VENTURA COUNTY
HEALTH CARE PLAN

Prior Authorization DRUG Guidelines

Bexarr (tositumomab)

Effective Date: 10/22/13
Date Developed: 9/3/13 by Albert Reeves MD
Last Approval Date: 1/26/16, 1/24/17, 1/23/18, 1/22/19, 2/18/20

Pharmacologic Category: Antineoplastic Agent, Monoclonal Antibody; Radiopharmaceutical

Preauthorizaion Criteria: Treatment of relapsed or refractory CD20 positive, low-grade, follicular, or transformed non-Hodgkin's lymphoma (NHL), with progression during or after rituximab treatment

Dosage: **Non-Hodgkin's lymphoma (NHL), relapsed or refractory:** I.V.: Dosing consists of four components administered in 2 steps. Refer to manufacturer's labeling for additional details. Indicated for a single treatment course. Thyroid protective agents (SSKI, Lugol's solution or potassium iodide) should be administered beginning at least 24 hours prior to step 1 (Refer to Additional Information or Pharmacotherapy Pearls). Premedicate with acetaminophen 650 mg and diphenhydramine 50 mg orally 30 minutes prior to step 1 and step 2.

Step 1: Dosimetric step (Day 0):

Tositumomab 450 mg administered over 60 minutes

Iodine I 131 tositumomab (containing I-131 5 mCi and tositumomab 35 mg) administered over 20 minutes

Note: Whole body dosimetry and biodistribution should be determined on Day 0; days 2, 3, or 4; and day 6 or 7 prior to administration of Step 2. If biodistribution is not acceptable, do not administer the therapeutic step. On day 6 or 7, calculate the patient specific activity of iodine I 131 tositumomab to deliver 75 cGy total body dose (TBD) or 65 cGy TBD (in mCi).

Step 2: Therapeutic step (one dose administered 7-14 days after step 1):

Tositumomab 450 mg administered over 60 minutes

Iodine I 131 tositumomab:

Platelets ≥150,000/mm^3: Iodine I 131 calculated to deliver 75 cGy total body irradiation and tositumomab 35 mg over 20 minutes

Platelets ≥100,000/mm^3 and <150,000/mm^3: Iodine I 131 calculated to deliver 65 cGy total body irradiation and tositumomab 35 mg over 20 minutes

Administration: I.V.: Refer to manufacturer's labeling for additional details.

Tositumomab: Infuse over 60 minutes

Iodine I 131 tositumomab: Infuse over 20 minutes

Administer via an I.V. tubing set with an in-line 0.22 micron filter; do not change primary infusion set or filter at any time during the dosimetric or therapeutic step; changing the filter may result in up to a 7% loss of the iodine I 131 tositumomab dose (use the same infusion set and filter for tositumomab and iodine I 131 tositumomab). Flush with NS after Iodine I 131 tositumomab infusion.

Prior to infusion, patients should be premedicated (with acetaminophen and an antihistamine) and a thyroid-protective agent should be started. Reduce the rate of tositumomab or iodine 131 tositumomab infusion by 50% for mild-to-moderate infusion-related toxicities; interrupt for severe infusion reaction (once severe infusion reaction has resolved, infusion may be restarted at half the previous rate). Discontinue for serious allergic reaction.

Major adverse reactions and Black Box Warnings:

>10%:

Central nervous system: Fever (37%), pain (19%), chills (18%), headache (16%)

Dermatologic: Rash (17%; grades 3/4: <1%)

Endocrine & metabolic: Hypothyroidism (7% to 19%)

Gastrointestinal: Nausea (36%), abdominal pain (15%), vomiting (15%), anorexia (14%), diarrhea (12%)

Hematologic: Myelosuppression (grades 3/4: 71%; nadir: 4-7 weeks; duration: ~30 days), neutropenia (grades 3/4: 63%; median duration: 31 days; grade 4: 25%), thrombocytopenia (grades 3/4: 53%; median duration: 32 days; grade 4: 21%), lymphocytopenia (recovery: ~12 weeks after treatment), anemia (grades 3/4: 29%; median duration: 23 days; grade 4: 5%), secondary leukemia/myelodysplastic syndrome (overall: 3% to 10%; 2-year follow-up: 2% to 5%; 5-year follow-up: 6% to 15%), hemorrhage (12%)

Neuromuscular & skeletal: Weakness (46%), myalgia (13%)

Respiratory: Cough (21%), pharyngitis (12%), dyspnea (11%)

Miscellaneous: Infusion-related reactions (29%, occurred within 14 days of infusion, included bronchospasm, chills, dyspnea, fever, hypotension, nausea, rigors, diaphoresis); infection (21% to 45%, serious: 9%);g HAMA-positive seroconversion (10% to 11%)

1% to 10%:

Cardiovascular: Hypotension (7%), peripheral edema (9%), chest pain (7%), vasodilation (5%)

Central nervous system: Dizziness (5%), somnolence (5%)

Dermatologic: Pruritus (10%)

Gastrointestinal: Constipation (6%), dyspepsia (6%), weight loss (6%)

Local: Injection site hypersensitivity

Neuromuscular & skeletal: Arthralgia (10%), back pain (8%), neck pain (6%)

Respiratory: Rhinitis (10%), pneumonia (6%)

Miscellaneous: Diaphoresis (8%), hypersensitivity/allergic reaction (6%), secondary malignancies (nonhematologic: 5%)

<1% (Limited to important or life-threatening): Anaphylactic reaction, angioedema, bacteremia, bronchitis, dehydration, flu-like syndrome, herpes virus infection, laryngismus, pleural effusion, septicemia, serum sickness, skin infections

Contraindications

There are no contraindications listed in the manufacturer's labeling.

Bone marrow suppression: **[U.S. Boxed Warning]: Severe and prolonged cytopenias, including neutropenia and thrombocytopenia are common; do not administer in patients with >25% lymphoma marrow involvement, platelet count <100,000/mm^3 or neutrophil count <1500/mm^3.** Hematologic toxicity is reported to be the most common adverse effect with 27% patients requiring supportive care; cytopenias may be prolonged and severe.

- Hypersensitivity/anaphylactoid reactions: **[U.S. Boxed Warning]: Serious hypersensitivity reactions (including anaphylaxis) have been reported; permanently discontinue for severe reaction; medications for the treatment of reactions should be readily available in the event of severe reactions.** Signs and symptoms of severe allergic reactions include fever, rigors/chills, sweating, hypotension, dyspnea, bronchospasm, or nausea; may occur during or within 48 hours of infusion. Premedicate with acetaminophen and diphenhydramine prior to both the dosimetric and therapeutic doses.

Special handling:

- Radioactive isotopes: **[U.S. Boxed Warning]: Treatment involves radioactive isotopes and should only be administered by or under supervision of physicians enrolled in the Bexxar® therapeutic regimen certification program; appropriate precautions for**

handling and administration must be followed. Patients must be instructed in measures to minimize exposure of others.

References:

1. Hamnvik OP, Larsen PR, and Marqusee E, "Thyroid Dysfunction From Antineoplastic Agents," *J Natl Cancer Inst*, 2011, 103(21):1572-87. [PubMed 22010182]
2. Kaminski MS, Radford JA, Gregory S, et al, "Re-Treatment With I-131 Tositumomab in Patients With Non-Hodgkin's Lymphoma Who Had Previously Responded to I-131 Tositumomab," *J Clin Oncol*, 2005, 23(31):7985-93. [PubMed 16204016]
3. Kaminski MS, Tuck M, Estes J, et al, "131I-Tositumomab Therapy as Initial Treatment for Follicular Lymphoma," *N Engl J Med*, 2005, 352(5):441-9. [PubMed 15689582]
4. Kaminski MS, Zelenetz AD, Press OW, et al, "Pivotal Study of Iodine I 131 Tositumomab for Chemotherapy-Refractory Low-Grade or Transformed Low-Grade B-Cell Non-Hodgkin's Lymphomas," *J Clin Oncol*, 2001, 19(19):3918-28. [PubMed 11579112]
5. Link BK, Martin P, Kaminski MS, et al, "Cyclophosphamide, Vincristine, and Prednisone Followed by Tositumomab and Iodine-131-Tositumomab in Patients With Untreated Low-Grade Follicular Lymphoma: Eight-Year Follow-Up of a Multicenter Phase II Study," *J Clin Oncol*, 2010, 28(18):3035-41. [PubMed 20458031]
6. Press OW, Eary JF, Appelbaum FR, et al, "Phase II Trial of 131I-B1 (Anti-CD20) Antibody Therapy With Autologous Stem Cell Transplantation for Relapsed B Cell Lymphomas," *Lancet*, 1995, 346(8971):336-40.
7. Press OW, Unger JM, Braziel RM, et al, "Phase II Trial of CHOP Chemotherapy Followed by Tositumomab/Iodine I-131 Tositumomab for Previously Untreated Follicular Non-Hodgkin's Lymphoma: Five-Year Follow-up of Southwest Oncology Group Protocol S9911," *J Clin Oncol*, 2006, 24(25):4143-9. [PubMed 16896003]
8. Press OW, Unger JM, LeBlanc ML, et al, "A Phase III Randomized Intergroup Trial (S0016) Comparing CHOP Plus Rituximab With CHOP Plus Iodine-131-Tositumomab for Front-Line Treatment of Follicular Lymphoma: Results of Subset Analyses and a Comparison of Prognostic Models," *J Clin Oncol*, 2012, 30(15s):8001 [abstract 8001 from 2012 ASCO Annual Meeting].

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1/24/17	No	Catherine Sanders, MD; Robert Sterling, MD	Annual review
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