adverse event. Radioimmunotherapy with (90)Y IT is an effective treatment in relapsed primary cutaneous follicle center lymphomas and diffuse large B-cell lymphoma leg-type. The authors stated that further investigations in controlled randomized clinical trials evaluating the role of (90)Y IT versus rituximab in PCBCL are needed.

Jain et al (2009) stated that radioimmunotherapy (RIT) with radio-labeled monoclonal antibodies to CD20 produce a high response rate in patients with relapsed lymphoma. Use of this modality in patients with chronic lymphocytic leukemia (CLL) has been hampered by the extensive marrow involvement seen in patients with CLL, which would produce a high risk for marrow aplasia after treatment with RIT. Patients with lymphoma and marrow involvement have been treated with RIT if involved marrow was less than 25 % of the total marrow. Thus, these investigators adapted this approach as consolidation therapy in patients with CLL responding to chemoimmunotherapy. A total of 14 patients with relapsed CLL either in partial remission or in complete remission but with disease documented by flow cytometry were treated with (90)Y IT. One patient responded and achieved a complete remission but with residual disease detected by flow cytometry. Of note was that grade 3 or 4 hematologic toxicity was seen in 12 of the 13 (92 %) evaluable patients, with grade 3 or 4 thrombocytopenia noted in 11 (85 %) of the patients. In addition, myelosuppression was prolonged with a median duration of grade 3 or 4 thrombocytopenia of 37 days. Five patients had persistent
thrombocytopenia 3 months post-therapy. The authors concluded that even in patients with CLL and limited marrow involvement, the use of RIT results in unacceptable hematologic toxicity.

Koechli et al (2015) noted that the addition of anti-CD20 antibodies to high intensity poly-chemotherapy regimens has improved response and survival rates in newly diagnosed patients with Burkitt lymphoma (BL). However, the role of additional anti-CD20 directed RIT for consolidation of first remission (CR1) has not been reported so far in BL patients receiving rituximab during first-line treatment. These researchers compared 5 BL patients receiving Y-90-IT RIT consolidation in CR1 to 22 consecutive BL patients without consolidation. They observed that Y-90-IT treatment was associated with clinically relevant myelosuppression. After a median follow-up of 50 months, none of the patients with Y-90-IT treatment relapsed, and no patient died. In contrast, 1 patient (4.5 %) in the non-Y-90-IT group relapsed (50 months-PFS 95.5 %; p = 0.6336), and 1 patient died (50 months-OS 95.5 %; p = 0.6171). The authors concluded that these findings suggested that survival rates are excellent and equal in rituximab pre-treated BL patients with or without Y-90-IT consolidation in first remission.

Rossignol et al (2015) stated that post-transplantation lymphoproliferative disorders (PTLDs) are life-threatening complications after solid organ and hematopoietic stem cell transplantation. Only 50 % of CD20-positive PTLDs respond to rituximab monotherapy, and outcomes remain poor for patients with relapsed/refractory disease, especially those who do not qualify for an anthracycline-containing regimen due to frailty or co-morbidities. Radioimmunotherapy might be an option in this particular setting. These investigators reported a panel of 8 patients with rituximab refractory/relapsed CD20-positive PTLDs including 3 ineligible for subsequent CHOP-like chemotherapy who received (90) Y-ibritumomab tiuxetan as a single agent (n = 7) or combined to chemotherapy (n = 1). Five out of 8 patients were kidney transplant recipients, while 2/8 had a liver transplant and 1/8 had a heart transplant. Patients received a median of 2 previous therapies. Overall response rate was 62.5 %. Importantly, all responders achieved CR. At a median follow-up of 37 months, CR was ongoing in 4 patients. Toxicity was predominantly hematological and easily manageable. No graft rejection was noticed concomitantly or following RIT administration despite immunosuppression reduction after diagnosis of PTLDs. The authors concluded that this report emphasized the potential efficiency of salvage RIT for early rituximab refractory PTLDs without any unexpected toxicity.
Zevalin for Diffuse Large B-Cell Lymphoma:

In a phase II clinical trial, Witzig and colleagues (2015) studied patients with early stage diffuse large B-cell lymphoma (DLBCL) who received RCHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone) alone or with involved field radiotherapy (IFRT). Anti-CD20 RIT delivers radiation to microscopic sites outside of known disease. This study aimed to achieve a functional CR rate of greater than or equal to 75% to RCHOP and 90 Yttrium-ibritumomab tiuxetan RIT. Patients with stages I/II DLBCL received 4 to 6 cycles of RCHOP followed by RIT [14.8 MBq/kg (0.4 mCi/kg)]; patients with positron emission tomography-positive sites of disease after RCHOP/RIT received 30 Gy IFRT. Of the 62 patients enrolled; 53 were eligible – 42% (22/53) had stage I/IE; 58% (31/53) stage II/IIE. After RCHOP, 79% (42/53) were in CR/unconfirmed CR; and 48 patients proceeded to RIT. One partial responder after RIT received IFRT and achieved a CR. The best response after RCHOP + RIT in all 53 patients was a functional CR rate of 89% (47/53; 95% CI: 77 to 96%). With a median follow-up of 5.9 years, 7 (13%) patients have progressed and 4 (8%) have died (2 with DLBCL). At 5 years, 78% of patients remain in remission and 94% are alive. The authors concluded that chemoimmunotherapy and RIT is an active regimen for early stage DLBCL patients; 89% of patients achieved functional CR without the requirement of IFRT. They stated that this regimen is worthy of further study for early stage DLBCL in a phase III trial.

Furthermore, per National Comprehensive Cancer Network’s Drugs & Biologics Compendium (2019), diffuse large B-cell non-Hodgkin lymphoma (DLBCL) is not a recommended indication of ibritumomab tiuxetan, with the exception of primary cutaneous diffuse large B-cell lymphoma (leg type) or histologic transformation to DLBCL.

In an open-label, single-center, phase II clinical trial, Karmali and associates (2017) evaluated the safety and effectiveness of dose-dense CHOP-R-14 followed by 90Y-ibritumomab RIT in patients with previously untreated DLBCL. A total of 20 patients, the majority presenting with high-risk characteristics, were enrolled to receive dose-dense cyclophosphamide, doxorubicin, vincristine, prednisone and rituximab every 14 days (CHOP-R-14), followed by 90Y-ibritumomab tiuxetan consolidation; 16 patients completed RIT consolidation (rituximab 250 mg/m2 on day 1 and day 7, 8, or 9, followed by a single injection of 90Y-ibritumomab); CR rates of 75 and 95% were observed after treatment with CHOP-R-14 and RIT,
respectively; 4 of the 5 patients who achieved a partial response (PR) after CHOP-R-14 converted to CR following treatment with RIT. With a median follow-up of 89.7 months, the PFS and OS rates for the cohort were 75 % and 85 %, respectively. Hematological adverse events (AEs) were common following CHOP-R-14 and RIT, but they were manageable with treatment interruption. The authors concluded that this regimen achieved promising survival outcomes in high-risk DLBCL on long term follow-up, with manageable toxicity. They noted that this study had several drawbacks, including the small sample size (n = 16 for completion of RIT consolidation) and incomplete accrual; thus, these findings on effectiveness must be interpreted with caution. Additionally, this trial pre-dated the PET era. Nonetheless, the long-term follow-up provided a reliable measure of response, with evidence of benefit in patients with high-risk characteristics. They noted that in an era of targeted therapies, closer investigation of RIT consolidation should not be entirely abandoned as a potential therapeutic option in DLBCL.

In a prospective multi-center. Phase-II clinical trial, Hertzberg and co-workers (2017) examined if treatment intensification with R-ICE (rituximab, ifosfamide, carboplatin, and etoposide) chemotherapy followed by 90YIT-BEAM (BCNU, etoposide, cytarabine, and melphalan) for high-risk DLBCL patients who are positive on interim PET scan after 4 cycles of R-CHOP-14 (rituximab, cyclophosphamide, doxorubicin, and prednisone) can improve 2-year PFS from a historically unfavorable rate of 40 % to a rate of 65 %. Patients received 4 cycles of R-CHOP-14, followed by a centrally-reviewed PET performed at day 17 to 20 of cycle 4 and assessed according to International Harmonisation Project criteria. Median age of the 151 evaluable patients was 57 years, with 79 % stages 3 to 4, 54 % bulk, and 54 % International Prognostic Index 3 to 5. Among the 143 patients undergoing interim PET, 101 (71 %) were PET-negative (96 of whom completed R-CHOP), 42 (29 %) were PET-positive (32 of whom completed R-ICE and 90YIT-BEAM). At a median follow up of 35 months, the 2-year PFS for PET-positive patients was 67 %, a rate similar to that for PET-negative patients treated with R-CHOP-14 (74 %, p = 0.11); OS was 78 % and 88 % (p = 0.11), respectively. In an exploratory analysis, PFS and OS were markedly superior for PET-positive Deauville score 4 versus score 5 (p = 0.0002 and p = 0.001, respectively). The authors concluded that DLBCL patients who were PET-positive after 4 cycles of R-CHOP-14 and who switched to R-ICE and 90YIT-BEAM achieved favorable survival outcomes similar to those for PET-negative R-CHOP-14-treated patients. Moreover, they stated that further studies are needed to confirm these promising results.
Chahoud and colleagues (2018) examined the effect on long-term survival of adding rituximab (R) to BEAM (carmustine, etoposide, cytarabine, and melphalan) conditioning with or without yttrium-90 ibritumomab tiuxetan (90YIT) in patients with relapsed DLBCL undergoing ASCT. Patients were enrolled on 3 consecutive phase-II clinical trials. Patients received 2 doses of rituximab (375 and 1,000 mg/m²) during mobilization of stem cells, followed by 1,000 mg/m² on days +1 and +8 after ASCT with R-BEAM or 90YIT-R-BEAM (90YIT dose of 0.4 mCi/kg) conditioning. A total of 113 patients were enrolled, with 73 receiving R-BEAM and 40 receiving 90YIT-R-BEAM. All patients had a prior exposure to rituximab. The median follow-up intervals for survivors were 11.8, 8.1, and 4.2 years in the 3 trials, respectively. The 5-year disease-free survival (DFS) rates were 62 % for R-BEAM and 65 % for 90YIT-R-BEAM (p = 0.82). The 5-year OS rates were 73 % and 77 %, respectively (p = 0.65). In patients with de-novo DLBCL, survival outcomes of the germinal center/activated b-cell histologic subtypes were similar with 5-year OS rates (p = 0.52) and DFS rates (p = 0.64), irrespective of their time of relapse (less than 1 versus greater than 1 year) after initial induction chemotherapy (p = 0.97). The authors concluded that administering ASCT with rituximab during stem cell collection and immediately after transplantation induced long-term disease remission and abolished the negative prognostic impact of cell-of-origin in patients with relapsed DLBCL. Moreover, they stated that the addition of 90YIT did not confer a further survival benefit.

Zevalin for Diffuse Mantle Cell Lymphoma:

In a phase II clinical trial, Wang et al (2009) evaluated the safety and effectiveness of (90)Y-IT in patients with relapsed or refractory mantle cell lymphoma (MCL). Patients were eligible for the study if they had adequate major organ function and performance status. Those with central nervous system disease, pleural effusion, circulating lymphoma cells greater than or equal to 5,000/microL, or history of stem-cell transplant were ineligible. Patients with a platelet count greater than or equal to 150,000/microL received a dose of 0.4 mCi/kg of (90)Y-IT, whereas those with a platelet count less than 150,000/microL received a dose of 0.3 mCi/kg. A total of 34 patients with a median age of 68 years (range of 52 to 79 years) received the therapeutic dose. The patients had received a median of 3 prior treatment regimens (range of 1 to 6 treatment regimens), including those that contained rituximab (n = 32) and bortezomib (n = 7). Of the 32 patients with measurable disease, 10 (31 %) achieved complete or partial remission. After a median follow-up of 22 months (range of 2 to 72+ months), an intent-to-treat analysis revealed a
median event-free survival (EFS) duration of 6 months and an OS duration of 21 months. The median EFS for those who achieved partial or complete remission was 28 months, while it was 3 months for those whose disease did not respond (p < 0.0001); it was 9 months for patients whose tumor measured less than 5 cm in the largest diameter before treatment and 3 months for those whose tumor measured greater than or equal to 5 cm (p = 0.015). The authors concluded that the single-agent activity of (90)Y-IT and its favorable safety profile warrant its further development for the treatment of MCL.

Mondello and co-workers (2016) MCL is an aggressive lymphoma with a dismal prognosis because of numerous relapses. Because the most promising results have been obtained with immunochemotherapy followed by ASCT, these investigators evaluated the effectiveness of (90)Y-IT consolidation after such an intensive treatment. They retrospectively assessed 57 patients affected by intermediate or high-risk MCL in CR or partial remission (PR) after 3 cycles of R-C HOP (rituximab, cyclophosphamide, doxorubicin [hydroxydaunorubicin], vincristine [Oncovin], prednisolone) plus 3 cycles of R-DHAP (dexamethasone, cytarabine [Ara-C], cisplatin [platinum]) followed by ASCT and additional consolidation treatment with (90)Y-IT in 28 cases. All patients underwent 2 years of rituximab maintenance. After ASCT, 94 % achieved CR and 4 % achieved PR. The median follow-up was 6.2 years (range of 1.8 to 9.7 years). Treatment intensification was well-tolerated and led to a significantly longer response duration in comparison to standard treatment. In contrast to the historical cohort, the addition of (90)Y-IT appeared to overcome important risk factors such as Mantle Cell Lymphoma International Prognostic Index (MIPI) score and bone marrow infiltration. The authors concluded that in the present retrospective analysis, immunochemotherapy followed by ASCT resulted in a very high response rate, and subsequent (90)Y-IT consolidation significantly reduced the number of relapses and increased survival, suggesting that (90)Y-IT consolidation might be a valid option in 1st-line treatment. Moreover, they stated that a prospective confirmatory trial is needed.

Jurczak and colleagues (2019) noted that the Polish Lymphoma Research Group performed a phase-II clinical trial to examine if 90Y ibritumomab tiuxetan radioimmunotherapy (Y90) may constitute an alternative consolidation for MCL patients unfit for high-dose therapy. A total of 46 patients were consolidated with Y90 following response to the 1st (n = 34) or 2nd line (n = 12) immunochemotherapy. Majority of the patients had advanced disease (stage IV and
presence of B-symptoms in 85 % and 70 %, respectively) and high MIPI (5.8, range of 4 to 7). Consolidation with Y90 increased the CR rate obtained by the 1st line therapy from 41 % to 91 % and allowed for median PFS of 3.3 and OS of 6.5 years. In the 1st relapse, CR rate increased from 16 % to 75 %, while median PFS and OS totaled 2.2 and 6.5 years, respectively. At 8 years, 30 % of patients, consolidated in the 1st line CR were alive, without relapse. Toxicity associated with Y90 was manageable, more severe after fludarabine-based regimens.

Zevalin for Hepatocellular Carcinoma:

An UpToDate review on "Nonsurgical therapies for localized hepatocellular carcinoma: Transarterial embolization, radiotherapy, and radioembolization" (Curley et al, 2017) does not mention ibritumomab as a therapeutic option.

Furthermore, National Comprehensive Cancer Network’s Drugs & Biologics Compendium does not list hepatocellular carcinoma as a recommended indication of ibritumomab tiuxetan.

Appendix

Zevalin Dosing for Non-Hodgkin's Lymphoma

Zevalin (ibritumomab tiuxetan) is available as Zevalin 3.2 mg/2 mL Kit for the Preparation of Yttrium-90 (Y-90) Solution for Injection.

- Only administer Zevalin (ibritumomab tiuxetan) in facilities where immediate access to resuscitative measures is available.
- The Zevalin (ibritumomab tiuxetan) therapeutic regimen consists of two distinct steps; step 1) involves an infusion of rituximab and step 2) 7 to 9 days later consists of a second infusion of rituximab followed by yttrium-90 ibritumomab tiuxetan.
- Do not administer Zevalin (ibritumomab tiuxetan) regimen to members with platelet counts less than 100,000 cells/mm(3).
- Non-Hodgkin’s lymphoma, Relapsed or refractory: Day 1, infuse rituximab 250 mg/m(2) IV, premedicate with acetaminophen 650 mg and diphenhydramine 50 mg ORALLY; Day 7, infuse rituximab 250 mg/m(2) IV (premedicate with acetaminophen and diphenhydramine) followed within 4
hours with yttrium-90 ibritumomab tiuxetan 0.4 mCi/kilogram (14.8 MBq/kg) actual body weight with a platelet count 150,000 cells/mm(3) or greater or 0.3 mCi/kg (11.1 MBq/kg) actual body weight with platelet count of 100,000 to 149,000 cells/mm(3); MAX dose is 32 mCi (1184 MBq) infused IV over 10 minutes.

- Non-Hodgkin’s lymphoma, Untreated: initiated at least 6 wk but no later than 12 wk following the last dose of first-line chemotherapy after recovery of platelet counts to 150,000 cells/mm(3) or greater: Day 1, infuse rituximab 250 mg/m(2) IV, premedicate with acetaminophen 650 mg and diphenhydramine 50 mg ORALLY; Day 7, infuse rituximab 250 mg/m(2) IV (premedicate with acetaminophen and diphenhydramine) followed within four hours with yttrium-90 ibritumomab tiuxetan 0.4 mCi/kg (14.8 MBq/kg) actual body weight; MAX dose is 32 mCi (1184 MBq) infused IV over 10 minutes.

CPT Codes / HCPCS Codes / ICD-10 Codes

Information in the [brackets] below has been added for clarification purposes. Codes requiring a 7th character are represented by "+":

<table>
<thead>
<tr>
<th>Code</th>
<th>Code Description</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CPT codes covered if selection criteria are met:</td>
</tr>
<tr>
<td>79403</td>
<td>Radiopharmaceutical therapy, radiolabeled monoclonal antibody by intravenous infusion</td>
</tr>
<tr>
<td></td>
<td>Other CPT codes related to the CPB:</td>
</tr>
<tr>
<td>78800 - 78804</td>
<td>Radiopharmaceutical localization of tumor or distribution of radiopharmaceutical agent(s)</td>
</tr>
<tr>
<td>85032</td>
<td>Blood count; manual cell count (erythrocyte, leukocyte, or platelet), each</td>
</tr>
<tr>
<td>85049</td>
<td>platelet, automated</td>
</tr>
<tr>
<td>96401 - 96450</td>
<td>Chemotherapy administration</td>
</tr>
</tbody>
</table>

Ibritumomab Tiuxetan (Zevalin):

HCPCS codes covered if selection criteria are met:

<table>
<thead>
<tr>
<th>Code</th>
<th>Code Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>A9543</td>
<td>Yttrium Y-90 ibritumomab tiuxetan, therapeutic, per treatment dose, up to 40 millicuries</td>
</tr>
</tbody>
</table>

Other HCPCS codes related to the CPB:

<table>
<thead>
<tr>
<th>Code</th>
<th>Code Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>A9542</td>
<td>Indium In-111 ibritumomab tiuxetan, diagnostic, per study dose, up to 5 millicuries</td>
</tr>
</tbody>
</table>
ICD-10 codes covered if selection criteria are met:

<table>
<thead>
<tr>
<th>Code</th>
<th>Code Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>C82.00 - C82.99</td>
<td>Follicular lymphoma</td>
</tr>
<tr>
<td>C83.00 - C83.09, C83.30 - C83.39, C83.90 - C83.99, C86.5 - C86.6</td>
<td>Lymphosarcoma and reticulosarcoma, other named variants</td>
</tr>
<tr>
<td>C84.a0 - C84.99</td>
<td>Cutaneous T-cell and mature T/NK-cell lymphomas</td>
</tr>
</tbody>
</table>

ICD-10 codes not covered for indications listed in the CPB (not all-inclusive):

<table>
<thead>
<tr>
<th>Code</th>
<th>Code Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>C22.0</td>
<td>Liver cell carcinoma</td>
</tr>
<tr>
<td>C83.80 - C83.89</td>
<td>Other lymphomas [diffuse large B-cell non-Hodgkin lymphoma]</td>
</tr>
<tr>
<td>C83.10 - C83.19</td>
<td>Mantle cell lymphoma</td>
</tr>
<tr>
<td>C83.70 - C83.79</td>
<td>Burkitt lymphoma</td>
</tr>
<tr>
<td>C88.4</td>
<td>Marginal zone lymphoma [gastric/nongastric MALT, primary cutaneous B-cell lymphoma]</td>
</tr>
<tr>
<td>C91.10 - C91.12, C91.90 - C91.92</td>
<td>Chronic lymphoid leukemia [chronic lymphocytic]</td>
</tr>
<tr>
<td>D47.Z1</td>
<td>Post-transplant lymphoproliferative disorder (PTLD)</td>
</tr>
</tbody>
</table>

The above policy is based on the following references:


AETNA BETTER HEALTH® OF PENNSYLVANIA

Amendment to
Aetna Clinical Policy Bulletin Number: 0659 Ibritumomab Tiuxetan (Zevalin)

For the Pennsylvania Medical Assistance plan Zevalin may be considered medically necessary for the treatment of:


2.) Gastric MALT lymphoma as:
   • first-line therapy for stage IIE, or II2, or stage IV disease (distant nodal or advanced stage)
   • additional therapy (after involved site radiation therapy or rituximab alone) for stage I1, or I2, or stage II1 disease.

3.) Nongastric MALT lymphoma as:
   • first-line therapy for stage IV disease in patients with indications for treatment

4.) Splenic marginal zone lymphoma as:
   • first-line therapy for progressive disease following initial treatment for splenomegaly.

5.) Treatment of histologic transformation to diffuse large B-cell lymphoma (DLBCL) in patients who have received:
   • minimal or no chemotherapy prior to histologic transformation to DLBCL and have partial response, no response, or progressive disease after chemoimmunotherapy
   • multiple prior therapies including ≥2 lines of chemoimmunotherapy for indolent or transformed disease

6.) Can be considered as maintenance therapy for patients with histologic transformation to diffuse large B-cell lymphoma that is coexisting with extensive follicular lymphoma who achieve a complete response to chemoimmunotherapy.

www.aetnabetterhealth.com/pennsylvania  revised 09/13/2019