Radioimmunotherapy for Non-Hodgkin's Lymphoma: Ibritumomab Tiuxetan (Zevalin) and Tositumomab (Bexxar)

Policy

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

I. Ibritumomab tiuxetan (Zevalin)

Aetna considers radioimmunotherapy with ibritumomab tiuxetan (Zevalin) medically necessary for the following types of non-Hodgkin's lymphoma: Follicular lymphoma, gastric MALT lymphoma, non-gastric MALT lymphoma, primary cutaneous B-cell lymphoma, and splenic marginal zone lymphoma for the following indications:

A. First-line therapy alone in elderly or infirm persons in the setting of comorbidities where tolerability of combination chemotherapy is a concern; or

B. First-line consolidation therapy following induction chemotherapy or chemoimmunotherapy; or
C. Second-line or subsequent therapy for refractory, recurrent or progressive disease in persons with indications for treatment

Radioimmunotherapy with ibritumomab tiuxetan for primary cutaneous B-cell lymphoma is also considered medically necessary for very extensive or refractory generalized T3 cutaneous disease.

Aetna considers the Zevalin therapeutic regimen experimental and investigational for all other indications (e.g., Burkitt lymphoma, chronic lymphocytic leukemia, diffuse large B-cell lymphoma, hepatocellular carcinoma, non-Hodgkin lymphoma, and mantle cell lymphoma, and post-transplantation lymphoproliferative disorders) because its effectiveness for these indications has not been established.

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.

II. Tositumomab (Bexxar)

Aetna considers radioimmunotherapy with tositumomab (Bexxar) medically necessary for the following types of non-Hodgkin's lymphoma: Follicular lymphoma, gastric MALT lymphoma, non-gastric MALT lymphoma, primary cutaneous B-cell lymphoma, and splenic marginal zone lymphoma.

Aetna considers the Bexxar therapeutic regimen experimental and investigational for all other indications (e.g., thyroid cancer and other solid tumors) because its effectiveness for these indications has not been established.

A single course of treatment with Bexxar therapeutic regimen is considered medically necessary. The FDA has stated that the safety of multiple courses of the Bexxar therapeutic regimen, or combination of this regimen with other forms of irradiation
Background
This policy is consistent with the Food and Drug Administration (FDA)-approved indications for ibritumomab tiuxetan (Zevalin) (IDEC Pharmaceuticals, San Diego, CA) and for tositumomab (Bexxar) (Corixa Corporation, Seattle, WA).

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. 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 (ibritumomab 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 thrombocytopenia 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.

Guidelines from the National Comprehensive Cancer Network
(2012) state that ibritumomab tiuxetan radioimmunotherapy alone is indicated in follicular lymphoma, gastric MALT lymphoma, non-gastric MALT lymphoma, or primary cutaneous B-cell lymphoma. For these indications, tositumomab is indicated following chemotherapy or as second-line radioimmunotherapy or refractory or progressive disease, or as first-line therapy for persons with comorbidities, including the elderly or infirm, where tolerability of combination chemotherapy is a concern.

The NCCN Drug and Biologics Compendium (2016) lists the following indications for ibritumomab tiuxetan:

- **Follicular Lymphoma** - Radioimmunotherapy as
  - First-line therapy alone in elderly or infirm patients in the setting of comorbidities where tolerability of combination chemotherapy is a concern for stage I or II disease or for patients with indications for treatment with stage II bulky, III, or IV disease
  - First-line consolidation therapy following induction chemotherapy or chemoimmunotherapy
  - Second-line or subsequent therapy for refractory or progressive disease in patients with indications for treatment

- **Gastric MALT Lymphoma** - Radioimmunotherapy in patients with indications for treatment as
  - First-line therapy for stage IIIE-IV disease in elderly or infirm patients in the setting of comorbidities where tolerability of combination chemotherapy is a concern
  - Additional therapy for stage IIE-IIE disease in elderly or infirm patients in the setting of comorbidities where tolerability of combination chemotherapy is a concern
  - First-line consolidation therapy following induction chemotherapy or chemoimmunotherapy
  - Second-line or subsequent therapy for recurrent or progressive disease

- **Nongastric MALT Lymphoma** - Radioimmunotherapy as
- First-line therapy alone for stage IV disease or recurrent stage I-II disease in elderly or infirm patients with indications for treatment in the setting of comorbidities where tolerability of combination chemotherapy is a concern
- First-line consolidation therapy following induction chemotherapy or chemoimmunotherapy
- Second-line or subsequent therapy for refractory or progressive disease in patients with indications for treatment

- Primary Cutaneous B-Cell Lymphoma - Radioimmunotherapy for primary cutaneous marginal zone or follicle center lymphoma as
  - First-line therapy for generalized extracutaneous disease in elderly or infirm patients in the setting of comorbidities where tolerability of combination chemotherapy is a concern
  - First-line consolidation therapy following induction chemotherapy or chemoimmunotherapy
  - Therapy for very extensive or refractory generalized T3 cutaneous disease
  - Second-line or subsequent therapy for refractory or progressive generalized extracutaneous disease in patients with indications for treatment

- Splenic Marginal Zone Lymphoma - Radioimmunotherapy as
  - First-line therapy alone for progressive disease following initial treatment for splenomegaly in elderly or infirm patients with indications for treatment in the setting of comorbidities where tolerability of combination chemotherapy is a concern
  - First-line consolidation therapy following induction chemotherapy or chemoimmunotherapy
  - As second-line or subsequent therapy for refractory or progressive disease in patients with indications for treatment
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 ≥ 25% lymphoma marrow involvement or impaired bone marrow reserve
- Members with platelet counts <100,000 cells/mm3 or neutrophil counts <1,500 cells/mm3

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
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 (2015), diffuse large B-cell non-Hodgkin lymphoma is not a recommended indication of ibritumomab tiuxetan.

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.

**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-CHOP (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.
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 (2017) does not list hepatocellular carcinoma as a recommended indication of ibritumomab tiuxetan.

Tositumomab (Bexxar):

Bexxar consists of a monoclonal antibody, tositumomab, linked to the radioactive isotope iodine iodine-131. The monoclonal antibody targets the CD20 antigen, which is found on the surface of mature B cells and B cell tumors.

The Bexxar therapeutic regimen is administered in 2 steps: (i) the dosimetric and (ii) therapeutic steps. Each step consists of a sequential infusion of tositumomab followed by iodine-131 (I-131) tositumomab. The therapeutic step is administered 7 to 14 days after the dosimetric step.

The purpose of the dosimetric step is to provide a consistent radiation dose by adjusting for the individual patient’s rate of clearance of the drug. Clinical studies found that patients with high tumor burden, splenomegaly, or bone marrow involvement have a faster clearance, shorter terminal half-life, and larger volume of distribution. Patient-specific dosing, based on total body clearance, has been found to provide a consistent radiation dose, despite variable pharmacokinetics, by allowing each patient’s administered activity to be adjusted for individual patient variables.

The efficacy of the Bexxar therapeutic regimen was evaluated in a multi-center, single-arm study in 40 patients with low-grade or
transformed low-grade or follicular large-cell lymphoma whose disease had not responded to or had progressed after rituximab therapy. Determination of clinical benefit of the Bexxar therapeutic regimen was based on evidence of durable responses. All patients in the study were required to have received prior treatment with at least four doses of rituximab without an objective response, or to have progressed following treatment.

Overall response rate was 68%, with a median duration of response of 16 months. One-third of patients demonstrated a complete response. Among a subset of patients who were refractory to rituximab, overall response rate was 63%, with a median duration of response of 25 months. Twenty-nine percent of patients who were refractory to rituximab exhibited a complete response to the Bexxar therapeutic regimen.

The results of this study were supported by demonstration of durable objective responses in 4 single-arm studies enrolling 190 patients evaluable for efficacy with rituximab-naïve, follicular non-Hodgkin lymphoma (NHL) with or without transformation, who had relapsed following or were refractory to chemotherapy. In these studies, the overall response rates ranged from 47% to 64% and the median durations of response ranged from 12 to 18 months. It is not known whether the Bexxar therapeutic regimen improves OS.

The most common adverse reactions associated with the Bexxar therapeutic regimen were severe or life-threatening cytopenias, which occurred among 71% of patients enrolled in clinical studies. These severe or life-threatening cytopenias consisted primarily of severe thrombocytopenia (53%) and severe neutropenia (63%). Sequelae of severe cytopenias observed in clinical studies included infections (45% of patients), hemorrhage (12%), a requirement for growth factors (12% hematopoietic colony stimulating factors; 7% erythropoietin) and blood product support (15% platelet transfusions; 16% red blood cell transfusions). Myelodysplastic syndrome or acute leukemia was reported in 8% of subjects enrolled in clinical studies.
According to the FDA, the safety of the Bexxar therapeutic regimen has not been established in patients with greater than 25% lymphoma marrow involvement, platelet count less than 100,000 cells/mm³ or neutrophil count less than 1,500 cells/mm³.

The FDA-approved labeling of Bexxar states that I-131 tositumomab is contraindicated for use in women who are pregnant. The labeling states that I-131 may cause harm to the fetal thyroid gland when administered to pregnant women, and that transplacental passage of radioiodide may cause severe, and possibly irreversible, hypothyroidism in neonates. The FDA recommends that the use of the Bexxar therapeutic regimen in women of child-bearing age should be deferred until the possibility of pregnancy has been ruled out. If the patient becomes pregnant while being treated with the Bexxar therapeutic regimen, the patient should be apprised of the potential hazard to the fetus.

The FDA-approved labeling states that the Bexxar therapeutic regimen may result in hypothyroidism. The labeling states that thyroid-blocking medications should be initiated at least 24 hours before receiving the dosimetric dose and continued until 14 days after the therapeutic dose. The FDA-approved labeling states that persons who are unable to tolerate thyroid blocking agents should not receive Bexxar.

Guidelines from the National Comprehensive Cancer Network (2012) state that tositumomab radioimmunotherapy alone is indicated in follicular lymphoma, gastric MALT lymphoma, non-gastric MALT lymphoma, or primary cutaneous B-cell lymphoma. For these indications, tositumomab is indicated following chemotherapy or as second-line radioimmunotherapy or refractory or progressive disease, or as first-line therapy for persons with co-morbidities, including the elderly or infirm, where tolerability of combination chemotherapy is a concern.

Song and Sgouros (2011) stated that radioimmunotherapy of solid tumors remains a challenge despite the tremendous success of 90Y-ibritumomab (Zevalin) and I-131 tositumomab (Bexxar) in
treated non-Hodgkin’s lymphoma. For a variety of reasons, clinical trials of radio-labeled antibodies against solid tumors have not led to responses equivalent to those seen against lymphoma. In contrast, promising responses have been observed with unlabeled antibodies that target solid tumor receptors associated with cellular signaling pathways. These observations suggest that anti-tumor efficacy of the carrier antibody might be critical to achieving clinical responses.

On February 20, 2014, GlaxoSmithKline announced that it will discontinue the manufacture and sale of the Bexxar therapeutic regimen (tositumomab and iodine I 131 tositumomab).

Vaklavas et al (2013) stated that radioimmunotherapy (RIT) capitalizes on the radio-sensitivity of NHL and the targeted nature of monoclonal antibodies. In an attempt to reverse bone marrow infiltration with B-cells and optimize the bio-distribution of 90 (90)Y-ibritumomab tiuxetan, these researchers conducted a phase I study combining a single course of (90)Y-ibritumomab tiuxetan after a 4-weekly course of rituximab in relapsed or refractory low-grade or transformed CD20+ B-cell NHLs with less than 25 % marrow involvement. The 0.4 mCi/kg dose was associated with 80 % grade-4 cytopenias. Dose escalation was held, and 6 patients were enrolled at a 0.3 mCi/kg cohort. As the 0.3 mCi/kg dose was well-tolerated, the 0.4 mCi/kg cohort was expanded to 6 additional patients. In the expansion cohort, grade-4 cytopenia developed in 33 %. Further dose escalation was held, and the maximum tolerated dose was determined at 0.4 mCi/kg. With this regimen, marrow involvement decreased in all patients with complete clearance in 50 %. The overall response rate (ORR) was 82 %. With a median follow-up of 31.7 months, the median PFS and time to next treatment were 12.3 and 10.9 months, respectively. The authors concluded that although this regimen was associated with a high response rate, the hematologic toxicity was higher than with the standard (90)Y-ibritumomab tiuxetan regimen.

Witzig and associates (2013) noted that RIT for relapsed indolent NHL produces ORR of 80 % with mostly partial remissions. Synthetic CpG oligonucleotides change the phenotype of
malignant B-cells, are immuno-stimulatory, and can produce responses when injected intra-tumorially and combined with conventional radiation. In a phase I clinical trial, these researchers tested systemic administration of both CpG and RIT. Eligible patients had biopsy-proven previously treated CD20+ B-cell NHL and met criteria for RIT. Patients received rituximab 250 mg/m(2) days 1,8, and 15; (111) In-ibritumomab tiuxetan days 1, 8; CpG 7909 days 6, 13, 20, 27; and 0.4 mCi/kg of (90) Y-ibritumomab tiuxetan day 15. The doses of CpG 7909 tested were 0.08, 0.16, 0.32 (6 patients each) and 0.48 mg/kg (12 patients) IV over 2 hours without dose limiting toxicity. The ORR was 93 % (28/30) with 63 % (19/30) complete remission (CR); median PFS of 42.7 months (95 % CI: 18 to NR); and median duration of response (DR) of 35 months (4.6 to 76+). Correlative studies demonstrated a decrease in IL10 and TNFα, and an increase in IL1β, in response to therapy. The authors concluded that CpG 7909 at a dose of 0.48 mg/kg is safe with standard RIT and produces a high CR rate and long DR; moreover, they state that these results warrant confirmation.

In a multi-center, phase II, pilot trial, Arranz et al (2013) evaluated the feasibility, safety and effectiveness of rituximab-hyperCVAD alternating with rituximab-methotrexate-cytarabine followed by consolidation with (90)Y-ibritumomab tiuxetan in patients with MCL. Patients received 6 cycles followed by a single dose of (90)Y-ibritumomab tiuxetan. A total of 30 patients were enrolled; their median age was 59 years. Twenty-four patients finished the induction treatment, 23 achieved CR (77 %, 95 % CI: 60 to 93) and 1 patient had progressive disease (3 %). Eighteen patients (60 %), all in CR, received consolidation therapy. In the intent-to-treat population, failure-free, PFS and OS rates at 4 years were 40 % (95 % CI: 20.4 to 59.6), 52 % (95 % CI: 32.4 to 71.6) and 81 % (95 % CI: 67.28 to 94.72), respectively. For patients who received consolidation, failure-free and OS rates were 55 % (95 % CI: 31.48 to 78.52) and 87 % (95 % CI: 70 to 100), respectively. Hematologic toxicity was significant during induction and responsible for 1 death (3.3 %). After consolidation, grade 3 to 4 neutropenia and thrombocytopenia were observed in 72 % and 83 % of patients, with a median duration of 5 and 12 weeks, respectively. Six (20 %) patients died, 3 due to secondary
malignancies (myelodysplastic syndrome and bladder and rectum carcinomas). The authors concluded that rituximab-hyperCVAD alternated with rituximab-methotrexate-cytarabine and followed by consolidation with (90)Y-ibritumomab tiuxetan was effective although less feasible than expected. Moreover, they stated that unacceptable toxicity observed, especially secondary malignancies, advised against the use of this strategy.

Kolstad and colleagues (2014) noted that the main objective of the MCL3 study was to improve outcome for patients with MCL not in CR before transplant by adding (90)Y-ibritumomab-tiuxetan (Zevalin) to the high-dose regimen. A total of 160 untreated, stage II to IV MCL patients less than 66 years received rituximab (R)-maxi-CHOP (cyclophosphamide, hydroxydaunorubicin, vincristine, and prednisone) alternating with R-high-dose cytarabine (6 cycles total), followed by high-dose BEAM/C (bis-chloroethylnitrosourea, etoposide, cytarabine, and melphalan or cyclophosphamide) and autologous stem cell transplantation from 2005 to 2009. Zevalin (0.4 mCi/kg) was given to responders not in CR before transplant. Overall response rate pre-transplant was 97%. The outcome did not differ from that of the historic control: the MCL2 trial with similar treatment except for Zevalin. Overall survival, EFS, and PFS at 4 years were 78%, 62%, and 71%, respectively. For responding non-CR patients who received Zevalin, DR was shorter than for the CR group. Inferior PFS, EFS, and OS were predicted by PET positivity pre-transplant and detectable minimal residual disease (MRD) after transplant. The authors concluded that positive PET and MRD were strong predictors of outcome. Intensification with Zevalin may be too late to improve the outcome of patients not in CR before transplant.

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>CPT codes covered if selection criteria are met:</th>
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| Other CPT codes related to the CPB: |
Radiopharmaceutical localization of tumor or distribution of radiopharmaceutical agent(s)

Blood count; manual cell count (erythrocyte, leukocyte, or platelet), each

platelet, automated

ibritumomab Tiuxetan (Zevalin):

HCPCS codes covered if selection criteria are met:

A9543 Yttrium Y-90 ibritumomab tiuxetan, therapeutic, per treatment dose, up to 40 millicuries

Other HCPCS codes related to the CPB:

A9542 Indium In-111 ibritumomab tiuxetan, diagnostic, per study dose, up to 5 millicuries

ICD-10 codes covered if selection criteria are met:

C82.00 - Follicular lymphoma
C82.99

C83.00 - Lymphosarcoma and reticulosarcoma, other named variants
C83.09,
C83.30 -
C83.39,
C83.90 -
C83.99,
C86.5 -
C86.6

C84.a0 - Cutaneous T-cell and mature T/NK-cell lymphomas
C84.99

C88.4 Marginal zone lymphoma [gastric/nongastric MALT, primary cutaneous B-cell lymphoma]

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

C83.80 - Other lymphomas [diffuse large B-cell non-Hodgkin lymphoma]
C83.89

C83.10 - Mantle cell lymphoma
C83.19

C83.70 - Burkitt lymphoma
C83.79
C91.10 - Chronic lymphoid leukemia [chronic lymphocytic]
C91.12,
C91.90 -
C91.92
D47.21 Post-transplant lymphoproliferative disorder (PTLD)

*Tositumomab (Bexxar):*

**HCPCS codes covered if selection criteria are met:**

A9545 Iodine I-131 tositumomab, therapeutic, per treatment dose
G3001 Administration and supply of tositumomab, 450 mg

**Other HCPCS codes related to the CPB:**

A9544 Iodine I-131 tositumomab, diagnostic, per study dose
J9310 Rituximab, 100 mg

**ICD-10 codes covered if selection criteria are met:**

C82.00 - Follicular lymphoma
C82.99
C83.00 - Lymphosarcoma and reticulosarcoma, other named variants
C83.09, C83.30 -
C83.39
C83.90 -
C83.99,
C86.5 -
C86.6
C83.80 - Marginal zone lymphoma [gastric/nongastric MALT,
C83.89, primary cutaneous B-cell lymphoma]
C88.4
C84.a0 - Other lymphomas
C84.99

**ICD-10 codes not covered for indications listed in the CPB:**

C00.0 - Malignant neoplasm [solid tumors]
C80.2
The above policy is based on the following references:


46. Pohar R, Clark M, Nkansah E. Radioimmunotherapies for


64. Witzig TE, Hong F, Micallef IN, et al. A phase II trial of


Amendment to
Aetna Clinical Policy Bulletin Number: 0659 Radioimmunotherapy for
Non-Hodgkin's Lymphoma: Ibritumomab Tiuxetan (Zevalin) and
Tositumomab (Bexxar)

There are no amendments for Medicaid.