DRUG NAME: Amivantamab

SYNONYM(S): JNJ-61186372[1], Amivantamab-vmjw[1]

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 bispecific IgG1 antibody that binds to the extracellular domains of epidermal growth factor receptor (EGFR) and mesenchymal-epithelial transition (MET) receptor. Amivantamab disrupts EGFR and MET signaling functions by blocking ligand binding and degrading 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.[2]

PHARMACOKINETICS:

Distribution	volume of distribution increases with increasing body weight	
	cross blood brain barrier?	no[3]
	volume of distribution	5.3 L
	plasma protein binding	no information found
Metabolism	has not been studied[2]; expected to be catabolized into amino acids[4]	
	active metabolite(s)	no information found
	inactive metabolite(s)	no information found
Excretion	clearance increases with increasing body weight	
	urine	not expected due to the large molecular size[5]
	feces	has not been studied[2]; however, minimal excretion is expected for an IgG antibody[4]
	terminal half life	13.7 days
	clearance	0.27 L/day
Sex	no clinically significant difference	
Elderly	no clinically significant difference	

Adapted from standard reference[2] unless specified otherwise.

USES:

Primary uses:

Lung cancer, non-small cell*

Other uses:

*Health Canada approved indication

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Revised:

SPECIAL PRECAUTIONS:

Caution:
- ***premedication*** with antihistamine and antipyretic is recommended prior to all infusions to prevent infusion-related reactions
- ***glucocorticoids*** are required as premedication for cycle 1 (days 1 and 2 only), but may also be needed for subsequent infusions[2]

Carcinogenicity: no information found

Mutagenicity: no information found

Fertility: In animal studies, there were no notable effects reported in male and female reproductive organs.[6]

Pregnancy: Human IgG is known to cross the placental barrier; therefore, as an IgG1 antibody, amivantamab is expected to be transmitted from mother to fetus. In animal studies, absence of EGFR or MET signaling resulted in embryolethality, malformations, and abortions. Inhibition of EGFR resulted in impaired embryo-fetal development affecting placental, lung, cardiac, skin, and neural development. Based on the mechanism of action and findings in animals, amivantamab may cause fetal harm and developmental anomalies in humans. Consider pregnancy tests prior to starting treatment. Contraception is recommended during treatment and for 3 months after the last dose of amivantamab for female patients of reproductive potential and male patients with female partners of childbearing potential. Semen should not be donated or stored during treatment and for 3 months after the last dose of amivantamab. [2,6]

Breastfeeding is not recommended due to the potential secretion into breast milk. Amivantamab is an IgG1 antibody and human IgG1 is known to be excreted in breast milk. Women should not breastfeed during treatment and for 3 months after the last dose of amivantamab.[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.[7,8]

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
blood and lymphatic system/ febrile neutropenia	anemia (18%, severe 2%)
	lymphopenia (36%, severe 8%)
	neutropenia (18%, severe 3%)
	thrombocytopenia (17%, severe 1%)
eye	keratitis (1%)
	ocular toxicity (9%); see paragraph following **Side Effects** table
	uveitis (<1%)
gastrointestinal	*emetogenic potential:* low[9]
	abdominal pain (11%, severe 1%)
	constipation (23%)

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ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
	diarrhea (16%, severe 3%)
	nausea (36%)
	stomatitis (26%, severe 1%)
	vomiting (13-22%)[2,10]
general disorders and administration site conditions	*extravasation hazard:* none[11]
	edema (27%, severe 1%)
	fatigue (33%, severe 2%)
	infusion-related reactions (64-66%, severe 3%); see paragraph following **Side Effects** table
	pyrexia (13%)
infections and infestations	***paronychia*** (50%, severe 3%)
	pneumonia (8-10%, severe <1%)
investigations	alkaline phosphatase increase (9-53%, severe 5%)
	ALT increase (17-38%, severe 2%)
	AST increase (13-33%)
	creatinine increase (46%)
	gamma-glutamyl transferase increase (6-27%, severe 4%)
metabolism and nutrition	appetite decrease (15%)
	hypoalbuminemia (33-79%, severe 8%)
	hypoglycemia (56%, severe 4%)
	hypokalemia (26%, severe 6%)
	hypomagnesemia (27%)
	hyponatremia (27%, severe 4%)
	hypophosphatemia (33%, severe 8%)
musculoskeletal and connective tissue	musculoskeletal pain (47%)
nervous system	dizziness (12%, severe 1%)
	headache (10%, severe 1%)
	peripheral neuropathy (13%)
respiratory, thoracic and mediastinal	cough (13-25%)
	dyspnea (20-37%, severe 2%)
	interstitial lung disease/pneumonitis (3%, severe 1%)
skin and subcutaneous tissue	alopecia (<1%); erosive pustular dermatosis of scalp may lead to scarring alopecia[12,13]
	dry skin (14%)
	nail toxicity, onychoclasis, and onycholysis (8-9%); usually grade 1 or 2

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ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
	pruritus (18%)
	rash (84%, severe 4%); see paragraph following **Side Effects** table
	skin fissures (9%)
vascular	hemorrhage (19%)
	venous thromboembolism (3%); see paragraph following **Side Effects** table

Adapted from standard reference [2,10] unless specified otherwise.

Infusion-related reactions (IRRs) are reported with amivantamab. Signs and symptoms include dyspnea, flushing, fever, chills, nausea, chest discomfort, hypotension, and vomiting. IRRs are common with the first infusion (66%) and are grade 1 to 2 in severity in most cases. The incidence of IRR decreases with subsequent doses (i.e., 3% at the second infusion [cycle 1, day 2] and less than 1% by day 8). 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 on cycle 1, days 1 and 2, but may also be needed for subsequent infusions if reactions occur. Infusion-related reactions are managed based on the severity of the reaction and may include infusion rate reduction or permanent discontinuation.[2] For management of infusion-related reactions, see BC Cancer Protocol SCDRUGRX ***Management of Infusion-Related Reactions to Systemic Therapy Agents***.

Ocular toxicity may present as dry eye symptoms, blurred vision, visual impairment, ocular itching, keratitis, or uveitis. Increased lacrimation, aberrant eyelash growth, and blepharitis have also been reported. Although severe cases of ocular toxicity are rare, ophthalmology referral is recommended for patients with worsening eye symptoms. Patients who wear contact lenses 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.[2,10]

Skin reactions and ***nail toxicity*** have been reported, including rash, dermatitis acneiform, pruritus, dry skin, toxic epidermal necrolysis, and paronychia. Median time to onset of rash is 14 days (range 1-276 days). Prophylactic measures such as use of topical antibiotics (clindamycin scalp lotion) or oral antibiotics (doxycycline or minocycline) have been used to reduce the severity of skin reactions.[2,14] Topical antiseptic solutions such as chlorhexidine 4% may be used to wash hands and feet during treatment. Application of moisturizers that provide long-lasting skin hydration (e.g., ceramide based) is recommended during treatment. Avoid drying agents like alcohol-based emollients. 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. Topical/oral steroids or topical/oral antibiotics may be required to treat infections. Dermatology consult is recommended for patients presenting with severe rash or rash with an atypical appearance or distribution, and patients whose skin reaction fails to show improvement within 2 weeks. Permanently discontinue amivantamab for severe bullous, blistering, or exfoliating conditions such as toxic epidermal necrolysis.[2]

Venous thromboembolism, including deep vein thrombosis and pulmonary embolism, has been reported. When amivantamab is administered in combination with an EGFR-targeted tyrosine kinase inhibitor, the incidence of venous thromboembolism is significantly increased compared to amivantamab monotherapy.[15] The exact mechanism is not well understood; however, it is hypothesized that rapid tumour cell death induced by combination therapies is thought to contribute to a transient prothrombotic state.[1] Anticoagulant prophylaxis may be required when amivantamab is administered in combination with an EGFR-targeted tyrosine kinase inhibitor.[6,16]

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INTERACTIONS: none known[2]

SUPPLY AND STORAGE:

Injection: Janssen 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.[2]

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.

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 rowspan="3">Intermittent infusion[2,10]</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
• administer using 0.2 micron polyethersulfone in-line filter</td></tr>
<tr><td>Refer to protocol by which patient is being treated.
In the absence of a protocol, the following infusion rates may be used for amivantamab monotherapy:
<table>
<tr><th colspan="4"><80 kg: 1050 mg dose</th></tr>
<tr><th>Cycle/day</th><th>dose (per 250 mL bag)</th><th>initial rate</th><th>subsequent rate*</th></tr>
<tr><td>Cycle 1, day 1 (split dose)</td><td>350 mg</td><td>50 mL/h</td><td>75 mL/h</td></tr>
<tr><td>Cycle 1, day 2 (split dose)</td><td>700 mg</td><td>50 mL/h</td><td>75 mL/h</td></tr>
<tr><td>Cycle 1, day 8</td><td>1050 mg</td><td colspan="2">85 mL/h</td></tr>
<tr><td>Cycle 1, days 15 and 22</td><td>1050 mg</td><td colspan="2">125 mL/h</td></tr>
<tr><td>subsequent cycles</td><td>1050 mg</td><td colspan="2">125 mL/h</td></tr>
</table></td></tr>
<tr><td>*in the absence of infusion-related reactions, increase the initial infusion rate to the subsequent infusion rate after 2 h</td></tr>
</table>

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

	≥80 kg: 1400 mg dose Cycle/day | dose (per 250 mL bag) | initial rate | subsequent rate* Cycle 1, day 1 (split dose) | 350 mg | 50 mL/h | 75 mL/h Cycle 1, day 2 (split dose) | 1050 mg | 35 mL/h | 50 mL/h Cycle 1, day 8 | 1400 mg | 65 mL/h Cycle 1, day 15 | 1400 mg | 85 mL/h Cycle 1, day 22 | 1400 mg | 125 mL/h subsequent cycles | 1400 mg | 125 mL/h * 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.

Adults:

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

Intravenous:

Cycle Length: ***3 weeks***[2,17-20]:

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

<80 kg:
Cycle 1:
day 1: ***350 mg IV for one dose***
day 2: ***1050 mg IV for one dose***
days 8 and 15: ***1400 mg*** (range 700-1400 mg) ***IV for one dose***
Cycle 2: ***1400 mg*** (range 700-1400 mg) ***IV for one dose on day 1***
Cycle 3 and onward: ***1750 mg*** (range 1050-1750 mg) ***IV for one dose on day 1***

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

Cycle Length:

≥80 kg:
Cycle 1:
day 1: ***350 mg IV for one dose***
day 2: ***1400 mg IV for one dose***
days 8 and 15: ***1750 mg*** (range 1050-1750 mg) ***IV for one dose***
Cycle 2: ***1750 mg*** (range 1050-1750 mg) ***IV for one dose on day 1***
Cycle 3 and onward: ***2100 mg*** (range 1400-2100 mg) ***IV for one dose on day 1***

4 weeks[2,21,22]: doses are based on baseline body weight (dose adjustments are not required for subsequent changes in body weight)

<80 kg:
Cycle 1:
day 1: 350 mg IV for one dose
day 2: 700 mg IV for one dose
days 8, 15, and 22**:** 1050 mg (range 350-1050 mg) IV for one dose
Cycle 2 and onward: 1050 mg (range 350-1050 mg) IV for one dose on days 1 and 15

≥80 kg:
Cycle 1:
day 1: 350 mg IV for one dose
day 2: 1050 mg IV for one dose
days 8,15, and 22**:** 1400 mg (range 700-1400 mg) IV for one dose
Cycle 2 and onward: 1400 mg (range 700-1400 mg) IV for one dose on days 1 and 15

Concurrent radiation: no information found

Dosage in renal failure: CrCl ≥30 mL/min: no adjustment required[2]
CrCl <30 mL/min: no information found

calculated creatinine clearance = $\frac{N^* \times (140 - Age) \times \text{weight in kg}}{\text{serum creatinine in micromol/L}}$

Dosage in hepatic failure: bilirubin ≤1.5 x ULN: no adjustment required[2]
bilirubin >1.5 x ULN: no information found

Dosage in dialysis: no information found

Children: safety and efficacy have not been established[2]

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