DRUG NAME: Elranatamab

SYNONYM(S): PF-06863135[1]

COMMON TRADE NAME(S):

CLASSIFICATION: immunotherapy

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

MECHANISM OF ACTION:

Elranatamab is a heterodimeric humanized (IgG2) full-length bispecific antibody against B-cell maturation antigen (BCMA) and Cluster of differentiation 3 T-cell co-receptor (CD3). Elranatamab has two binding arms (one each for BCMA and CD3) and a modified IgG2 Fc region. It is proposed that elranatamab acts through direct bridging of the BCMA cell-surface antigen and the extracellular CD3 epsilon subunit expressed on T cells. Bispecific antibodies offer a novel immunotherapeutic approach allowing the direct targeting of cytotoxic T cells to tumour cells.[1]

USES:

Primary uses:

Multiple myeloma[1]

Other uses:

*Health Canada approved indication

SPECIAL PRECAUTIONS:

Caution:

- ***premedication*** with acetaminophen, diphenhydramine, and dexamethasone is required for both priming doses and the first full dose of elranatamab in cycle one[2] to reduce the risk of cytokine release syndrome and immune effector cell-associated neurotoxicity syndrome[1]; administer 60 min (45-75 min) prior to elranatamab dose[2]
- ***antimicrobial/antiviral prophylaxis*** may be required for high risk patients to prevent bacterial, fungal, and viral infections secondary to elranatamab-related immune suppression[1,2]
- risk of ***impaired wound healing and bleeding*** may be increased following surgical procedures; after surgery, wait to reinitiate elranatamab until surgical recovery and wound healing is satisfactory[2]
- plasma cell depletion and hypogammaglobulinemia may occur with elranatamab treatment; monitor ***immunoglobulin*** levels and consider IV administration of immunoglobulin for IgG levels <400 mg/dL[1,2]

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. When placebo-controlled trials are available, adverse events will generally be included if the incidence is ≥5% higher in the treatment group.

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ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
blood and lymphatic system/ febrile neutropenia	***anemia*** (44-61%, severe 34-46%)
	febrile neutropenia (5%)
	leukopenia (16-27%, severe 12-22%)
	lymphopenia (severe 23-39%)
	neutropenia (38-78%, severe 37-73%)
	thrombocytopenia (29-49%, severe 20-32%)
cardiac	sinus tachycardia (12%)
gastrointestinal	*emetogenic potential:* low[3]
	constipation (12-15%)
	diarrhea (29-39%, severe 2-5%)
	nausea (22-29%, severe 7%)
	vomiting (13-24%)
general disorders and administration site conditions	asthenia (13%, severe 4%)
	fatigue (31-46%, severe 2-7%)
	injection site reactions (27-56%); including erythema, pruritus, pain, inflammation, rash, induration, itching, edema
	malaise (5%)
	peripheral edema (12-14%, severe 1%)
	pyrexia (7-24%, severe 2%)
immune system	***cytokine release syndrome*** (15-88%); see paragraph following **Side Effects** table
	hypogammaglobulinemia (12%)
infections and infestations	herpes zoster (5-10%)
	infection (52%, severe 22%); see paragraph following **Side Effects** table
	pneumocystis *jirovecii* pneumonia (4%)
	pneumonia (6-22%, severe 9-10%) and COVID-19 pneumonia (7%)
	sinusitis (7%)
	upper respiratory tract infection (11%)
	urinary tract infection (5-12%)
investigations	alkaline phosphatase (blood) increase (20%, severe 2%)
	ALT increase (12-17%, severe 4%)
	AST increase (14-27%, severe 3-10%)
	hypercalcemia (17%, severe 5%)
	hyperkalemia (12%, severe 2%)
	hypoalbuminemia (12%, severe 10%)
	hypocalcemia (20%, severe 2%)

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ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
	hypokalemia (15-24%, severe 6-12%)
	hypomagnesemia (32%)
	hyponatremia (15%, severe 5%)
	hypophosphatemia (27-39%, severe 27%)
	weight decrease (24%)
metabolism and nutrition	appetite decrease (27-37%, severe 1-2%)
musculoskeletal and connective tissue	arthralgia (14-22%, severe 1-2%)
	back pain (13-34%, severe 2-7%)
	extremity pain (20%)
	muscular weakness (7%)
	musculoskeletal chest pain (12%)
nervous system	***immune effector cell-associated neurotoxicity syndrome*** (17%); see paragraph following **Side Effects** table
	headache (19-22%, severe 2%)
	paresthesia (3-15%)
	peripheral neuropathy (24%); see paragraph following **Side Effects** table
psychiatric	confusion (15%)
	insomnia (12%)
renal and urinary	acute kidney injury (5%)
respiratory, thoracic and mediastinal	cough (20%)
	dyspnea (20%, severe 5%)
	hypoxia (7-12%, severe 7%)
skin and subcutaneous tissue	dry skin (16-37%)
	pruritus (17%)
vascular	hypertension (7%, severe 6%)

Adapted from standard reference[1] unless specified otherwise.

Cytokine release syndrome (CRS) is a non-antigen-specific cytokine-associated toxicity that occurs as a result of high-level immune activation and can be life-threatening. As a CD3-targeting bispecific antibody, elranatamab stimulates cytokine release and therefore, CRS is an identified risk of treatment and expected to be a common toxicity. Risk of CRS is mitigated by a priming dose regimen for elranatamab and premedication with acetaminophen, diphenhydramine, and dexamethasone prior to the initial doses of elranatamab. The main signs and symptoms of CRS include fever, hypotension and hypoxia, but other accompanying symptoms such as tachypnea, headache, tachycardia, myalgia, arthralgia, rash, and malaise may also be present. Median time to onset is 2 days. Median time to resolution is 2 days. CRS can be managed through supportive care and anti-cytokine interventions at the first signs of CRS.[1,2] Refer to protocol by which patient is being treated. In the absence of other guidelines, see BC Cancer Protocol SCCRS ***Cytokine Release Syndrome Management***.

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Immune effector cell-associated neurotoxicity syndrome (ICANS) is a neuropsychiatric disorder characterized by the involvement of the CNS following any immune therapy that results in the activation/engagement of endogenous or infused T cells and/or other immune effector cells. Like CRS, it is considered an identified risk of elranatamab although it is less common. Risk of ICANS is mitigated by a priming dose regimen for elranatamab and premedication with acetaminophen, diphenhydramine, and dexamethasone prior to the initial doses of elranatamab. Symptoms of ICANS may be progressive and can include aphasia, altered level of consciousness, cognitive impairment, motor weakness, seizures, and cerebral edema. Median time to onset is 2.5 days. Median time to resolution is 3 days. Management of ICANS requires neurologic assessment and supportive care.[1,2]

Patients may be predisposed to ***infection*** because elranatamab causes plasma cell depletion. Infections have been reported in more than 50% of patients, and 22% of those were grade 3 or 4 in severity. The most commonly reported infections are upper respiratory tract infection, pneumonia, COVID-19 pneumonia, and urinary tract infection. Bacterial, fungal, and/or viral prophylaxis may be required for patients at increased risk of infection secondary to treatment.[1,2]

Peripheral neuropathy (including Guillain Barré Syndrome) has been associated with administration of BCMA-directed bispecific T-cell engagers and is considered a risk of elranatamab treatment. Symptoms of treatment-related neuropathy are usually symmetric, distal, and progressive and include paresthesias, numbness, burning sensations, and muscle weakness. Although usually mild, in rare cases symptoms can be disabling or even life-threatening. Pre-existing peripheral neuropathy, prior/concurrent treatment with medications associated with peripheral neuropathy, and recent infections are common clinical features. Median time to onset is 83 days. Median time to resolution is 14.5 days.[1] For grade 2 peripheral sensory or motor neuropathy, hold elranatamab until resolution of symptoms to grade 1 (or less) and resume treatment at a reduced dose. Permanently discontinue elranatamab for recurrent grade 2 neuropathy or grade 3-4 events.[2]

INTERACTIONS:

Cytokines have been shown to cause modest and temporary inhibition of CYP 3A4 and CYP 2C9, resulting in modest and temporal increases in the exposure to substrates of these enzymes. Substrates with narrow therapeutic index should be used cautiously with elranatamab; monitor for toxicity of the substrate.[2]

SUPPLY AND STORAGE:

Injection:

Pfizer Inc. and Affiliates Global Product Development supplies elranatamab (via Health Canada Special Access Program) as 76 mg single-use (preservative free) vials of solution in a concentration of 40 mg/mL (extractable volume of 1.9 mL). Solution is colourless to slightly yellow or yellow-brown. Diluent is supplied as a single-use (preservative free) vial of colourless solution (fill volume of 1.35 mL). Refrigerate. Protect from light.[4]

Pfizer Canada ULC supplies elranatamab as 44 mg and 76 mg ready-to-use single dose (preservative free) vials in a concentration of 40 mg/mL Refrigerate. Store in original packaging to protect from light.[5]

Additional information:
SAP supply:

- the supplied diluent is only used to prepare doses greater than 2 mg and less than 8 mg[4]
- unopened vials can be returned to fridge after storage of up to 8 hours at room temperature (not exceeding 25°C); discard after 8 hours at room temperature[4]
- elranatamab may be prepared in normal room light conditions; avoid direct sunlight/UV light exposure[4]
- minimize exposure to room light during storage[4]

For basic information on the current brand used at BC Cancer, see Chemotherapy Preparation and Stability Chart in Appendix.

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SOLUTION PREPARATION AND COMPATIBILITY:

For basic information on the current brand used at BC Cancer, see Chemotherapy Preparation and Stability Chart in Appendix.

Additional information:

SAP supply:

- allow vials and prepared solutions to reach room temperature (approximately 15 min) prior to use; prepared solutions should not be cold to the touch at time of administration[4]
- solutions may be prepared and handled in normal room light conditions[4]
- closed system transfer devices (CSTDs) are acceptable for dose preparation (exception: ChemoClave® "Genie®" vial access device is not acceptable)[4]; but CSTDs may not be used during storage of prepared doses[4,6]

Commercial supply:

- do not administer if particulates are present[5]
- allow vials to reach room temperature prior to use[5]
- closed system transfer devices may be used during preparation and storage[5]

Compatibility: consult detailed reference

PARENTERAL ADMINISTRATION:

BC Cancer administration guideline noted in ***bold***, ***italics***

Subcutaneous	injection into the abdomen (lower quadrants) is preferred; if abdomen is not available, injections can be administered into the thigh in a distributed manner[2] • do NOT inject into the deltoid OR upper or lower arm[2] • limit of 1 injection per quadrant[2] • up to 2 mL volume can be injected in a single site[2]
Intramuscular	no information found
Direct intravenous	no information found
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.

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Adults:

BC Cancer usual dose noted in ***bold, italics***

	Cycle Length:	
Subcutaneous:	4 weeks[2]:	**Cycle 1 day 1** (1st priming dose): 12 mg SC for one dose **Cycle 1 day 4** (2nd priming dose): 32 mg SC for one dose **Cycle 1 day 8** (first full dose): 76 mg SC for one dose **Cycle 1 days 15 and 22**: 76 mg (range 32-76 mg) SC for one dose (total dose for cycle 1: 272 mg [range 184-272 mg]) **Cycle 2 onwards**: 76 mg (range 32-76 mg) SC for one dose on days 1, 8, 15, and 22 (total dose per cycle: 304 mg [range 128-304 mg]) **Cycle 7 onwards**: Starting on cycle 7 day 1, dosing interval may be increased to q2 weekly at prescriber's discretion. Dose reductions are only applicable after the first full dose of 76 mg is administered. [2] Dose reductions below 32 mg are not permitted for toxicity; permanently discontinue treatment.[2] A minimum of 6 days should be maintained between weekly doses.[2]

REFERENCES:

1. Pfizer Inc and Affiliates Global Product Development. PF-06863135 (Elranatamab) Investigator's Brochure Version 7.0. New York, NY; May 2022
2. Pfizer Inc and Affiliates Global Product Development. Elranatamab Dosing Guidelines Version 3.0 (Pre-Approval Single-Patient Expanded Access for Elranatamab (PF-06863135)). New York, NY; August 25, 2022
3. BC Cancer Supportive Care Tumour Group. (SCNAUSEA) BC Cancer Guidelines for Prevention and Treatment of Chemotherapy-Induced Nausea and Vomiting in Adults. Vancouver, British Columbia: BC Cancer; September 1 2022
4. Pfizer Inc and Affiliates Global Product Development. PF-06863135 Solution for Subcutaneous Injection (40 mg/mL) Investigational Product Manual Version 1.0. New York, NY; December 7, 2021
5. Pfizer Canada-ULC. ELREXFIO® product monograph. Kirkland, Québec; December 6, 2023
6. Hicham Gonzalez. Medical Liaison. Pfizer Canada Oncology. Personal Communication. March 29,2023
7. Pfizer Inc. ELREXFIO® full prescribing information. New York, New York, USA; August 2023

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