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Facts About
The ZEVALIN® (Ibritumomab Tiuxetan)
Therapeutic Regimen

Radioimmunotherapy is an innovative form of cancer therapy, combining a monoclonal antibody against a specific target antigen with a source of radiation such as a radioisotope. The ZEVALIN therapeutic regimen is a novel form of radioimmunotherapy. On February 19, 2002, the ZEVALIN therapeutic regimen became the first radioimmunotherapy approved by the U.S. Food and Drug Administration (FDA).

Because Indium-111 radiolabeled ZEVALIN (In-111 ZEVALIN) and Yttrium-90 radiolabeled ZEVALIN (Y-90 ZEVALIN) are radiopharmaceuticals, they should be used only by physicians and other professionals qualified by training and experienced in the safe use and handling of radionuclides.

Indication: ZEVALIN, as part of the ZEVALIN therapeutic regimen, is for the treatment of patients with relapsed or refractory low-grade, follicular or transformed B-cell Hodgkin's lymphoma (NHL), including patients with Rituximab-refractory follicular NHL.

Determination of the effectiveness of the ZEVALIN therapeutic regimen in a relapsed or refractory patient population is based on overall response rates. The effects of the ZEVALIN therapeutic regimen on survival are not known.

Composition: ZEVALIN is composed of monoclonal antibody ibritumomab bound to tiuxetan, which is a linker for the radioisotopes Yttrium-90 or Indium-111. Ibritumomab is directed against the CD20 antigen, a protein found on the surface of malignant B-lymphocytes in patients with B-cell non-Hodgkin's lymphoma (NHL) as well as on normal mature B-lymphocytes. The ZEVALIN therapeutic regimen consists of 3 components – Rituximab, In-111 ZEVALIN and Y-90 ZEVALIN.

Mechanism of Action: After Y-90 ZEVALIN (the therapeutic component of the ZEVALIN regimen) enters the bloodstream, the monoclonal antibody ibritumomab recognizes and attaches to the CD20 antigen, allowing beta radiation emitted by the Yttrium-90 isotope to penetrate and damage the B-cell as well as neighboring cells.

Treatment with the ZEVALIN Therapeutic Regimen: The ZEVALIN therapeutic regimen is delivered over 7 to 9 days. On the first day of therapy, an IV infusion of Rituximab is followed by an injection of In-111 ZEVALIN, which is used for imaging purposes. One required set of whole-body gamma camera images are obtained between 48 and 72 hours after the administration of In-111 ZEVALIN to evaluate biodistribution. At the physician's discretion, additional imaging studies may be performed. If biodistribution is acceptable, a second IV infusion of Rituximab is given on treatment day 7, 8 or 9, followed by a therapeutic dose of Y-90 ZEVALIN.

Y-90 ZEVALIN should not be given to patients with an altered biodistribution as determined by imaging with In-111 ZEVALIN. In a post-marketing registry designed to collect biodistribution images and other information in reported cases of altered biodistribution, there were 12 patients (1.3%) reported to have altered biodistribution among 953 patients registered.

Clinical Trial Results: Clinical studies with the ZEVALIN therapeutic regimen have demonstrated high response rates and durable responses in patients with relapsed, refractory follicular or transformed B-cell NHL.

- A pivotal Phase 3 randomized, controlled trial was conducted in 143 patients with relapsed or refractory, low-grade or follicular NHL or transformed B-cell NHL comparing the ZEVALIN therapeutic regimen versus Rituximab administered alone. The overall response rate in 73 patients who received the ZEVALIN therapeutic regimen was 80% (with 30% complete responses) compared to an overall response rate of 56% (with 16% complete responses) in patients who received Rituximab alone. This difference in overall response rates was statistically significant (P = .002).

  The estimated median duration of response was 13.9 months for patients receiving the ZEVALIN therapeutic regimen and 11.8 months for patients receiving Rituximab. Median time to disease progression in the intent-to-treat populations was 10.6 months and 10.1 months for the ZEVALIN therapeutic regimen and Rituximab, respectively. The secondary endpoints, duration of response, and time to progression were not significantly different between the 2 treatment arms.

- In a nonrandomized Phase 2 study in 54 patients with follicular B-cell NHL that was refractory to Rituximab, the overall response rate to the ZEVALIN therapeutic regimen was 74% (with 15% complete responses).

The registrational trials of the ZEVALIN therapeutic regimen involved more than 30 academic and community cancer centers in the United States. Included among these trials was the only randomized clinical study to date comparing radioimmunotherapy to another standard therapy.

ZEVALIN Benefits

Ready to go at first relapse: The ZEVALIN therapeutic regimen is a first-relapse treatment option for the treatment of patients with relapsed or refractory low-grade, follicular or transformed B-cell Hodgkin's lymphoma (NHL), including patients with Rituximab-refractory follicular NHL.

Short treatment regimen: Many NHL chemotherapies require multiple treatments over weeks or even months. However, the entire ZEVALIN regimen is completed in 7 to 9 days. Patients then receive follow-up care by a physician for at least an additional 12 weeks.

Outpatient administration: The ZEVALIN therapeutic regimen can be administered entirely on an outpatient basis. No isolation or lead shielding is necessary.

Subsequent therapy options: Treatment with the ZEVALIN therapeutic regimen does not preclude patients from receiving other lymphoma therapies in the event of a relapse, including chemotherapy, Rituximab, external beam radiation therapy or bone-marrow transplant.

The ZEVALIN therapeutic regimen is intended as a one-time treatment. The safety profile from multiple courses of the ZEVALIN therapeutic regimen or other forms of therapeutic radiation preceding, following, or in combination with the ZEVALIN therapeutic regimen has not been established.

The right dose for each patient: The optimal dose of Yttrium-90 ZEVALIN for each patient is calculated based on body weight and baseline blood platelet count. The ZEVALIN therapeutic regimen does not require doctors to complete complex radiation calculations (dosimetry) to determine the right dose for each patient.

The prescribed, measured and administered dose of Y-90 ZEVALIN should not exceed the absolute maximum allowable dose of 32.0 mCi.

Ongoing Studies

Clinical studies at major medical centers are currently investigating the use of the ZEVALIN therapeutic regimen in a variety of other lymphoma subtypes including aggressive disease. The ZEVALIN therapeutic regimen is also being studied in a number of different treatment strategies including combinations with front-line and salvage chemotherapy regimens and as part of autologous and allogeneic stem cell transplantation.

Safety Information

Severe Infusion Reactions: The ZEVALIN therapeutic regimen may cause severe, and potentially fatal, infusion reactions. These severe reactions typically occur during the first Rituximab infusion with time to onset of 30 to 120 minutes. Signs and symptoms of severe infusion reaction may include hypotension, angioedema, hypoxia, or bronchospasm, and may require interruption of Rituximab, In-111 ZEVALIN, or Y-90 ZEVALIN administration. The most severe manifestations and sequelae may include pulmonary infiltrates, acute respiratory distress syndrome, myocardial infarction, ventricular fibrillation, and cardiogenic shock.

Prolonged and Severe Cytopenias: Y-90 ZEVALIN administration results in severe and prolonged cytopenias (low blood cell counts) in most patients. The most common severe adverse events reported with the ZEVALIN therapeutic regimen were low platelet counts or thrombocytopenia (61% of patients with platelet counts <50,000 cells/mm^3) and low white cell counts or neutropenia (57% of patients with absolute neutrophil counts (ANC) <1,000 cells/mm^3) in patients with ≥150,000 platelets/mm^3 prior to treatment. The incidence rates of both severe thrombocytopenia and neutropenia increased to 78% and 74% in patients with mild thrombocytopenia at baseline (platelet count of 100,000 to 149,000 cells/mm^3). For all patients, the median time to nadir was 7-9 weeks and the median duration of cytopenias was 22-35 days.

The risk of hematologic toxicity correlated with the degree of bone marrow involvement prior to ZEVALIN therapy. The ZEVALIN therapeutic regimen should not be administered to patients with 25% or more lymphoma bone marrow involvement and/or impaired bone marrow reserve, e.g., prior myeloablative therapies; platelet count less than 100,000 cells/mm^3; neutrophil count less than 1,500 cells/mm^3; hypocellular bone marrow (≤15% cellularity or marked reduction in bone marrow precursors); or to patients with a history of failed stem cell collection.

Low blood cell counts can occur up to 7 to 9 weeks following therapy, and counts may stay low for 22 to 35 days. In less than 5% of cases, patients experienced severe cytopenia that extended beyond 12 weeks following administration of the therapy. Some of these patients eventually recovered from cytopenia, while others experienced progressive disease, received further anti-cancer therapy, or died of their lymphoma without having recovered from cytopenia. The cytopenias may have influenced subsequent treatment decisions.

Hemorrhage, including fatal cerebral hemorrhage, and severe infections have occurred in a minority of patients in clinical studies. Careful monitoring for and management of cytopenias and their complications (e.g., febrile neutropenia, hemorrhage) for up to 3 months after use of the ZEVALIN therapeutic regimen are necessary. Caution should be exercised in treating patients with drugs that interfere with platelet function or coagulation following the ZEVALIN therapeutic regimen and patients receiving such agents should be closely monitored.

Severe Cutaneous and Mucocutaneous Reactions: There have been postmarketing reports of erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis, bullous dermatitis, and exfoliative dermatitis in patients who received the ZEVALIN therapeutic regimen. Some of these events were fatal. The onset of the reactions was variable: in some cases acute (days) and in others, delayed (3-4 months). Patients experiencing a severe cutaneous or mucocutaneous reaction should not receive any further components of the ZEVALIN therapeutic regimen and should seek prompt medical evaluation.

Infectious Events: During the first 3 months after initiating the ZEVALIN therapeutic regimen, 29% of patients developed infections. 3% of patients developed serious infections comprising urinary tract infection, febrile neutropenia, sepsis, pneumonia, cellulitis, colitis, diarrhea, osteomyelitis, and upper respiratory tract infection. Life threatening infections were reported for 2% of patients that included sepsis, empyema, pneumonia, febrile neutropenia, fever, and biliary stent-associated cholangitis. During follow-up from 3 months to 4 years after the start of treatment with ZEVALIN, 6% of patients developed infections. 2% of patients had serious infections comprising urinary tract infection, bacterial or viral pneumonia, febrile neutropenia, perihilar infiltrate, pericarditis, and intravenous drug-associated viral hepatitis. 1 % of patients had life threatening infections that included bacterial pneumonia, respiratory disease, and sepsis.

Secondary Malignancies: Out of 349 patients treated with the ZEVALIN therapeutic regimen, three cases of acute myelogenous leukemia and two cases of myelodysplastic syndrome have been reported following the ZEVALIN therapeutic regimen.

Contraindications: The ZEVALIN therapeutic regimen is contraindicated in patients with known Type 1 hypersensitivity or anaphylactic reactions to murine proteins or to any component of the regimen, including Rituximab, yttrium chloride, and indium chloride.

Pregnancy Category D: Y-90 ZEVALIN can cause fetal harm when administered to a pregnant woman.

Creutzfeldt-Jakob Disease (CJD): This product contains albumin, a derivative of human blood. Based on effective donor screening and product manufacturing processes, it carries an extremely remote risk for transmission of viral diseases. A theoretical risk for transmission of Creutzfeldt-Jakob Disease (CJD) also is considered extremely remote. No cases of transmission of viral diseases or CJD have ever been identified for albumin.

Safety Data: In safety data based upon 349 patients, the most serious adverse reactions of the ZEVALIN therapeutic regimen were prolonged and severe cytopenias, infections (predominately bacterial in origin), hemorrhage while thrombocytopenic (resulting in deaths) and allergic reactions (bronchospasm and angioedema).

The most common toxicities reported were neutropenia, thrombocytopenia, anemia, gastrointestinal symptoms (nausea, vomiting, abdominal pain, and diarrhea), increased cough, dyspnea, dizziness, arthralgia, anorexia, anxiety, and ecchymosis. Hematologic toxicity was often severe and prolonged, whereas most non-hematologic toxicity was mild in severity.

Non-hematologic side effects that occurred in 5% or more of patients include weakness (43%), infection (29%), chills (24%), fever (17%), abdominal pain (16%), general pain (16%), headache (12%), sore throat (10%), back pain (8%), flushing (6%), hypotension (6%), nausea (31%), vomiting (12%), diarrhea (9%), anorexia (8%), abdominal enlargement (5%), constipation (5%), swelling (8%), joint pain (7%), muscular pain (7%), dizziness (10%), insomnia (5%), shortness of breath (14%), increased cough (10%), rhinitis (6%), bronchospasm (5%), itching (9%) and rash (8%) .

Marketing and Distribution

The ZEVALIN therapeutic regimen is marketed and distributed by Biogen Idec in the United States. Schering AG, Biogen Idec's corporate partner, holds marketing and distribution rights for the ZEVALIN therapeutic regimen outside the United States.

About Non-Hodgkin's Lymphoma

- Non-Hodgkin's lymphoma (NHL) is the fifth most common type of cancer in the United States.
- Incidence of NHL has increased over the past 20 years.
- It is estimated that approximately 300,000 people are currently living with NHL in the United States.
- Virtually all patients with low-grade NHL demonstrate a continuous pattern in which they initially respond to treatment then experience relapse of the disease, with shorter remissions following each treatment regimen. New treatment options for these patients are needed.

Please see enclosed full prescribing information for ZEVALIN and Rituximab, including Boxed Warnings, or call 1-877-878-4332 or visit *www.zevalin.com*.