Drug Monograph

A - Drug Name

amivantamab

COMMON TRADE NAME(S): Rybrevant®

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B - Mechanism of Action and Pharmacokinetics

Amivantamab is a human, IgG1 bispecific antibody that targets both the epidermal growth factor receptor (EGFR) and mesenchymal-epithelial transition (MET). By binding to the extracellular domains of the EGFR and MET receptors, amivantamab disrupts signaling by blocking ligand binding and leads to degradation of EGFR and MET. The presence of EGFR and MET on the tumour cell surface also allows for targeted cell destruction by immune effector cells (e.g. natural killer cells, macrophages) via antibody-dependent cellular cytotoxicity and trogocytosis mechanisms.

Absorption	AUC increased proportionally over a dose range from 350 - 1750 mg.	
	Time to reach steady state	13 weeks (for both 3- and 2-week dosing regimens)
	T max	4.1 h (1050 mg dose) 5.7 h (1400 mg dose)
Distribution	Volume of distribution increased with increasing body weight; exposures were 30 - 40% lower in patients who weighed ≥ 80 kg compared to those < 80 kg, when receiving the same dose.	
	Cross blood brain barrier?	Unknown

Metabolism	Expected to be metabolized into small peptides by catabolic pathways.	
Elimination	Clearance increased with increasing body weight.	
	Half-life	13.7 days

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C - Indications and Status

Health Canada Approvals:

- Non-small cell lung cancer (NSCLC)

(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 table lists adverse effects that occurred in ≥ 5% of patients treated with amivantamab monotherapy in a Phase 1 trial of previously treated NSCLC patients with EGFR Exon 20 insertion mutation. It also includes severe or life-threatening adverse effects from other sources or post-marketing. Incidences denoted with "†" were reported from Phase 3 studies of amivantamab in combination with carboplatin and pemetrexed.

ORGAN SITE	SIDE EFFECT* (%)	ONSET**
Cardiovascular	Venous thromboembolism (8%) (3% severe) (including PE and DVT) †	D
Dermatological	Dry skin (16%) (including eczema)	E
	Paronychia (50%) (3% severe)	E
	Rash, pruritus (82%) (4% severe) (including acne, dermatitis, acneiform, hand-foot syndrome, maculopapular and papular)	E

	Toxic epidermal necrolysis (rare)	D
Gastrointestinal	Anorexia (15%)	E
	Constipation (23%)	E
	Diarrhea (15%) (3% severe)	E
	Mucositis (26%) (<1% severe)	E
	Nausea, vomiting (24%)	E
General	Edema (26%)	E
	Fatigue (33%)	E
Hepatobiliary	↓ albumin (33%)	E D
	↑ LFTs (17%)	E D
Hypersensitivity	Infusion related reaction (64%) (3% severe)	I
Infection	Infection (8%) (pneumonia)	E
Metabolic / Endocrine	Abnormal electrolyte(s) (21%) (↓ K, ↓ Ca, ↓ Mg, ↓ Na) †	E
Musculoskeletal	Musculoskeletal pain (45%) (mild to moderate)	E
Nervous System	Dizziness (10%)	E
	Headache (6%)	E
	Peripheral neuropathy (9%)	E
Ophthalmic	Eye disorders (13%)	E
Respiratory	Cough, dyspnea (19%)	E
	Interstitial lung disease (3%) (1% severe) †	D

* "*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)

The most common side effects for amivantamab include rash, pruritus, infusion related reaction, paronychia, musculoskeletal pain, ↓ albumin, fatigue, edema, mucositis, nausea, vomiting and constipation.

Infusion-related reactions (IRR) occurred commonly with amivantamab treatment, and included chills, nausea or vomiting, dyspnea, flushing, chest discomfort and hypotension. IRR onset was approximately 1 hour after start of infusion (range 0.1 to 18 hours). The majority of reactions occurred with the first infusion (65%) and were mild (Grade 1 or 2) in severity (97%). The incidence of IRR was significantly reduced with subsequent doses, with only 3% of patients experiencing an IRR with Day 2 infusion and <1% with subsequent infusions. In addition to administering

premedications, the initial amivantamab infusion should be split over 2 days and cycle 1 doses administered via peripheral line to reduce incidence of IRR.

Ocular toxicity, including keratitis (1%), occurred in patients treated with amivantamab both as monotherapy and in combination with carboplatin and pemetrexed or lazertinib. All events in the clinical trials were grade 1 or 2, except when in combination with lazertinib (<1% Grade 3 or 4). Reported toxicities included dry eye, blurred vision, pruritus, increased lacrimation, visual impairment, unusual eyelash growth and uveitis. Ophthalmologist consult is recommended for patients with ocular toxicities.

Skin toxicity, including nail reactions, has been reported in patients treated with amivantamab monotherapy or combination treatment. Rash, pruritus and dry skin, mostly grade 1 or 2, have occurred and sometimes lead to dose reduction or discontinuation. Rash generally developed within the first 4 weeks of treatment (Cycle 1), with a median onset of 14 days. Paronychia events were mostly Grade 1 or 2 (1% Grade 3). Sun exposure should be limited and patients should be advised to use sunscreen and protective clothing during and for the first 2 months after treatment. Topical steroids, antibiotics and/ or dermatologic consults may be required.

Interstitial lung disease (ILD) has been reported in 2 -3% of patients treated with amivantamab, with 1% of patients discontinuing treatment due to ILD/pneumonitis. Patients should be monitored for symptoms of ILD/pneumonitis (e.g., dyspnea, cough, fever) and managed appropriately, if confirmed.

Venous thromboembolic (VTE) events have occurred with amivantamab, mostly in combination with lazertinib, including fatal cases. In one clinical trial (MARIPOSA), VTEs occurred in 36% of patients that received this combination (10% Grade 3 and <1% Grade 4). During the course of the trial, 1% of patients experienced a VTE while receiving anticoagulants. The majority of events occurred during the first 4 months of treatment (median time to onset 84 days), so prophylactic anticoagulation is recommended for the first 4 months of treatment, when given in this combination.

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E - Dosing

Refer to protocol by which patient is being treated.

EGFR Exon 19 deletion, Exon 21 L858R substitution, or Exon 20 insertion mutation should be confirmed using a validated test, prior to starting treatment with amivantamab.

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

Premedications (prophylaxis for infusion reaction):

Cycle 1, Day -1 to 0:

- Dexamethasone 8 mg PO BID

Cycle 1, Day 1:

- Dexamethasone 8 mg PO, AND
- Dexamethasone 20 mg IV (or equivalent) 60 minutes pre-infusion
- Acetaminophen 650 to 1000 mg IV/ PO 30 minutes pre-infusion
- Diphenhydramine 25 to 50 mg IV/ PO (or equivalent) 30 minutes pre-infusion

Cycle 1, Day 2:

- Dexamethasone 10 mg IV (or equivalent) 45 to 60 minutes pre-infusion
- Acetaminophen 650 to 1000 mg IV/ PO 30 minutes pre-infusion
- Diphenhydramine 25 to 50 mg IV/ PO (or equivalent) 30 minutes pre-infusion

Subsequent Doses:

- Acetaminophen 650 to 1000 mg IV/ PO 30 minutes pre-infusion
- Diphenhydramine 25 to 50 mg IV/ PO (or equivalent) 30 minutes pre-infusion
- (Optional) Dexamethasone 10 mg IV (or equivalent) 45 to 60 minutes pre-infusion

Other Supportive Care:

- Sun exposure may exacerbate skin reactions; patients should limit sun exposure during and for 2 months after treatment, use protective clothing and broad spectrum sunscreen (UVA, UVB) with SPF ≥ 30.
- Alcohol- and fragrance-free emollient cream for skin and nail moisturization while on treatment and for 2 months after treatment ends.
- Consider antibiotic prophylaxis for rash prevention.
- Refer to EGFR inhibitor-induced skin toxicity management guidelines for more information (e.g. Alberta Health Services, ESMO, NCCN).

Adults:

In combination with carboplatin and pemetrexed*:

Each cycle is 3 weeks

< 80 kg at baseline:

- Cycle 1:
  - 350 mg IV Day 1
  - 1050 mg IV Day 2 (total 1400 mg split over 2 days)

    - 1400 mg IV Day 8 and 15
- Cycle 2: 1400 mg IV Day 1
- Cycle 3 and beyond: 1750 mg IV Day 1, Q3 weeks

≥ 80 kg at baseline:

- Cycle 1:
    - 350 mg Day 1
    - 1400 mg Day 2 (total 1750 mg split over 2 days)
    - 1750 mg IV Day 8 and 15
- Cycle 2: 1750 mg IV Day 1
- Cycle 3 and beyond: 2100 mg IV Day 1, Q3 weeks

Refer to related regimen monographs for more information, including carboplatin and pemetrexed dosing.

Other combination regimens and dosing schedules exist. Refer to the product monograph or related regimen monographs for details.

Monotherapy*:

< 80 kg at baseline:

- 1050 mg IV weekly x 4 weeks (split infusion on Day 1 & 2 of Week 1), then
- 1050 mg IV Q2 weeks, starting Week 5

≥ 80 kg at baseline:

- 1400 mg IV weekly x 4 weeks (split infusion on Day 1 & 2 of Week 1), then
- 1400 mg IV Q2 weeks, starting Week 5

*Note: dose adjustments for subsequent body weight changes are not required.

Dosage with Toxicity:

Table 1 - Dose Levels

Dose Level	Amivantamab Dose (mg)			
0	1050	1400	1750	2100
-1	700	1050	1400	1750
-2	350	700	1050	1400

-3	Discontinue

Table 2 - Toxicity Management

Toxicity	Severity/ Grade	Action
Skin and nail[a]	Grade 2	If no improvement after 2 weeks of supportive care (e.g. topical corticosteroids and topical and/or oral antibiotics), consider ↓ dose (Table 1).[b]
	Grade 3	Hold until ≤ Grade 2.[b] Resume at ↓ dose (Table 1). If no improvement in 2 weeks, permanently discontinue.
	Grade 4, severe bullous, blistering, or exfoliating skin conditions (including TEN)	Permanently discontinue.
ILD/ Pneumonitis	Any	Hold if suspected. Permanently discontinue if confirmed.
Other toxicity[c]	Grade 3	Hold until ≤ Grade 1 or baseline. • If recovery ≤ 1 week, resume at same dose. • If recovery > 1 week, resume at ↓ dose (Table 1). If no recovery after 4 weeks, permanently discontinue.
	Grade 4	Hold until ≤ Grade 1 or baseline. If recovery ≤ 4 weeks, resume at ↓ dose (Table 1). If no recovery after 4 weeks, permanently discontinue. If Grade 4 recurs, permanently discontinue.

[a]Patients should be referred to a dermatologist if rash is severe, presents with atypical appearance/distribution or lack of improvement within 2 weeks.

[b]Administer systemic antibiotics and oral steroids as clinically indicated. Consider dermatologic consult.

[c]Patients with worsening eye symptoms should be referred promptly to an ophthalmologist. Contact lenses should be discontinued.

Table 3 - Management of Infusion-related Reactions (IRR):

Also refer to the CCO guideline for detailed description of Management of Cancer Medication-Related Infusion Reactions.

Grade	Management	Re-challenge
1 or 2	• Stop the infusion. • Manage the symptoms (e.g., additional glucocorticoids, antihistamine, antipyretics and antiemetics). **Restart:** • Restart the infusion at 50% of the rate at which the IRR occurred. • If there are no additional symptoms, the rate may be increased (see Table 4 and 5).	• Administer pre-medications prior to next infusion.
3	• Stop the infusion. • Manage the symptoms (e.g., additional glucocorticoids, antihistamine, antipyretics and antiemetics). **Restart:** • Restart the infusion at 50% of the rate at which the IRR occurred. • If there are no additional symptoms, the rate may be increased (see Table 4 and 5). • If Grade 3 IRR **recurs,** stop infusion and do not restart (discontinue permanently).	• Administer pre-medications prior to next infusion. • If Grade 3 IRR **recurs**, discontinue permanently (do not re-challenge).
4	• Stop the infusion. • Aggressively manage symptoms.	• Discontinue permanently (do not re-challenge).

Dosage with Hepatic Impairment:

Total bilirubin		AST	Amivantamab Dose
≤ ULN	and	> ULN	No dose adjustment required
≤ 1.5 x ULN	and	Any	
>1.5 to 3 x ULN	and	Any	No data available
> 3 x ULN	and	Any	

Dosage with Renal Impairment:

Creatinine Clearance (mL/min)	Amivantamab Dose
≥ 29	No dose adjustment required
< 29	No data available

Dosage in the elderly:

No dose adjustment is required in patients aged 65 years or older. No clinically relevant differences in effectiveness were observed based on age, however there was a higher incidence of adverse effects in patients 65 years or older compared to younger patients, in clinical trials.

Dosage based on gender:

No clinically significant differences were observed based on gender, however, amivantamab clearance was higher in males compared to females and exposure of amivantamab was 35% higher in women than men at steady state according to PK analysis.

Children:

The safety and efficacy of amivantamab have not been established in pediatric patients.

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F - Administration Guidelines

- Dilute in 5% dextrose (D5W) or 0.9% sodium chloride (NS) to a final volume of 250 mL. Mix by gentle inversion; do not shake.
- Compatible with polyvinylchloride (PVC), polypropylene (PP), polyethylene (PE), or polyolefin blend (PP+PE) infusion bags, and polyurethane (PU), polybutadiene (PBD), PVC, PP, or PE infusion sets.
- Administer by IV infusion using sterile, non-pyrogenic, low protein-binding 0.2 micron polyethersulfone in-line filter, primed with diluent. See Tables 4 & 5 for infusion rates.
- Infuse via peripheral line for all Cycle 1 doses (Weeks 1 to 4) to minimize IRR (unless medically acceptable to use central line after Week 2). Administration via central line may be considered for subsequent doses.
- When chemotherapy is given on the same day administer pemetrexed first, carboplatin second, and amivantamab last.
- Do not co-administer other drugs through the same infusion line.
- Store unopened vials refrigerated (2°C to 8°C) and protect from light.

Also refer to the CCO guideline for detailed description of Management of Cancer Medication-Related Infusion Reactions.

Table 4 - Infusion rates for amivantamab in combination with chemotherapy

Week[a]	Cycle	Body weight	Dose	Total volume	Initial infusion rate	Subsequent infusion rate[b]
1	Cycle 1, Day 1 (split dose)	Any	350 mg	250 mL	50 mL/hr	75 mL/hr
1	Cycle 1, Day 2 (split dose)	< 80kg	1050 mg	250 mL	33 mL/hr	50 mL/hr
		≥ 80kg	1400 mg	250 mL	25 mL/hr	50 mL/hr
2	Cycle 1, Day 8	< 80kg	1400 mg	250 mL	65 mL/hr	N/A

		≥ 80kg	1750 mg	250 mL		
3	Cycle 1, Day 15	< 80kg	1400 mg	250 mL	85 mL/hr	N/A
		≥ 80kg	1750 mg	250 mL		
4	Cycle 2, Day 1	< 80kg	1400 mg	250 mL	125 mL/hr	N/A
		≥ 80kg	1750 mg	250 mL		
7 +	Cycle 3, Day 1 and subsequent doses	< 80kg	1750 mg	250 mL	125 mL/hr	N/A
		≥ 80kg	2100 mg	250 mL		

[a]Dosing is every 3 weeks starting Week 7.
[b]Increase initial infusion rate after 2 hours if no IRR.

Table 5 - Infusion rates for monotherapy

Week[a]	Cycle	Body weight	Dose	Total volume	Initial infusion rate	Subsequent infusion rate[b]
1	Cycle 1, Day 1 (split dose)	Any	350 mg	250 mL	50 mL/hr	75 mL/hr
1	Cycle 1, Day 2 (split dose)	< 80kg	700 mg	250 mL	50 mL/hr	75 mL/hr
		≥ 80kg	1050 mg	250 mL	35 mL/hr	50 mL/hr
2	Cycle 1, Day 8	< 80kg	1050 mg	250 mL	85 mL/hr	N/A
		≥ 80kg	1400 mg	250 mL	65 mL/hr	
3	Cycle 1, Day 15	< 80kg	1050 mg	250 mL	125 mL/hr	N/A
		≥ 80kg	1400 mg	250 mL	85 mL/hr	
4	Cycle 1, Day 22	< 80kg	1050 mg	250 mL	125 mL/hr	N/A
		≥ 80kg	1400 mg	250 mL		
5 +	Cycle 2, Day 1 and subsequent doses	< 80kg	1050 mg	250 mL	125 mL/hr	N/A
		≥ 80kg	1400 mg	250 mL		

[a]Dosing is every 2 weeks starting Week 5.
[b]Increase initial infusion rate after 2 hours if no IRR.

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G - Special Precautions

Contraindications:

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

Other Warnings/Precautions:

- Patients with active interstitial lung disease/ pneumonitis should not receive amivantamab.
- Caution in patients with a history of thrombotic events receiving amivantamab in combination with lazertinib. VTE occurred in trials with this combination, in some cases despite prophylactic anticoagulation.
- Blurred vision and visual impairment have been observed; caution is required when driving or operating machinery.

Other Drug Properties:

- Carcinogenicity: No information available
  - No formal studies, however antibodies are large proteins and cannot diffuse into cells and therefore cannot interact with DNA or chromosomal material.

Pregnancy and Lactation:

- Fetotoxicity: Documented in animals
  - EGFR and MET inhibitors have resulted in higher incidence of embryo-fetal development impairment, embryolethality and abortion in animal studies.
- Embryotoxicity: Documented in animals
- Pregnancy:
  - Amivantamab is not recommended for use in pregnancy. Adequate contraception should be used by patients and their partners during treatment, and for **3 months** after the last dose.
  - Patients should not donate sperm during treatment, and for **3 months** after the last dose.
- Breastfeeding:
  Breastfeeding is not recommended during treatment and for **3 months** after the last dose.
- Excretion into breast milk:
  - Human IgGs are known to be excreted into breast milk during the first few days after birth, with decreasing concentrations soon afterwards. Amivantamab is a human IgG1 bispecific antibody and therefore has potential to harm breast-fed infants.
- Fertility effects: No information available

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H - Interactions

No known drug interactions as no formal drug interaction studies have been conducted.

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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.

Recommended Clinical Monitoring

Monitor Type	Monitor Frequency
CBC	Baseline and before each cycle
Electrolytes, including magnesium, potassium and calcium	Baseline and before each cycle
Renal function tests	Baseline and before each cycle
Liver function tests	Baseline and before each cycle
Clinical toxicity assessment for infusion-related reactions, venous thromboembolic events, dermatologic (including nail), ocular, respiratory and GI toxicity	At each visit

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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