DRUG NAME: Ibritumomab tiuxetan

SYNONYM(S): ibritumomab, ^{90}Y-ibritumomab[1]

COMMON TRADE NAME(S): ZEVALIN®

CLASSIFICATION: radiopharmaceutical

Special pediatric considerations are noted when applicable, otherwise adult provisions apply.

MECHANISM OF ACTION:

Ibritumomab is a murine IgG1 monoclonal antibody which is covalently bound to the chelating agent tiuxetan. Unlabelled ibritumomab tiuxetan is chelated with the radioactive compound yttrium-90 (^{90}Y) to prepare the active therapeutic agent ^{90}Y-ibritumomab. The radiolabelled ibritumomab binds to the CD20 antigen on the target B lymphocytes and the long β-energy pathlength of the yttrium-90 (^{90}Y) allows neighboring tumour cells to be killed without direct binding of the antibody.[1] Ibrutumomab tiuxetan does not appear to be cell cycle phase specific.

USES:

Primary uses:
*Lymphoma, non-Hodgkin's

*Health Canada approved indication

Other uses:

SPECIAL PRECAUTIONS:

Contraindications:
- history of hypersensitivity reaction to ibritumomab, yttrium-90, or Chinese hamster ovary cell proteins[1]

Caution[1]:
- ibritumomab tiuxetan is a ***radiopharmaceutical*** and should be received, used, and administered only by professionals trained in the safe handling of ***radionuclides***
- ***rituximab*** is an essential component of ibritumomab-based regimens; rituximab precautions apply, including standard premedication for infusion reactions
- severe and prolonged ***cytopenias*** may occur; especially in patients:
  - who have received prior radiation or multiple chemotherapies
  - who have been treated with fludarabine, especially if <4 months ago
  - with ≥25% marrow involvement and/or impaired bone marrow reserve
  - with thrombocytopenia at baseline
- avoid ***live viral vaccines*** due to risk of developing viral infections; patients may also have a limited ability to generate a humoral response to any vaccine following ibritumomab tiuxetan[1]
- avoid ***growth factor*** treatment (e.g., G-CSF) for 3 weeks prior to ibritumomab tiuxetan and 2 weeks following treatment to enable accurate assessment of bone marrow reserve and because of the sensitivity of rapidly dividing cells to radiation[1]
- ibritumomab tiuxetan contains ***albumin*** which presents a remote risk of transmission of viral diseases[1]

SIDE EFFECTS:

The table includes adverse events that presented during drug treatment but may not necessarily have a causal relationship with the drug. Because clinical trials are conducted under very specific conditions, the adverse event

rates observed may not reflect the rates observed in clinical practice. Adverse events are generally included if they were reported in more than 1% of patients in the product monograph or pivotal trials, and/or determined to be clinically important. When placebo-controlled trials are available, adverse events are included if the incidence is ≥5% higher in the treatment group.

****Side effects and incidence are based on a regimen containing radiolabelled ibritumomab, unless specified.**

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
blood/bone marrow/ febrile neutropenia	anemia (61%, severe 17%)
	neutropenia (77%, severe 60%); incidence of severe reaction increases to 74% in patients with baseline thrombocytopenia; nadir 7-9 weeks, duration 22-35 days
	thrombocytopenia (95%, severe 63%); incidence of severe reaction increases to 78% in patients with baseline thrombocytopenia; nadir 7-9 weeks, duration 22-35 days
gastrointestinal	*emetogenic potential:* low[2]
	abdominal pain (16%, severe 3%)
	diarrhea (9%, severe <1%)
	gastrointestinal hemorrhage (1%)
	gum hemorrhage (1%)
	nausea (31%, severe 1%)
	rectal hemorrhage (1%)
	vomiting (12%, severe 0%)
general disorders and administration site conditions	*extravasation hazard:* vesicant[1,3]
	asthenia (43%, severe 3%)
	chills (24%, severe <1%)
	fever (17%, severe 1%)
	infusion reactions; see paragraph following **Side Effects** table
	injection site pain (1%)
	injection site reactions; see paragraph following **Side Effects** table
	pain (13%, severe 1%)
immune system	angioedema (5%, severe <1%)
infection	infection (29%, severe 5%); sometimes fatal
metabolism and nutrition	anorexia (8%)
musculoskeletal	arthralgia (7%, severe 1%)
	back pain (8%, severe 1%)
	myalgia (7%, severe <1%)
neoplasms	myeloid malignancies and dysplasias (1%)
nervous system	cerebral hemorrhage (<1%); may be fatal
	dizziness (10%, severe <1%)
	headache (12%, severe 1%)
	insomnia (5%)
psychiatric	anxiety (4%)
respiratory, thoracic and	bronchospasm (5%)

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
mediastinal	cough (10%)
	dyspnea (14%, severe 2%)
skin and subcutaneous tissue	ecchymosis (7%, severe <1%)
	mucocutaneous reactions (<1%); including erythema multiforme, Stevens-Johnson syndrome; variable onset (i.e., days to months)
	pruritus (9%, severe <1%)
	rash (8%, severe <1%)

Adapted from standard reference[1,4] unless specified otherwise.

The most ***serious adverse reactions*** associated with ^{90}Y-ibritumomab include: infections (predominantly bacterial), allergic reactions, hemorrhage while thrombocytopenic, and severe and prolonged cytopenias. Hematologic toxicity is the most frequently observed adverse event and is dose-limiting. Most non-hematologic toxicities are mild in severity.[1]

Injection site reactions such as infusion site dermatitis, desquamation, and ulcer have been reported following extravasation. Close monitoring is suggested to avoid radiation associated tissue damage. Infusion should be immediately terminated following extravasation and restarted in another vein.[1]

Rituximab is an essential component of ibritumomab-based regimens***. Infusion reactions*** may occur during or after ^{90}Y-ibritumomab administration following pretreatment with rituximab. Deaths have occurred within 24 h of rituximab infusion, with the majority occurring with the first rituximab infusion. Signs and symptoms of infusion reactions may include dizziness, cough, nausea, vomiting, rash, pruritus, tachycardia, asthenia, pyrexia, and rigors. Rituximab and ^{90}Y-ibritumomab infusions should be discontinued in patients who develop severe infusion reactions and appropriate treatment with epinephrine, antihistamines, and corticosteroids given.[1] For management of hypersensitivity reactions, see BCCA Protocol SCDRUGRX Management of Hypersensitivity Reactions to Chemotherapeutic Agents.

SUPPLY AND STORAGE:

Injection: Servier Canada Inc. supplies ibritumomab tiuxetan as a 3.2 mg vial containing 2 mL normal saline for a concentration of 1.6 mg/mL (in a kit containing the non-radioactive components for radiolabelling with yttrium-90 to produce ^{90}Y-ibritumomab). Other kit components include: one 50 mM/2 mL vial of sodium acetate, one formulation buffer vial containing 750 mg/10 mL human serum albumin plus other buffering agents, and one empty reaction vial. The contents of all vials are preservative-free. Refrigerate. Protect from light.[1]

SOLUTION PREPARATION AND COMPATIBILITY:

Additional information:
- ibritumomab tiuxetan should only be prepared by a qualified specialist in handling radiopharmaceuticals[1]
- after radiolabelling, the final formulation contains 2.08 mg ^{90}Y-ibritumomab in 10 mL total volume[1]
- immediate use is recommended after radiolabelling (within 8 h)[1]
- after injection, flush line with at least 10 mL NS[1]

Compatibility: consult detailed reference

PARENTERAL ADMINISTRATION:

BCCA administration guideline noted in ***bold***, ***italics***

Subcutaneous	no information found
Intramuscular	no information found
Direct intravenous[1]	***over 10 min;*** use a 0.2-0.22 micron in-line filter for administration
Intermittent infusion	no information found
Continuous infusion	no information found
Intraperitoneal	no information found
Intrapleural	no information found
Intrathecal	no information found
Intra-arterial	no information found
Intravesical	no information found

DOSAGE GUIDELINES:

Refer to protocol by which patient is being treated. Numerous dosing schedules exist and depend on disease, response and concomitant therapy. Guidelines for dosing also include consideration of absolute neutrophil count (ANC). Dosage may be reduced, delayed or discontinued in patients with bone marrow depression due to cytotoxic/radiation therapy or with other toxicities.

Adults:

BCCA usual dose noted in ***bold, italics***

Intravenous[1]***:*** ***0.4 mCi/kg IV for one dose* only on day 7, 8, or 9*** (total dose 0.4 mCi/kg)
Absolute max dose = 32.0 mCi (1200 MBq), regardless of patient weight.

*as ^{90}Y-ibritumomab

Dosage in myelosuppression[1]*:* modify according to protocol by which patient is being treated; if no guidelines available, see suggested dose modification below:

Platelet count ($\times 10^9$/L)	Dose* (mCi/kg)
>149	0.4
100-149	0.3
<100	do not administer

Absolute max dose = 32.0 mCi (1200 MBq), regardless of patient weight.

*as ^{90}Y-ibritumomab

REFERENCES:

1. Servier Canada Inc. ZEVALIN® product monograph. Laval, Quebec; 8 July 2016.
2. BC Cancer Agency. (SCNAUSEA) Guidelines for Prevention and Treatment of Chemotherapy-induced Nausea and Vomiting in Adults. Vancouver, British Columbia: BC Cancer Agency; 1 Mar 2012.
3. BC Cancer Agency Provincial Systemic Therapy Program. Provincial Systemic Therapy Program Policy III-20: Prevention and Management of Extravasation of Chemotherapy. Vancouver, British Columbia: BC Cancer Agency; January 2016.
4. Berlex Canada. ZEVALIN® product monograph. Pointe-Claire, Quebec; 10 May 2005.