

DRUG NAME: Rituximab

SYNONYM(S): anti-CD20 antibody, IDEC-C2B8¹

COMMON TRADE NAME(S): RITUXAN®, RITUXAN® SC, RIXIMYO® (biosimilar), RUXIENCE® (biosimilar), TRUXIMO® (biosimilar)

CLASSIFICATION: molecular targeted therapy

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

MECHANISM OF ACTION:

Rituximab is a chimeric murine/human monoclonal antibody based on human immunoglobulin G (IgG). Rituximab binds to the antigen CD20 on normal and malignant B lymphocytes in the blood, bone marrow, thymus, spleen, lymph nodes, and elsewhere in the body, then regulates the activation process for cell cycle initiation and differentiation.²⁻⁵ Rituximab activates the complement cascade (complement-mediated cytotoxicity) and immune effector cells (antibody-dependent cell-mediated cytotoxicity), causing depletion of circulating and tissue-based B cells.²⁻⁴ Antibody-dependent cell-mediated cytotoxicity recruits other immune mediators to cause cell destruction and apoptosis. Rituximab sensitizes malignant B cells to the effects of chemotherapy synergistically enhancing cell lysis.^{4,6,7}

PHARMACOKINETICS:

Absorption	steady state concentrations reached after 6-8 weekly infusions ⁸	
Distribution	CD-20 binding capacity of rituximab remains stable over 96 h ¹ ; detectable in serum 3-6 months after treatment completion ²	
	cross blood brain barrier? ⁸	detected in CSF
	volume of distribution	4.5 L (range 2-7 L)
	plasma protein binding	little to none
Metabolism	degraded into amino acids [similar to natural immunoglobulins (antibodies)] ⁵	
	active metabolite(s)	no information found
	inactive metabolite(s)	no information found
Excretion	may undergo phagocytosis and catabolism in the reticuloendothelial system ⁹	
	urine	no information found
	feces	no information found
	terminal half life ^{2,8,10}	20-32 days
	clearance ^{2,8,10}	13-18 mL/h
Sex	no differences observed	
Elderly	no differences observed	
Children	no differences observed	

Adapted from standard reference² unless specified otherwise.

USES:

Primary uses:

- *Lymphoma, non-Hodgkin
- *Leukemia, chronic lymphocytic

*Health Canada approved indication

Other uses:

- Lymphoma, Hodgkin⁹
- Lymphoma, intraocular¹¹

SPECIAL PRECAUTIONS:

Contraindications:

- history of hypersensitivity reaction to rituximab, mouse proteins, or Chinese Hamster Ovary cell proteins² or hyaluronidase (for SC formulation only)¹²
- history of progressive multifocal leukoencephalopathy²

Caution:

- rituximab formulations for IV and SC administration are **NOT interchangeable**; formulations differ in concentration and dosing¹²
- RITUXAN® SC 1400 mg and 1600 mg vials are **NOT interchangeable**; although given by the same route, the formulations are **single-dose** vials and are intended for **different indications**¹²
- **reactivation of Hepatitis B (HBV)** has been reported with rituximab¹²; for recommended HBV screening and prophylaxis, see BC Cancer Protocol SCHBV [Hepatitis B Virus Reactivation Prophylaxis](#)¹³
- **reactivation of tuberculosis** has been reported; consider screening for TB antibody titres prior to rituximab treatment²
- **infusion reactions** commonly occur with the first infusion; routine premedication is required
- **antihypertensive medications** may enhance the hypotensive effect of rituximab; consider withholding anti-hypertensive medications 12 hours prior to and during rituximab infusion²
- **tumour lysis syndrome** may occur in patients with an initial high tumour burden (e.g., CLL, mantle cell lymphoma); treat with extreme caution, at a reduced infusion rate, and closely monitor for signs of tumour lysis syndrome during the first infusion²
- **vaccinations** should be completed 4 weeks prior to the first treatment with rituximab or wait at least 6 months after the last dose of chemotherapy^{2,5}

Special populations: Patients over 65 years of age are at greater risk of adverse cardiac events and serious pulmonary infections.²

Carcinogenicity: no information found

Mutagenicity: no information found

Fertility: no information found

Pregnancy: There are no controlled studies in pregnant women. However, IgG immunoglobulins are known to pass the placental barrier. Transient B-cell depletion and lymphocytopenia has also been reported in some infants born to mothers exposed to rituximab during pregnancy. Developmental toxicity studies in animals revealed no evidence of embryotoxicity *in utero*; but, newborn offspring of treated maternal subjects had depleted B-cell populations during the postnatal phase. Contraception is recommended for women of reproductive potential during treatment and up to 12 months after treatment.¹⁴

Breastfeeding is not recommended due to the potential secretion into breast milk.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, and/or determined to be clinically important.^{5,15}

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in <i>bold, italics</i>	
blood and lymphatic system/ febrile neutropenia	anemia (4%, severe 1%); aplastic and hemolytic anemias have been reported
	leukopenia (12-32%, severe 3-5%)
	<i>neutropenia</i> (11-25%, severe 4-11%)
	thrombocytopenia (10%, severe <1%)
cardiac	angina (1-2%)
eye	excessive lacrimation (3%)
gastrointestinal	<i>emetogenic potential: rare</i> ¹⁶
	abdominal pain (7%, severe <1%)
	anorexia (3%)
	bowel obstruction (1%)
	bowel perforation (<1%) ^{5,15}
	diarrhea (4%)
	<i>nausea</i> (17%, severe <1%)
	vomiting (7%, severe <1%)
general disorders and administration site conditions	<i>extravasation hazard: none</i> ¹⁷
	asthenia (18%, severe <1%)
	<i>chills</i> (32%, severe 2%)
	<i>fever</i> (48%, severe <1%)
	<i>infusion reactions</i> (14-77%, severe 0-7%); decreasing incidence with each subsequent infusion; see paragraph following Side Effects table
	injection site reactions (20%); see paragraph following Side Effects table
	malaise (2%)
immune system	<i>hypersensitivity</i> (1-10%); typically occur after second or subsequent infusion
infections and infestations	<i>hepatitis B reactivation</i> (2%); see paragraph following Side Effects table
	herpes zoster (2%, severe <1%)
	<i>infection</i> (30-47%, severe 4-11%); see paragraph following Side Effects table
	sinusitis (2%)
	tuberculosis reactivation (<1%)
investigations	alanine transferase, increased (13%)
	immune gamma globulin, decreased (>10%)

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in bold, italics	
	lactate dehydrogenase, increased (2%)
metabolism and nutrition	hyperglycemia (5%, severe <1%)
	hypocalcemia (2%)
	tumour lysis syndrome ; see paragraph following Side Effects table
musculoskeletal and connective tissue	arthralgia (6%, severe <1%)
	back pain (5%, <1%)
	myalgia (8%)
nervous system	headache (13%, severe <1%)
	progressive multifocal leukoencephalopathy ; see paragraph following Side Effects table
	reversible posterior leukoencephalopathy syndrome ; see paragraph following Side Effects table
psychiatric	insomnia (2%)
respiratory, thoracic and mediastinal	bronchospasm (8%, severe <1%)
	chest pain, non-cardiac (1-10%)
	cough (5%, severe <1%)
	dyspnea (2%, severe <1%)
	pneumonia (2%, severe <1%)
	rhinitis (7%, severe <1%)
	sore throat (8%)
skin and subcutaneous tissue	alopecia (1-10%)
	angioedema (11%, severe <1%)
	pruritis (12%, severe <1%)
	rash (11%, severe <1%)
	mucocutaneous reactions ; see paragraph following Side Effects table
	urticaria (7%, severe <1%)
vascular	flushing (4%)
	hypotension (10%, severe <1%)
	hypertension (5%, severe <1%)
	peripheral edema (5%)

Adapted from standard reference² unless specified otherwise.

Infusion reactions are predictable, occurring in 77% of patients with the first infusion, 30% with the 4th infusion, and 14% with the 8th infusion.² Reactions occur within the first 30 to 120 minutes of the first exposure in over 50% of patients. The mechanism is thought to be an antibody-antigen interaction between rituximab (the antibody) and CD20 (the antigen) on lymphocytes, resulting in cytokine release from cells.¹⁸ Symptoms include hypotension, fever, chills, rigors, urticaria, bronchospasm, sensation of tongue or throat swelling, nausea, fatigue, headache, pruritis,

dyspnea, rhinitis, vomiting, and flushing. Symptoms may progress in severity and include acute respiratory distress syndrome and angioedema. Severe, potentially fatal, infusion-related reactions (0.04-0.07%) may occur within 24 hours of the first infusion, and may be clinically indistinguishable from anaphylactic reactions.²

The high incidence of **infusion reactions** has led to the general practice of **premedicating** with an antihistamine and antipyretic prior to each infusion. Start the first infusion at 50 mg/h and increase the rate by 50 mg/h every 30 minutes to a maximum of 400 mg/h.² For patients receiving corticosteroid-containing chemotherapy regimens, further cycles of rituximab may be given over a total of 90 minutes (20% of the dose in the first 30 minutes and the remaining 80% over 60 minutes) in the absence of an infusion reaction. However, a faster infusion rate is not recommended for patients with clinically significant cardiovascular disease or high circulating lymphocyte counts.¹⁹ For patients receiving rituximab monotherapy outside of maintenance protocols, further cycles can be started at 100 mg/h and increased by 100 mg/h every 30 minutes to a maximum of 400 mg/h.^{18,20} For management of infusion-related reactions, see BC Cancer Protocol SCDRUGRX [Management of Infusion-Related Reactions to Systemic Therapy Agents](#).

Cytokine release syndrome may be clinically indistinguishable from anaphylactic or severe infusion-related reactions. Patients with a high tumour burden, at risk of cytokine release syndrome, should be cautiously treated during the 1st infusion and may require a reduced infusion rate or split dosing over 2 days. In most patients, symptoms resolve completely following interruption of treatment. Once all symptoms have resolved, most patients will tolerate resumption of treatment with a 50% reduction in rituximab rate and additional premedication.²

Tumour Lysis Syndrome (TLS) is an oncologic emergency caused by massive tumour cell lysis which releases large amounts of potassium, phosphate, and nucleic acids into the circulation within 12 to 24 hours after the first infusion of rituximab. Metabolic consequences of TLS include: hyperkalemia, hyperphosphatemia, secondary hypocalcemia, hyperuricemia, acute renal failure, elevated lactate dehydrogenase, and high fevers.^{2,10} Symptoms reflective of hyperkalemia, hyperphosphatemia, and hypocalcemia include: nausea, vomiting, diarrhea, anorexia, lethargy, hematuria, heart failure, cardiac dysrhythmias, seizures, muscle cramps, tetany, syncope, and possibly death. Risk factors for developing TLS are cancers with a high tumour burden (e.g., CLL, mantle cell lymphoma), high tumour cell proliferation rate, chemo-sensitive disease, and impaired renal function or dehydration in the patient. Prophylaxis with adequate hydration and allopurinol starting 48 hours prior to start of therapy is recommended to reduce the risk of TLS. Aggressive treatment of TLS involves correcting electrolyte abnormalities, administering supportive care, monitoring renal function, and the use of dialysis as indicated.^{10,18,21}

Hepatitis B virus (HBV) reactivation is characterized by an increase in serum HBV DNA levels, followed by an increase in alanine aminotransferase (ALT) levels, with or without symptoms of hepatitis. Most patients are asymptomatic and flares are detected through regular monitoring of ALT and hepatitis symptoms. Non-Hodgkin's lymphoma may be an independent risk factor for HBV reactivation.^{2,22} Symptoms of hepatitis include fatigue, anorexia, or nausea, with severe symptoms progressing to jaundice, hepatic failure, and death.²² Median time to diagnosis of hepatitis is approximately 4 months from initiation of rituximab to approximately 1 month after the last dose in those patients who have had hepatitis B previously.² Patients who test positive for HBsAg have detectable HBV DNA in their serum and should be started on antiviral therapy to decrease the incidence and morbidity of HBV reactivation. Patients who have resolved HBV will test negative for HBsAg and positive for anti-HBc, and are at risk of reactivation regardless of anti-HBs status.²³ Carriers of hepatitis B, or those with a history of hepatitis B should be monitored for signs of hepatitis during and up to 1 year following rituximab treatment. Patients who develop reactivation of viral hepatitis B should discontinue rituximab and initiate antiviral treatment. There is insufficient data on the safety of resuming rituximab in patients who develop hepatitis subsequent to HBV reactivation.² For recommended HBV screening and prophylaxis, see BC Cancer Protocol SCHBV [Hepatitis B Virus Reactivation Prophylaxis](#).¹³

Infections are predominately mild to moderate in severity and consist mainly of upper respiratory tract and urinary tract infections; however, serious viral infections have also been reported, most commonly in patients who were profoundly immunosuppressed, or who were receiving rituximab with chemotherapy or after hematopoietic stem cell transplant. Reported infections include new, exacerbated, or reactivated: John Cunningham (JC) virus, cytomegalovirus, herpes simplex virus, parvovirus B19, varicella zoster virus, West Nile virus, tuberculosis, pneumocystis jiroveci pneumonia, and hepatitis B and C. In some cases, viral infections occurred up to 1 year following the completion of rituximab, and resulted in death. Reactivation of tuberculosis has been reported in

patients receiving rituximab in combination with chemotherapy. Patients who develop serious infections should discontinue rituximab and initiate appropriate medical treatment.²

Injection site reactions and local cutaneous reactions are common following **subcutaneous injection** of rituximab. Symptoms may include pain, swelling, induration, hemorrhage, erythema, pruritus, and rash at the injection site. Some reactions occur more than 24 hours after SC administration. Reactions are the most common during the first cycle of subcutaneous administration, and occur with decreasing incidence with subsequent injections. The majority of reactions are mild or moderate in severity and resolve within 1-2 days without any specific treatment. Other medications which require subcutaneous administration should not be given at the same injection site as rituximab SC due to the duration of the effect of hyaluronidase present in the rituximab SC formulation.²⁴⁻²⁶

Severe **mucoctaneous reactions**, some fatal, have been reported, including Stevens-Johnson syndrome, lichenoid dermatitis, vesiculobullous dermatitis, toxic epidermal necrolysis, and paraneoplastic pemphigus. Onset of reaction varies from days to months after rituximab therapy.²

Progressive Multifocal Leukoencephalopathy (PML) is a rare (less than 0.1% of hematologic malignancies) brain infection caused by reactivation of JC virus.^{2,27} The virus occurs almost exclusively in immunocompromised patients and presents with progressive weakness on one side of the body, clumsiness of limbs, disturbances of vision, and changes in thinking, memory, and orientation leading to confusion and personality changes. The disease course is usually progressive over days to weeks and can result in disability or death. Diagnosis is confirmed with cerebral spinal fluid analysis for JC viral DNA. Risk factors for developing PML in patients treated with rituximab are unknown. There are no known interventions to prevent or treat PML if it occurs. Further treatment with rituximab should be withheld at the first sign of any new neurological signs or symptoms resembling PML. Consider consultation with a neurologist for management.^{2,27,28}

Reversible posterior leukoencephalopathy syndrome (RPLS; also known as PRES) has been reported with rituximab. Symptoms include visual disturbances, headache, seizures, and altered mental status, with or without hypertension.² Causes of RPLS may include hypertension, eclampsia, renal failure, and cytotoxic or immunosuppressive medications.²⁹ Management is usually supportive, with control of hypertension, electrolyte replacement, seizure management, and discontinuation of rituximab. Full recovery is generally achieved within 2 weeks; however, permanent complications and fatal cases have been reported.³⁰

Vaccinations should be completed 4 weeks prior to the first treatment with rituximab or wait at least 6 months after the last dose of chemotherapy.^{2,5} Non-live vaccines may be given during rituximab treatment; however, patients may experience reduced response rates.² The safety of live vaccines has not been studied during cancer treatment and their use is not recommended unless otherwise advised by the oncologist.² Influenza A vaccinations are recommended for lymphoid cancer patients annually each autumn. Rituximab may blunt or even ablate the antibody response to influenza A vaccination; however, some benefit may occur.⁵

INTERACTIONS:

AGENT	EFFECT	MECHANISM	MANAGEMENT
cyclophosphamide ^{2,10}	no effect on rituximab or cyclophosphamide pharmacokinetics		
fludarabine ^{2,10}	no effect on rituximab or fludarabine pharmacokinetics		
methotrexate ^{2,10}	no effect on rituximab pharmacokinetics		

SUPPLY AND STORAGE:

Biosimilar formulations of rituximab are available.

Injection:

Hoffmann-La Roche Ltd. supplies rituximab (RITUXAN®) as 100 mg and 500 mg single-use (preservative free) vials in a concentration of 10 mg/mL. Refrigerate. Protect from light.²

Hoffmann-La Roche Ltd. supplies rituximab SC (RITUXAN® SC) for subcutaneous use as 1400 mg and 1600 mg single-dose (preservative free) vials in a concentration of 120 mg/mL. RITUXAN® SC contains recombinant human hyaluronidase (rHuPH20). Refrigerate. Protect from light.¹²

Celltrion Healthcare Co. Ltd. (distributed by Teva Canada Limited) supplies rituximab (TRUXIMA®) as 100 mg and 500 mg single-use (preservative free) vials in a concentration of 10 mg/mL. Refrigerate. Protect from light.³¹

Pfizer Canada ULC supplies rituximab (RUXIENCE®) as 100 mg and 500 mg single-use (preservative free) vials in a concentration of 10 mg/mL. Refrigerate. Protect from light.³²

Sandoz Canada Inc supplies rituximab (RIXIMYO®) as 100 mg and 500 mg single-use (preservative free) vials in a concentration of 10 mg/mL. Refrigerate. Protect from light.³³

Additional information:

- human **hyaluronidase** (rHuPH20) is an enzyme used to increase the dispersion and absorption of other drugs administered subcutaneously (such as rituximab SC), allowing for a larger injection volume to be administered with limited swelling or pain; subcutaneous tissue returns to normal within 24-48 h after injection^{24,34}
- RITUXAN® SC: 1400 mg vial contains **overfill** in the amount of 0.55 mL per vial³⁵; 1600 mg vial contains overfill in the amount of 0.8 mL per vial³⁶

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:

- compounded solutions of rituximab are stable for an additional 12 h at room temperature once removed from the fridge^{37,38}

Compatibility: consult detailed reference

PARENTERAL ADMINISTRATION:

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

Subcutaneous* (for rituximab SC only†)	dose to be administered undivided into a single injection site in the abdominal wall ¹² <ul style="list-style-type: none"> • 1400 mg* (11.7 mL): over ~5 min • 1600 mg* (13.4 mL): over ~7 min
Intramuscular	no information found
Direct intravenous	do not use ²

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

Intermittent infusion (rituximab SC must never be given IV†)	<p>Initial infusion:</p> <ul style="list-style-type: none"> • starting rate of 50 mg/h • after 60 minutes, increase rate by 50 mg/h every 30 minutes until 400 mg/h² <p>Subsequent Infusions: For combined chemotherapy or maintenance regimens^{19,20,39-48}:</p> <ul style="list-style-type: none"> • may administer subsequent doses over a total of 90 minutes (20% of the dose in the first 30 minutes and remaining 80% over 60 minutes) <p>For monotherapy^{2,20,49,50}:</p> <ul style="list-style-type: none"> • may administer subsequent doses at 100 mg/h and increase rate by 100 mg/h every 30 minutes until 400 mg/h
Continuous infusion	no information found
Intralesional	has been given ⁵¹⁻⁵⁴
Intraperitoneal	has been given ^{51,55}
Intrapleural	has been given ^{51,56}
Intrathecal	has been given ^{51,57}
Intra-arterial	no information found
Intraventricular	has been given ^{51,58}
Intravesical	no information found
Intraocular (rituximab SC must never be given intraocularly†)	has been used ^{11,59-61} ; give 0.1 mL as intravitreal injection in the affected eye

* rituximab SC (RITUXAN® SC) 1400 mg and 1600 mg vial formulations are used for different indications and are not interchangeable.

† rituximab SC (RITUXAN® SC) is intended for subcutaneous use only and is not interchangeable with rituximab formulations that are intended for other routes of administration.

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**

<i>Intravenous:</i> (rituximab SC must never be given IV†)	Cycle Length: 1 week ^{2,50,62} :	250 mg/m² IV for one dose on days 1 and 9 (total dose per cycle 500 mg/m ²)
	1 week ^{2,39,49,63-66} :	375 mg/m² IV for one dose on day 1 (total dose per cycle 375 mg/m ²)

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

Cycle Length:		
	2 weeks ^{45,67} :	<i>375 mg/m² IV for one dose on days 1 and 8</i> (total dose per cycle 750 mg/m ²)
	3 weeks ^{46,68-71} :	<i>375 mg/m² IV for one dose on day 4</i> (total dose per cycle 375 mg/m ²)
	3 weeks ^{41,68-71} :	<i>375 mg/m² IV for one dose on day 8</i> (total dose per cycle 375 mg/m ²)
	3 weeks ^{2,5,20,40,42,44,47,72-78} :	<i>375 mg/m² IV for one dose on days 1, 2, or 3</i> (total dose per cycle 375 mg/m ²)
	4 weeks ^{2,5,43,79-81} :	<i>375 mg/m² IV for one dose on days 1, 2, or 3</i> (total dose per cycle 375 mg/m ²)
	4 weeks ² :	500 mg/m ² IV for one dose on day 1 (total dose per cycle 500 mg/m ²)
	2-3 months ² :	375 mg/m ² IV for one dose on day 1 (total dose per cycle 375 mg/m ²)
	3 months ^{2,20,48,82} :	<i>375 mg/m² IV for one dose on day 1</i> (total dose per cycle 375 mg/m ²)
Subcutaneous: (for rituximab SC only†)	3 weeks ^{24,83} :	<i>1400 mg (fixed dose) SC for one dose on day 1</i> , starting with cycle 2 onwards* (total dose per cycle 1400 mg)
		*Tolerance to rituximab must be established in cycle 1 using rituximab IV infusion before proceeding to SC administration for cycle 2 and subsequent doses.
	2-3 months ^{24,84} :	<i>1400 mg (fixed dose) SC for one dose on day 1</i> (total dose per cycle 1400 mg)
	4 weeks ^{12,85,86} :	<i>1600 mg (fixed dose) SC for one dose on day 1</i> , starting with cycle 2 onwards* (total dose per cycle 1600 mg)
		*Tolerance to rituximab must be established in cycle 1 using rituximab IV infusion before proceeding to SC administration for cycle 2 and subsequent doses.
Intraocular ^{11,59-61} : (rituximab SC must never be given intraocularly†)	2-4 weeks:	1 mg/0.1 mL by intravitreal injection in the affected eye for 1 dose

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

<i>Concurrent radiation:</i>	Cycle Length: no information found
<i>Dosage in myelosuppression:</i>	modify according to protocol by which patient is being treated; if no guidelines available, refer to Appendix "Dosage Modification for Myelosuppression"
<i>Dosage in renal failure:</i>	has been given ⁸⁷
<i>Dosage in hepatic failure:</i>	no information found
<i>Dosage in dialysis:</i>	no significant removal; may give standard dose before or after peritoneal or hemodialysis ^{87,88}

† rituximab SC (RITUXAN® SC) is intended for subcutaneous use only and is not interchangeable with rituximab formulations that are intended for other routes of administration. RITUXAN® SC 1400 mg and 1600 mg vial formulations are used for different indications and are not interchangeable.

Children:

<i>Intravenous:</i>	Cycle Length: weekly: ⁸⁹	375 mg/m ² IV for one dose on day 1 (total dose per cycle 375 mg/m ²)
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