DRUG NAME: Amivantamab

SYNONYM(S):

COMMON TRADE NAME(S): RYBREVANT®

CLASSIFICATION: molecular targeted therapy

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

MECHANISM OF ACTION:

Amivantamab is a low-fucose human IgG1 antibody. It is a bispecific antibody that binds to the extracellular domains of epidermal growth factor receptor (EGFR) and mesenchymal-epithelial transition (MET) thus blocking ligand binding and disrupting EGFR and MET signalling functions. In exon 20 insertion mutation models, amivantamab disrupts EGFR and MET signalling through degradation of EGFR and MET. The presence of EGFR and MET on the tumour cell surface allows immune effector cells (e.g., natural killer cells, macrophages) to target the tumour cells for destruction through antibody-dependent cellular cytotoxicity and trogocytosis mechanisms.[1]

USES:

Primary uses:

Lung cancer, non-small cell[1]

*Health Canada approved indication

Other uses:

SPECIAL PRECAUTIONS:

Caution:

- to prevent infusion-related reactions, ***premedication*** with antihistamine and antipyretic are recommended prior to all infusions; glucocorticoids are required as premedication for week 1 (days 1 and 2) only, but may also be administered as necessary for subsequent infusions[1]
- amivantamab can cause ***embryo-fetal toxicity***; females of reproductive potential should use effective contraception during treatment with amivantamab and for 3 months following treatment[1]
- ***initial dosing is weight based*** (increased volume of distribution and clearance is observed with increases in body weight); systemic exposure is comparable between patients weighing <80 kg receiving a 1050 mg dose and patients weighing ≥80 kg receiving a 1400 mg dose[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. When placebo-controlled trials are available, adverse events will generally be included if the incidence is ≥5% higher in the treatment group.

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
blood and lymphatic system/ febrile neutropenia	lymphopenia(36%, severe 8%)
eye	keratitis (1%)

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ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
	ocular toxicity; see paragraph following **Side Effects** table
	uveitis (<1%)
gastrointestinal	*emetogenic potential:* low[2]
	abdominal pain (11%, severe 1%)
	constipation (23%)
	diarrhea (16%, severe 3%)
	nausea (36%)
	stomatitis (26%, severe 1%)
	vomiting (22%)
general disorders and administration site conditions	*extravasation hazard:* none[3]
	edema (27%, severe 1%)
	fatigue (33%, severe 2%)
	infusion-related reaction (64-66%, severe 3%; incidence distributed by infusion as follows: week 1, day 1 (65%); week 1, day 2 (3%); week 2 (<1%); cumulative incidence for remaining infusions (1%)); see paragraph following **Side Effects** table
	pyrexia (13%)
infections and infestations	***paronychia*** (50%, severe 3%)
	pneumonia (10%, severe 1%); fatal reactions reported
investigations	alkaline phosphatase increase (53%, severe 5%)
	ALT increase (38%, severe 2%)
	AST increase (33%)
	creatinine increase (46%)
	gamma-glutamyl transferase increase (27%, severe 4%)
metabolism and nutrition	albumin decrease (79%, severe 8%)
	appetite decrease (15%)
	glucose increase (56%, severe 4%)
	magnesium decrease (27%)
	phosphate decrease (33%, severe 8%)
	potassium decrease (26%, severe 6%)
	sodium decrease (27%, severe 4%)
musculoskeletal and connective tissue	***musculoskeletal pain*** (47%)
nervous system	dizziness (12%, severe 1%)
	headache (10%, severe 1%)
	peripheral neuropathy (13%)
respiratory, thoracic and	cough (25%)

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ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
mediastinal	dyspnea (37%, severe 2%)
	interstitial lung disease/pneumonitis (3%, severe 1%); permanently discontinue if diagnosis confirmed
	pulmonary embolism (≥2%)
skin and subcutaneous tissue	dry skin (14%)
	pruritus (18%)
	rash (including acne, dermatitis acneiform, eczema, maculopapular and papular rash, toxic epidermal necrolysis) (84%, severe 4%); see paragraph following **Side Effects** table
vascular	hemorrhage (19%)

Adapted from standard reference[1] unless specified otherwise.

Amivantamab can cause ***infusion-related reactions***. Signs and symptoms include dyspnea, flushing, fever, chills, nausea, chest discomfort, hypotension, and vomiting. The majority of reactions occur with the first infusion (week 1, day 1) and are grade 1 to 2 in severity. Median time to onset is 1 hour (range 0.1-18 hours) after start of infusion. Premedicate with antihistamines and antipyretics before each infusion. Glucocorticoid premedication is only required for infusions administered week 1, days 1 and 2, but may be needed for subsequent infusions as well if reactions occur. Infusion-related reactions are managed based on the severity of the reaction and may include infusion rate reduction or permanent discontinuation. For grade 1 to 3 reactions, interrupt the infusion until symptoms resolve and then resume the infusion at a rate that is 50% of the previous rate. If there are no further symptoms after 30 minutes, the infusion rate may be escalated to 100% of the previous rate. Permanently discontinue amivantamab for grade 4 or recurrent grade 3 reactions.[1]

Ocular toxicity can present as dry eye symptoms, conjunctival redness, blurred vision, visual impairment, ocular itching, keratitis, or uveitis. Reactions appear to be only grade 1 or 2 in severity. Ophthalmology consult is recommended for ocular toxicity. Contact lens wearers should stop wearing their lenses until symptoms are evaluated. Reactions are managed based on the severity of the reaction, by withholding amivantamab, dose reduction, or permanent discontinuation.[1]

Skin reactions have been reported, including rash, dermatitis acneiform, pruritus, dry skin, and toxic epidermal necrolysis. Median time to onset of rash is 14 days (range 1-276 days). Sun exposure should be limited during treatment with amivantamab and for 2 months following treatment. Use protective clothing and broad-spectrum UVA/UVB sunscreen if sun exposure cannot be avoided. Skin reactions are managed based on the severity of the reaction, by withholding amivantamab, dose reduction, or permanent discontinuation. Alcohol-free emollient creams may be used to manage dry skin. Start topical corticosteroids and oral/topical antibiotics as needed for grade 2 reactions. Add oral steroids for grade 3 reactions. Dermatology consult is recommended for patients presenting with severe rash or rash with an atypical appearance or distribution, or patients whose skin reaction fails to show improvement within 2 weeks. Permanently discontinue amivantamab for grade 4 reactions or severe bullous, blistering, or exfoliating conditions such as toxic epidermal necrolysis.[1]

INTERACTIONS: none known[1]

SUPPLY AND STORAGE:

Injection: Janssen Biotech, Inc. supplies amivantamab as 350 mg ready-to-use, single-use (preservative free) vials in a concentration of 50 mg/mL. Refrigerate. Protect from light.[1]

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

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:

Compatibility: consult detailed reference

PARENTERAL ADMINISTRATION:

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

<table>
<tr><td>Subcutaneous</td><td>no information found</td></tr>
<tr><td>Intramuscular</td><td>no information found</td></tr>
<tr><td>Direct intravenous</td><td>no information found</td></tr>
<tr><td>Intermittent infusion[1]</td><td>

infusion rates are based on doses established from baseline body weight
week 1 doses are administered as a split dose over days 1 and 2
given the high incidence of infusion-related reactions during initial treatment, suggest to administer week 1 doses via a peripheral line only
administer using 0.2 micron in-line filter

<table>
<tr><th colspan="4"><80 kg: 1050 mg dose</th></tr>
<tr><th>week</th><th>dose (per 250 mL bag)</th><th>initial rate</th><th>subsequent rate*</th></tr>
<tr><td>week 1, day 1 (split dose)</td><td>350 mg</td><td>50 mL/h</td><td>75 mL/h</td></tr>
<tr><td>week 1, day 2 (split dose)</td><td>700 mg</td><td>50 mL/h</td><td>75 mL/h</td></tr>
<tr><td>week 2</td><td>1050 mg</td><td colspan="2">85 mL/h</td></tr>
<tr><td>weeks 3, 4</td><td>1050 mg</td><td colspan="2">125 mL/h</td></tr>
<tr><td>subsequent weeks</td><td>1050 mg</td><td colspan="2">125 mL/h</td></tr>
</table>
* in the absence of infusion-related reactions, increase the initial infusion rate to the subsequent infusion rate after 2 h
<table>
<tr><th colspan="4">≥80 kg: 1400 mg dose</th></tr>
<tr><th>week</th><th>dose (per 250 mL bag)</th><th>initial rate</th><th>subsequent rate*</th></tr>
<tr><td>week 1, day 1 (split dose)</td><td>350 mg</td><td>50 mL/h</td><td>75 mL/h</td></tr>
<tr><td>week 1, day 2 (split dose)</td><td>1050 mg</td><td>35 mL/h</td><td>50 mL/h</td></tr>
<tr><td>week 2</td><td>1400 mg</td><td colspan="2">65 mL/h</td></tr>
<tr><td>week 3, 4</td><td>1400 mg</td><td colspan="2">85 mL/h</td></tr>
<tr><td>subsequent weeks</td><td>1400 mg</td><td colspan="2">125 mL/h</td></tr>
</table>
</td></tr>
</table>

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

	* in the absence of infusion-related reactions, increase the initial infusion rate to the subsequent infusion rate after 2 h
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:

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

Intravenous:

Cycle Length: ***4 weeks***[1]:

doses are based on baseline body weight (dose adjustments are not required for subsequent changes in body weight)

<80 kg:
Cycle 1, week 1: 1050 mg IV given as split dose on day 1 and 2
day 1: ***350 mg IV for one dose***
day 2: ***700 mg IV for one dose***
Cycle 1, weeks 2 to 4: ***1050 mg*** (range 350-1050 mg) ***IV*** for one dose ***on day 1***
Cycle 2 onward (starting week 5): ***1050 mg*** (range 350-1050 mg) ***IV*** for one dose ***on days 1 and 15***

≥80 kg:
Cycle 2, week 1: 1400 mg IV given as split dose on day 1 and 2
day 1: ***350 mg IV for one dose***
day 2: ***1050 mg IV for one dose***
Cycle 1, weeks 2 to 4: ***1400 mg*** (range 700-1400 mg) ***IV*** for one dose ***on day 1***
Cycle 2 onward (starting week 5): ***1400 mg*** (range 700-1400 mg) ***IV*** for one dose ***on days 1 and 15***

REFERENCES:

1. Janssen Biotech Inc, ed. *RYBREVANT® full prescribing information.* Horsham, PA, USA: ; May 2021.
2. BC Cancer. *(SCNAUSEA) guidelines for prevention and treatment of chemotherapy-induced nausea and vomiting in adults.* Vancouver, British Columbia: BC Cancer; 1 July 2020.
3. BC Cancer Provincial Systemic Therapy Program. *Provincial systemic therapy program policy III-20: Prevention and management of extravasation of chemotherapy.* Vancouver, British Columbia: BC Cancer; 1 March 2021.

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