Drug Monograph

A - Drug Name

elranatamab

COMMON TRADE NAME(S): Elrexfio™

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B - Mechanism of Action and Pharmacokinetics

Elranatamab is a humanized, bispecific IgG2, T-cell engaging antibody targeting B-cell maturation antigen (BCMA) on multiple myeloma (MM) cells and CD3 on T-cells. Elranatamab binds to both BCMA and CD3, re-directing T-cells to BCMA-expressing MM cells. This leads to T-cell activation, proinflammatory cytokine release and multiple myeloma cell lysis.

Absorption	Bioavailability	56.2% (subcutaneous)
	T max	3 to 7 days
Distribution	Distribution Sites	Central > peripheral compartment
Metabolism	Expected to be metabolized into small peptides by catabolic pathways.	
Elimination	Half-life	22 days (at 76 mg dose level)

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C - Indications and Status

Health Canada Approvals:

- Multiple myeloma

(Includes conditional approvals)

Refer to the product monograph for a full list and details of approved indications.

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D - Adverse Effects

Emetogenic Potential: Low

The following adverse events were reported in a Phase II, open-label study that evaluated patients with relapsed or refractory multiple myeloma (MM) who received elranatamab monotherapy, after 3 prior lines of therapy. These adverse effects were reported in ≥ 10% of patients in the trial; severe or life-threatening adverse events may also be included from other sources.

ORGAN SITE	SIDE EFFECT* (%)	ONSET**
Cardiovascular	Arrhythmia (16%) (2% severe)	E
Dermatological	Rash, pruritus (26%)	E D
Gastrointestinal	Anorexia, weight loss (26%)	E
	Constipation (14%)	E
	Diarrhea (36%)	E
	Nausea, vomiting (21%)	E
General	Edema (18%)	E
	Fatigue (43%)	E
Hematological	Anemia (54%) (42% severe)	E D
	Myelosuppression ± infection, bleeding (44%) (43% severe, 2% febrile neutropenia) (including opportunistic and reactivated viral infections)	E D
Hepatobiliary	↑ LFTs (16%) (5% severe)	E D
Immune	Cytokine release syndrome (58%) (< 1% severe)	I
	↓ Immunoglobulins (13%)	E D
Injection site	Injection site reaction (37%)	I
Metabolic /	Abnormal electrolyte(s) (21%) (↓ K)	E

Endocrine		
Musculoskeletal	Musculoskeletal pain (22%)	E
Nervous System	Cognitive disturbance (14%) (including encephalopathy; 2% severe)	E
	Guillain-Barre syndrome (<1%)	E
	Headache (18%)	E
	Immune effector cell-associated neurotoxicity syndrome (3%)	I E
	Insomnia (13%)	E
	Motor dysfunction (14%) (such as ataxia, balance disorder, gait disturbance, muscle weakness, tremor etc.)	E
	Sensory neuropathy (13%)	E
Respiratory	Cough, dyspnea (24%)	E

* "*Incidence*" may refer to an absolute value or the higher value from a reported range.
"*Rare*" may refer to events with < 1% incidence, reported in post-marketing, phase 1 studies, isolated data or anecdotal reports.

** I = *immediate* (onset in hours to days) E = *early* (days to weeks)
D = *delayed* (weeks to months) L = *late* (months to years)

Refer to the T-Cell Engaging Antibodies guideline for a detailed description of CRS, ICANS and their management.

The most common side effects for elranatamab include cytokine release syndrome, anemia, myelosuppression ± infection, bleeding, fatigue, injection site reaction, diarrhea, anorexia, weight loss, rash, pruritus, cough, dyspnea and musculoskeletal pain.

Cytokine release syndrome (CRS) occurred in over half of patients treated with elranatamab. The majority were Grade 1 (44%), occurred after the first step-up dose (43%), and were single occurrences (recurrence in 13% of patients). Incidence of CRS decreased over the course of treatment (19% after second step-up dose, 7% after first treatment dose and 2% after subsequent doses) and onset ranged from 1 to 9 days (median 2 days) with a median duration of 2 days. Patients should be monitored for signs and symptoms of CRS after administration of step-up doses (e.g. for 48 hours after the dose). Symptoms reported include fever, hypoxia, chills, hypotension, tachycardia, headache, and elevated liver enzymes. Severe cases were uncommon, with 0.5% of patients experiencing Grade 3 and no Grade 4 CRS reported in the pivotal trial, however, CRS can be life-threatening and patients should be evaluated at the first sign of CRS for the need to hospitalize. Patients should receive treatment according to the recommended step-up schedule, with the appropriate premedications to reduce the incidence and severity of CRS. Tocilizumab or siltuximab were administered in 19% and corticosteroids in 9% of patients to treat CRS.

Neurological toxicity was observed in 59% of patients that received elranatamab in the clinical trial. The majority of cases were Grade 1 or 2 in severity, with Grade 3 or 4 events occurring in 7% of patients. **Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS)** occurred in 3.3% of patients in the clinical trial, including recurrent events (1.1%); most patients experienced ICANS

within the step-up dosing schedule (2.7% after the first step up dose). The median time to onset was 3 days, with a median duration of 2 days (range 1 to 18 days). ICANS may occur with or without the presence of CRS; the most frequent manifestations were depressed level of consciousness and declining ICE scores (Grade 1 or 2).

Serious **infections** occurred in 42% of patients that received elranatamab in the pivotal trial. Almost one third of patients had infections that were Grade 3 or 4 in severity, and 7% were fatal. This included opportunistic infections, such as PJP, PML, adenovirus infection, and hepatitis B and CMV reactivation. Hepatitis B reactivation has resulted in hepatic failure or death in some cases with other drugs that target B cells. Elranatamab treatment should not start in patients with active infections. **Hypogammaglobulinemia** occurred in 13% of patients with elranatamab; IV/Subcut immunoglubulin treatment should be considered as necessary, according to local practice guidelines. Infection precautions and antimicrobial prophylaxis should be instituted according to current local practice standards.

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E - Dosing

Refer to protocol by which patient is being treated.

Do not start treatment with elranatamab in patients with active infection.

Screen for hepatitis B virus in all cancer patients starting systemic treatment. Refer to the hepatitis B virus screening and management guideline.

Pre-medications (prophylaxis for CRS)

Administer 1 hour prior to the first 3 elranatamab doses* (step-up doses & first treatment dose):

- Acetaminophen 650 mg PO(or equivalent)
- Dexamethasone 20 mg PO or IV (or equivalent)
- Diphenhydramine 25 mg PO (or equivalent)**

*Assess the need for premedications with subsequent doses (see Table 3)

** Central nervous system (CNS) effects of diphenhydramine may make it challenging to identify ICANS. Consider cetirizine, which has a lower incidence of CNS effects.

Other Supportive Care:

- Consider prophylaxis against Pneumocystis jirovecii pneumonia (PJP) and herpes virus infections.
- Consider other antimicrobial prophylaxis as per local guidelines.
- Elranatamab should be administered to adequately hydrated patients.

Adults:

Administer elranatamab using the following ramp-up dosing schedule to reduce the risk of CRS.

Cycle (28 days)	Day*	Dose (mg, Subcut)	
Cycle 1	Day 1	12	Step-up Dose 1
	Day 4	32	Step-up Dose 2
	Day 8	76	First Treatment Dose
	Day 15, 22	76	Weekly dosing
Cycle 2 to 6	Day 1, 8, 15, and 22	76	Weekly dosing
Cycle 7 and onwards	Day 1, and 15**	76	Every 2 week dosing**

*Maintain a minimum of 2 days between Step-up dose 1 & 2, a minimum of 3 days between Step-up dose 2 & First Treatment Dose, and a minimum of 6 days between remaining treatment doses.
**Q2W schedule only if patients have achieved & maintained a partial response or better for at least 2 months.

Note: Inpatient admission may be required for CRS monitoring. ST-QBP funding for ambulatory administration only.

Dosage with Toxicity:

Dose reductions are not recommended.

Doses may be delayed due to toxicity. Recommendations on restarting after a dose delay are listed in Table 3.

Refer to the T-Cell Engaging Antibodies guideline for a detailed description of CRS, ICANS and their management.

Table 1 - CRS and ICANS Toxicity

Toxicity	Grade[a]	Action
CRS, or ICANS	Grade 1	• Hold until CRS / ICANS has resolved.[b] • Manage and treat symptoms as appropriate. Refer to the T-Cell Engaging Antibodies guideline for details.
	Grade 2	• Hold until CRS / ICANS has resolved.[b] • Manage and treat symptoms as appropriate. Refer to the T-Cell Engaging Antibodies guideline for details. • Monitor daily for 48 hours following next dose; consider hospitalization.[c]
	Grade 3	• First occurrence: ◦ Hold until CRS / ICANS has resolved.[b] ◦ Manage and treat symptoms as appropriate. Refer to the T-Cell Engaging Antibodies guideline for details. ◦ Monitor daily for 48 hours following next dose, or hospitalize.[c] • Recurrent: ◦ Permanently discontinue ◦ Manage and treat symptoms as appropriate. Refer to the T-Cell Engaging Antibodies guideline for details.
	Grade 4	• Permanently discontinue • Manage and treat symptoms as appropriate. Refer to the T-Cell Engaging Antibodies guideline for details.

[a] Grade based on American Society for Transplantation and Cellular Therapy (ASTCT) consensus grading (Lee et al 2019).

[b] Resume dose as recommended in Table 3.

[c] For daily monitoring, patients should remain within proximity of a healthcare facility.

Table 2 - Other Toxicity

Toxicity	Severity	Action
Neutropenia	ANC < 0.5 × 10^9/L	Hold* until ANC ≥ 0.5 × 10^9/L.
Febrile neutropenia	Any	Hold* until ANC ≥ 1 × 10^9/L and fever has resolved.
Thrombocytopenia	Platelets < 25 × 10^9/L	Hold* until platelets ≥ 25 × 10^9/L and no

	Platelets 25 - 50 × 10^9/L with bleeding	evidence of bleeding
Anemia	Hb < 80 g/L	Hold* until Hb ≥ 80 g/L.
Infection	Grade 3	Hold* until resolves to Grade ≤ 1 or baseline.
	Grade 4	Consider permanently discontinuing, OR Hold subsequent treatment doses (76 mg) until resolved to Grade ≤ 1
Hypogammaglobulinemia	IgG < 4 g/L	Consider IV or Subcut immunoglobulin treatment, according to local guidelines
Other non-hematologic toxicity	Grade 3	Hold* until resolves to Grade ≤ 1 or baseline.
	Grade 4	Consider permanently discontinuing, OR Hold subsequent treatment doses (76 mg) until resolved to Grade ≤ 1

*Resume dose as recommended in Table 3.

Table 3 - Restarting Doses After Dose Delay

Last Administered Dose	**Duration of Delay**	**Action for Next Dose**
Step-up Dose 1 (12mg)	≤ 14 days	Administer premedications. Resume at 32 mg and continue step-up dosing schedule, if tolerated.
	> 14 days	Administer premedications. Restart step-up dosing schedule at 12 mg.
Step-up Dose 2 (32mg)	≤ 14 days	Administer premedications. Resume at 76 mg.
	15 to 28 days	Administer premedications. Restart dosing at 32 mg and continue step-up dosing schedule, if tolerated.
	> 28 days	Administer premedications. Restart step-up dosing schedule at 12 mg.
Any Treatment Dose (76mg)	≤ 42 days	Resume at 76 mg.
	43 to 84 days	Administer premedications. Restart dosing at 32 mg and continue step-up dosing schedule, if tolerated.
	> 84 days	Administer premedications. Restart step-up dosing schedule at 12 mg.

Dosage with Hepatic Impairment:

Severity	Total Bilirubin		AST	Elranatamab Dose
Mild	≤ ULN	AND	> ULN	No dose adjustment
	> 1 to 1.5 x ULN	AND	any	No dose adjustment
Moderate or Severe	> 1.5 x ULN	AND	any	No data

Dosage with Renal Impairment:

Severity	Creatinine Clearance (mL/min)	Elranatamab Dose
Mild or Moderate	≥ 30	No dose adjustment
Severe	< 30	Limited data

Dosage in the elderly:

No dose adjustment is required. No overall differences in safety or effectiveness were observed between patients ≥ 65 and ≥ 75 years of age (62% and 19% of patients in clinical trials, respectively) compared to younger patients.

Dosage based on ethnicity:

No clinically relevant differences in PK were observed between white, Asian and Black groups.

Children:

The safety and efficacy of elranatamab in children have not been established.

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F - Administration Guidelines

- Elranatamab should be administered by **subcutaneous injection only.**
- Elranatamab vials do not require dilution. Refer to product monograph for details on preparation.
- Allow vials to come to room temperature before administration. Do not warm solution.
- Inject into abdomen (preferred); may be injected at other sites (e.g. thigh). Do not inject into areas where skin is red, bruised, scarred, tattooed or not intact.
- Monitor patients daily for 48 hours after administration of step-up doses for signs and symptoms of CRS or ICANS. Refer to the T-Cell Engaging Antibodies guideline for more information.
- Store unopened vials refrigerated (2°C to 8°C) and protect from light.

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G - Special Precautions

Contraindications:

- Patients who are hypersensitive to this drug or to any of its components.

Other Warnings/Precautions:

- Serious and life-threatening CRS and ICANS have occurred with elranatamab; ensure step-up schedule is followed and infusions are administered where there is immediate access to medications and equipment required to manage CRS and ICANS.
- Patients should avoid driving or operating heavy machinery for 48 hours following each dose in the step-up dosing schedule, or if any new neurological symptoms present due to the risk of a depressed level of consciousness from ICANS.
- Vaccination with live virus vaccines is not recommended for at least 4 weeks prior to, during and for at least 4 weeks after treatment with elranatamab. The risk of vaccine-associated infection may be increased or immune response to vaccines may be reduced.
- Patients with conditions such as active infection, stem cell transplant (within 12 weeks), history of Guillain-Barre syndrome, or sensory or motor neuropathy (Grade ≥ 2) were excluded from clinical trials; assess benefit-risk of elranatamab treatment in these patients.

Other Drug Properties:

- Carcinogenicity: Unknown

Pregnancy and Lactation:

- Genotoxicity: Unknown
- Fetotoxicity: Probable
    - Human IgG is known to cross the placenta after the first trimester of pregnancy and

elranatamab may cause fetal harm based on its mechanism of action.
    - Consider assessment of immunoglobulin levels in newborns of patients treated with elranatamab.

- Pregnancy:
  Elranatamab is not recommended for use in pregnancy. Adequate contraception should be used by patients and their partners during treatment, and for **5 months** after the last dose.

- Breastfeeding:
  Breastfeeding is not recommended during treatment and for **5 months** after the last dose.
- Excretion into breast milk: Probable
    - Human IgG is known to be excreted in breast milk. The effects on breastfed infants and milk production are unknown.

- Fertility effects: Unknown

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H - Interactions

Elranatamab causes a transient release of cytokines that may suppress CYP450 enzymes and therefore increase exposure to CYP substrates. The highest risk of drug interactions is expected during the step-up dosing schedule, after the first dose (12mg) and up to 14 days after the second dose (32mg), and up to 7 days after a CRS event. Monitor patients receiving concomitant CYP450 substrates, especially those that have a narrow therapeutic index, for increased substrate concentrations or toxicity.

AGENT	EFFECT	MECHANISM	MANAGEMENT
CYP 2C9 substrates (e.g. warfarin, meloxicam, fluvastatin)	↑ substrate concentration and/or toxicity	cytokines may suppress CYP450	Monitor and adjust dose of substrates with narrow therapeutic index (e.g. warfarin) if necessary
CYP3A4 substrates (e.g. cyclosporine, pimozide, tacrolimus, triazolo-benzodiazepines, dihydropyridine calcium-channel blockers, certain HMG-CoA reductase inhibitors)	↑ substrate concentration and/or toxicity	cytokines may suppress CYP450	Monitor and adjust dose of substrates with narrow therapeutic index (e.g. cyclosporine) if necessary

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I - Recommended Clinical Monitoring

Treating physicians may decide to monitor more or less frequently for individual patients but should always consider recommendations from the product monograph.

Refer to the hepatitis B virus screening and management guideline for monitoring during and after treatment.

Refer to the T-Cell Engaging Antibodies guideline for monitoring of CRS and ICANS during and after treatment.

Recommended Clinical Monitoring

Monitor Type	Monitor Frequency
CBC	Baseline and before each dose; more frequently if clinically indicated
Clinical toxicity assessment for CRS and ICANS	Monitor frequently during and after ramp-up doses*; At each visit and as clinically indicated after ramp-up phase.
Coagulation tests (e.g. aPTT, INR, PT, fibrinogen)	Baseline and as clinically indicated
CRP, ferritin	Baseline and as clinically indicated
LFTs, bilirubin	Baseline and as clinically indicated
Renal function tests	Baseline and as clinically indicated
Immunoglobulin levels	As clinically indicated
Clinical toxicity assessment for infection, bleeding, injection-site reactions, disseminated intravascular coagulation (DIC), rash, motor or sensory neuropath, pulmonary, cardiac and GI toxicity	At each visit

*Ramp-up doses are step-up dose 1, 2 and first treatment dose.

Grade toxicity using the current NCI-CTCAE (Common Terminology Criteria for Adverse Events) version

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K - References

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L - Disclaimer

Refer to the New Drug Funding Program or Ontario Public Drug Programs websites for the most up-to-date public funding information.

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