

DRUG NAME: Gemcitabine**SYNONYM(S):** gemcitabine hydrochloride, difluorodeoxycytidine, 2',2'-difluorodeoxycytidine, dFdC, LY 188011**COMMON TRADE NAME(S):** GEMZAR® (notice of compliance,¹ December 1996; patent expires² March 2004)**CLASSIFICATION:** antimetabolite*Special pediatric considerations are noted when applicable, otherwise adult provisions apply.***MECHANISM OF ACTION:**

Gemcitabine, a pyrimidine analog, is structurally similar to cytarabine, but has a wider spectrum of antitumour activity due to its different cellular pharmacology and mechanism of action.³ Gemcitabine is metabolized intracellularly to two active metabolites, gemcitabine diphosphate (dFdCDP) and gemcitabine triphosphate (dFdCTP). The cytotoxic effects of gemcitabine are exerted through incorporation of dFdCTP into DNA with the assistance of dFdCDP, resulting in inhibition of DNA synthesis and induction of apoptosis.^{4,5} Gemcitabine is a radiation-sensitizing agent.⁵ It is cell-cycle phase specific (S and G₁/S-phases).⁵

PHARMACOKINETICS:

Interpatient variability	3- to 4-fold interpatient and inpatient variability ⁶	
Oral absorption	no information found	
Distribution	widely distributed into tissues; also present in ascitic fluid. ⁷	
	cross blood brain barrier?	no information found
	volume of distribution	IV infusion < 70 min: 50 L/m ² ; IV infusion 70-285 min: 370 L/m ²
	plasma protein binding	< 10% ⁵
Metabolism	Metabolized intracellularly by nucleoside kinases to active metabolites dFdCDP and dFdCTP; also metabolized intracellularly and extracellularly by cytidine deaminase to inactive metabolite difluorodeoxyuridine (dFdU). ^{5,6}	
	active metabolite(s)	dFdCDP, dFdCTP
	inactive metabolite(s)	dFdU
Excretion	mainly renal excretion	
	urine	92-98% over one week (89% as dFdU, < 10% as gemcitabine) after a single dose of 1000 mg/m ² given over 30 minutes. ⁵
	terminal half life	IV infusion <70 min: 0.7-1.6 h; IV infusion 70-285 min: 4.1-10.6 h
	clearance	IV infusion < 70 min: 41-92 L/h/m ² (male) 31-69 L/h/m ² (female)
Gender	decreased volume of distribution and clearance in women	
Elderly	decreased clearance and increased half-life with increasing age	
Children	no information found	
Ethnicity	no information found	

Adapted from reference⁴ unless specified otherwise.

USES:**Primary uses:***Lung cancer, non-small cell^{3,8-10,11,12}*Pancreatic cancer^{16,17}Bladder cancer¹⁹⁻²¹**Other uses:**Breast cancer¹³⁻¹⁵Cervical Cancer¹⁸Head and neck cancer^{22,23}Lung cancer, small cell^{24,25}Lymphoma, cutaneous T-cell²⁶Lymphoma, Hodgkin's disease²⁷Mesothelioma²⁸Ovarian cancer²⁹

*Health Canada Therapeutic Products Programme approved indication

No pediatric indications.

SPECIAL PRECAUTIONS:**Carcinogenicity:** No information found.**Mutagenicity:** Not mutagenic in Ames test but mutagenic in mammalian *in vitro* mutation test. Gemcitabine is clastogenic in mammalian *in vitro* and *in vivo* chromosome tests.⁵**Fertility:** Decreased spermatogenesis and fertility in male mice.⁵**Pregnancy:** FDA Pregnancy Category D.⁵ There is positive evidence of human fetal risk, but the benefits from use in pregnant women may be acceptable despite the risk (eg, if the drug is needed in a life-threatening situation or for a serious disease for which safer drugs cannot be used or are ineffective).**Breastfeeding** is not recommended due to the potential secretion into breast milk.⁵**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.

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in <i>bold, italics</i>	
allergy/immunology	allergic reaction (4%, severe 0.2%) ³⁰
blood/bone marrow febrile neutropenia	<i>anemia</i> (68%, severe 8%)
	leukopenia (62%, severe 9%)
	<i>neutropenia</i> (63%, severe 25%); nadir 7-10 days, recovery within 7 days ³¹
	<i>thrombocytopenia</i> (24%, severe 5%); nadir 7-10 days, recovery within 7 days ³¹
cardiovascular (arrhythmia)	cardiac arrhythmia (2%, severe 0.2%) ³⁰
cardiovascular (general)	edema/peripheral edema (28%, severe 3%) ³²
coagulation	hemolytic uremic syndrome (0.3%); see paragraph following Side Effects table
constitutional symptoms	asthenia (42%, severe 2%) ³⁰
	fever (37%, severe <1%); see paragraph following Side Effects table

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in bold, italics	
dermatology/skin	<i>extravasation hazard: none</i> ^{4,30,31}
	alopecia (14%)
	skin rash (25%, severe <1%); see paragraph following Side Effects table
gastrointestinal	<i>emetogenic potential: low moderate</i> ³³
	constipation (8%, severe <1%)
	diarrhea (12%, severe <1%)
	nausea and vomiting (64%, severe 18%)
	stomatitis (8%, severe <1%)
hemorrhage	hematuria (31%, severe <1%)
hepatic	elevated alkaline phosphatase (55%, severe 9%); see paragraph following Side Effects table
	elevated AST (67%, severe 9%); see paragraph following Side Effects table
	elevated ALT (68%, severe 10%); see paragraph following Side Effects table
	elevated bilirubin (13%, severe 2%); see paragraph following Side Effects table
infection	infection (9%, severe 1%)
neurology	decreased level of consciousness (9%, severe <1%)
	peripheral neuropathy (3%) ¹⁷
pain	pain (16%, severe 1%)
pulmonary	dyspnea (8%, severe 1%); see paragraph following Side Effects table
renal/genitourinary	elevated BUN (16%, severe 0%)
	elevated creatinine (7%, severe <1%)
	proteinuria (36%, severe <1%)
syndromes	flu-like symptoms (19%, severe 1%) ³⁰ ; see paragraph following Side Effects table
vascular	digital ischemia ; see paragraph following Side Effects table
	peripheral vasculitis (<1%) ^{34,35} ; see paragraph following Side Effects table

Adapted from reference⁴ unless specified otherwise.

Dosing schedule and toxicity: Infusion time prolonged beyond 60 minutes has been shown to increase volume of distribution and has been associated with an increase in toxicity.³⁴ However, given in the context of a fixed dose rate (FDR) regimen, prolonged infusions have also been reported to produce a higher response rate than standard regimens in association with a higher intracellular accumulation of its active metabolite (dFdCTP).³⁶⁻³⁹ Refer to protocol by which patient is being treated for direction regarding duration of infusion.

Hemolytic uremic syndrome has been infrequently reported⁴ and is characterized by microangiopathic hemolytic anemia, thrombocytopenia and renal failure. The syndrome can present either acutely with severe hemolysis, thrombocytopenia and rapidly progressive renal failure, or more insidiously with mild or no thrombocytopenia and slowly progressive renal failure. The etiology of hemolytic uremic syndrome is unknown.⁴⁰ The onset of the syndrome has been reported to occur during and shortly after gemcitabine therapy. If not treated promptly, the syndrome may result in irreversible renal failure requiring dialysis.⁵ Therefore, patients with impaired renal function should be monitored closely while being treated with gemcitabine.^{4,30}

Elevated liver enzymes: Gemcitabine causes transient and reversible elevations of liver function enzymes in about two-thirds of patients. However, these increases are rarely of clinical significance and there is no evidence of increasing hepatic toxicity with either longer duration of gemcitabine treatment or cumulative dose.^{4,30}

Fever/Flu-like symptoms: Fever of any severity was reported in 37% of patients. It is frequently associated with other flu-like symptoms such as headache, chills, cough, rhinitis, myalgia, fatigue, sweating and insomnia.⁴ These symptoms are usually mild and transient, and rarely dose-limiting. The use of acetaminophen may provide symptomatic relief.³⁰

Severe pulmonary toxicity: Acute dyspnea may sometimes occur with gemcitabine therapy, but is usually self-limiting. However, severe pulmonary toxicities such as pulmonary edema, interstitial pneumonitis and adult respiratory distress syndrome have rarely been reported.⁴ The symptoms are manifested as progressive dyspnea, tachypnea, hypoxemia and pulmonary infiltrates on chest radiograph that are sometimes accompanied by fever and cough.⁴¹⁻⁴³ Pulmonary toxicities usually occur after several cycles of gemcitabine, but have also been seen as early as the first cycle. Risk factors for pulmonary toxicities include prior radiation to the mediastinum. Because of its structural similarities to cytarabine, gemcitabine is thought to cause lung injury by the same mechanism by inducing pulmonary capillary leakage.^{41,42} Management of pulmonary toxicities consists of discontinuation of gemcitabine and early supportive care with bronchodilators, corticosteroids, diuretics, and/or oxygen.^{4,41-43} Although pulmonary toxicities may be reversible with treatment, fatal recurrence of severe pulmonary symptoms was reported in one patient upon rechallenge with gemcitabine.⁴¹

Skin rash: Typically mild to moderate in severity, with macular or finely granular maculopapular pruritic eruption on the trunk and extremities. It is not dose-limiting and usually responds to topical corticosteroids.^{4,17} If needed, antihistamines such as diphenhydramine can be used.¹⁷

Vascular toxicity, including cases of thrombotic microangiopathy, veno-occlusive disease, and digital ischemic changes and necrosis, have been reported. The exact mechanism is unknown, although it is suggested to be more common and more severe after cumulative doses of 10,000 mg/m² or in the setting of combination therapy.^{34,44-46}

INTERACTIONS:

AGENT	EFFECT	MECHANISM	MANAGEMENT
warfarin ⁴⁷	increased anticoagulant effect of warfarin	possibly decreased metabolism of warfarin and decreased hepatic synthesis of clotting factors	monitor INR carefully during and for 1-2 months after gemcitabine therapy; adjust warfarin dose as needed

SUPPLY AND STORAGE:

Injection:

Hospira Healthcare Corporation supplies gemcitabine hydrochloride as 200 mg, 1000 mg and 2000 mg vials of sterile lyophilized powder. Store at room temperature.⁴

Accord Healthcare Inc., Eli Lilly Canada, Novopharm Limited, and Sandoz Canada supply gemcitabine hydrochloride as 200 mg and 1000 mg vials of sterile lyophilized powder. Store at room temperature.⁴⁸⁻⁵¹

For basic information on the current brand used at the BC Cancer Agency, see [Chemotherapy Preparation and Stability Chart in Appendix](#).

SOLUTION PREPARATION AND COMPATIBILITY:

For basic information on the current brand used at the BC Cancer Agency, see [Chemotherapy Preparation and Stability Chart](#) in Appendix.

Additional information: Solutions of reconstituted gemcitabine should not be refrigerated as crystallization may occur.³⁴

Compatibility: consult detailed reference

PARENTERAL ADMINISTRATION:

BCCA administration guideline noted in ***bold, italics***

Subcutaneous	no information found
Intramuscular	no information found
Direct intravenous	no information found
<i>Intermittent infusion</i>	<ul style="list-style-type: none"> • <i>over 30 min</i>³⁴; can also be given over 60 min^{13,19,21} • <i>over greater than 60 minutes using a fixed dose rate (FDR) of 10 mg/m²/min</i>^{52,53}
Continuous infusion	investigational, has been used in clinical trials at lower dosages (100 mg/m ²) over 24 h ^{54,55}
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 in patients with other toxicities.

Adults:

BCCA usual dose noted in ***bold, italics***

<i>Intravenous:</i>	Cycle length:	
	2 weeks ^{13,56} :	2500 mg/m ² (range 1250-2500 mg/m ²) IV for one dose on day 1
	3 weeks:	1250 mg/m ² (range 800-1250 mg/m ²) IV for one dose on days 1 and 8 (total dose per cycle 2500 mg/m ² [range 1600-2500 mg/m ²]) ^{4,29}
	<i>4 weeks:</i>	<i>1000 mg/m²</i> (range 500-1250 mg/m ²) <i>IV for one dose on days 1, 8 and 15</i> (<i>total dose per cycle 3000 mg/m²</i> [range 1500-3750 mg/m ²]) ^{4,16,17}

	8 weeks:	1000 mg/m² (range 500-1000 mg/m ²) IV for one dose on days 1, 8, 15, 22, 29, 36 and 42 for the first cycle, then continue with the 4-week dose schedule (see above) (total dose per 8-week cycle 7000 mg/m² [range 3500-7000 mg/m ²]). ^{4,17}
	3 weeks:	900 mg/m² (range 750-1200 mg/m ²) IV for one dose on days 1 and 8. ^{52,53}
<i>Concurrent with radiation:</i>	investigational, 100-400 mg/m ² IV once daily every week ^{57,58}	
<i>Dosage in myelosuppression:</i>	modify according to protocol by which patient is being treated; if no guidelines available, refer to Appendix 6 "Dosage Modification for Myelosuppression"	
<i>Dosage in renal failure:</i>	No dosing recommendation available. However, caution should be used in patients with renal dysfunction. ⁵⁹	
<i>Dosage in hepatic failure:</i>	When used as a single agent in 4-week cycle treatment, no dose adjustment is required with elevated AST; may consider using a lower starting dose of 800 mg/m ² with total bilirubin > 27 µmol/L. ⁵⁹ Dosage adjustment for increased bilirubin does not appear to be necessary in regimens using fixed dose rate infusion of gemcitabine. ⁶⁰	
<i>Dosage in dialysis:</i>	no information found	

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