Drug Monograph

A - Drug Name

gemcitabine

COMMON TRADE NAME(S): Gemzar®

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B - Mechanism of Action and Pharmacokinetics

Gemcitabine is a deoxycytidine analogue that is cell phase specific, primarily killing cells undergoing DNA synthesis (S-phase) and also blocking the progression of cells through the G1/S-phase boundary. Gemcitabine is a pro-drug and is metabolized intracellularly to the active diphosphate (dFdCDP) and triphosphate (dFdCTP) nucleosides. The cytotoxic effects of gemcitabine are exerted through dFdCDP inhibition of ribonucleotide reductase and incorporation of dFdCTP into DNA, resulting in inhibition of DNA synthesis and induction of apoptosis.

Distribution	Gemcitabine pharmacokinetics are linear. After infusions < 70 minutes, gemcitabine is not extensively distributed into tissues.	
	Cross blood brain barrier?	Unknown
	PPB	Negligible
Metabolism	Gemcitabine undergoes intracellular metabolism to the active moieties and is rapidly deaminated in the blood, liver, kidneys and other tissues. In the plasma, it is metabolized to its inactive metabolite.	
	Active metabolites	Yes
	Inactive metabolites	Yes
Elimination	Urine	92-98% (< 10% unchanged)

Half-life	32 to 94 min (< 70 minute infusion) 245 to 638 min (> 70 minute infusion)

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C - Indications and Status

Health Canada Approvals:

- Locally advanced (unresectable) or metastatic adenocarcinoma of the pancreas
- Locally advanced or metastatic non-small cell lung cancer (NSCLC) as a single agent or in combination with cisplatin
- In combination with cisplatin for locally advanced or metastatic transitional cell carcinoma (TCC) of the bladder
- In combination with paclitaxel for unresectable, locally recurrent or metastatic breast cancer, who have good performance status and have relapsed following adjuvant anthracycline-based chemotherapy

Other Uses:

- Breast cancer
- Gastrointestinal cancer (advanced biliary tract cancer, adjuvant treatment of pancreatic cancer)
- Genitourinary cancers (adrenal, testicular cancer, renal cell)
- Gynecological cancers (ovarian, cervical)
- Germ cell cancers
- Sarcoma (leiomyosarcoma of the uterus, soft tissue sarcoma)
- Head and neck cancer
- Mesothelioma
- Non-Hodgkin's and Hodgkin's lymphoma
- Unknown primary cancer

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D - Adverse Effects

Emetogenic Potential: Low

Extravasation Potential: Irritant

The following table contains adverse effects with ≥ 5% frequency, in patients treated with gemcitabine 800-1250 mg/m^2 as a single agent 30 minute weekly infusion, for various malignancies. Severe adverse events from other studies or post-marketing, may also be included.

ORGAN SITE	SIDE EFFECT* (%)	ONSET**
Cardiovascular	Arrhythmia (rare)	E
	Arterial thromboembolism (rare)	E
	Heart failure (rare)	E
Dermatological	Alopecia (14%) (≤ grade 2)	E
	Rash (25%) (rarely severe eg. toxic epidermal necrolysis (TEN), stevens Johnson syndrome (SJS))	E
Gastrointestinal	Constipation (8%)	E
	Diarrhea (12%)	E
	Mucositis (8%)	E
	Nausea, vomiting (64%) (18% severe)	I E
General	Edema (20%)	E
	Flu-like symptoms (37%)	I
	Other - radiosensitizer (may be severe)	E D
Hematological	Hemolytic uremic syndrome (<1%)	E
	Myelosuppression ± infection, bleeding (68%) (may be severe)	E
Hepatobiliary	Hepatotoxicity including liver failure (rare)	E
	↑ LFTs (68%) (10% severe)	E
Hypersensitivity	Hypersensitivity (rare)	I
Injection site	Injection site reaction (4%)	I
Musculoskeletal	Musculoskeletal pain (16%)	I
Nervous System	Peripheral neuropathy (3%)	E
	Posterior reversible leukoencephalopathy syndrome (PRES) (rare)	E D
	Somnolence (9%)	E
Renal	Creatinine increased (7%)	E
	Proteinuria (36%)	E
Respiratory	Acute respiratory distress syndrome (ARDS) (rare)	E
	Dyspnea (8%)	I
	Interstitial lung disease (rare)	E
Vascular	Capillary leak syndrome (rare)	E D

	Vasculitis (rare)	E

* "*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 gemcitabine include ↑ LFTs, myelosuppression ± infection, bleeding, nausea, vomiting, flu-like symptoms, proteinuria, rash, edema, musculoskeletal pain, alopecia and diarrhea.

Myelosuppression, usually of short duration, reversible and not cumulative over time, is the main dose-limiting toxicity with gemcitabine. Grade 3 or 4 hematologic toxicity has been reported and is increased when used in combination with other chemotherapy. Blood counts may continue to deteriorate even after gemcitabine administration has stopped. Patients should receive supportive therapy as necessary.

Typically mild to moderate in severity, transient **rashes** of macular, erythematous, and pruritic types involving the trunk and the extremities were reported. They are not dose-limiting and usually respond to topical corticosteroids.

Acute **shortness of breath** has been associated with gemcitabine. Bronchodilators, corticosteroids and/or oxygen may be administered to produce symptomatic relief.

Edema was frequently reported but was usually mild to moderate, reversible after stopping gemcitabine treatment and rarely resulted in discontinuation. The mechanism of edema is unknown but was not associated with any evidence of cardiac, hepatic or renal failure.

Flu-like symptoms are common and consist of low-grade fever, headache, fatigue, malaise, myalgia, arthralgia, cough and rhinitis. Fever was usually mild and clinically manageable.

Capillary leak syndrome with serious consequences has been reported rarely in single agent or combination therapy.

Posterior reversible encephalopathy syndrome (PRES) has been reported rarely in single agent or combination therapy and may be severe. Acute hypertension and seizure activity were reported in most patients. The onset of PRES signs and symptoms occurred from a few days to 6 months after initiation of gemcitabline. PRES was typically reversible.

Rare occurrences of **hemolytic uremic syndrome**, including fatal cases, were reported. Renal failure associated with this syndrome may not be reversible even with discontinuation of therapy and dialysis may be required. Patients with pre-existing renal dysfunction should be followed closely while being treated with gemcitabine.

Patients receiving concurrent radiation while receiving full dose gemcitabine should be closely monitored for reactions. Potentially life-threatening **esophagitis** and **pneumonitis**, particularly in patients receiving large volumes of radiotherapy, have been observed. The optimum regimen for

safe administration of gemcitabine with therapeutic doses of radiation has not yet been determined. Radiation injury has been observed on targeted tissues (e.g. esophagitis, colitis, and pneumonitis) with both concurrent and non-concurrent gemcitabine use. In addition, radiation recall has been seen when gemcitabine and radiation therapy are given >7 days apart.

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E - Dosing

Refer to protocol by which patient is being treated. Numerous dosing schedules exist depending on disease, response and concomitant therapy.

Adults:

Pancreatic cancer:

Cycle 1: 1000 mg/m^2 weekly for 7 weeks with 1 week rest

Cycle 2 +: 1000 mg/m^2 weekly for 3 weeks with 1 week rest (Q4W)

NSCLC:

Q 4 W: 1000 mg/m^2 weekly for 3 weeks ± cisplatin 100 mg/m^2 after infusion Day 1 ONLY

Q 3 W: 1250 mg/m^2 weekly for 2 weeks ± cisplatin 100 mg/m^2 after infusion Day 1 ONLY

TCC of the Bladder:

Q 4 W: 1000 mg/m^2 weekly for 3 weeks, with cisplatin 70mg/m^2 day 1 ONLY

Breast cancer:

Q 3 W: 1250 mg/m^2 weekly for 2 weeks, with paclitaxel 175mg/m^2 on day 1 ONLY

Dosage with Toxicity:

The dose modifications described here relate to gemcitabine use only.

Doses should not be re-escalated if they are reduced for non-hematological toxicities, febrile neutropenia or thrombocytopenic bleeding.

Table 1 - Day 1 of Cycle:

Worst Toxicity in Previous Cycle	% Full Dose
Non-hematologic Grade 3**	75%*
Non-hematologic Grade 4	Consider discontinuing, or 50-75%*
Febrile neutropenia, thrombocytopenic bleeding	75%*
> 1 Occurrence of Day 8/15 holds	75%*
• Pneumonitis • Hemolytic Uremic Syndrome (HUS) • Stevens-Johnson syndrome (SJS) • Toxic epidermal necrolysis (TEN) • Capillary Leak Syndrome (CLS) • Posterior reversible encephalopathy syndrome (PRES)	Discontinue

* Do not start new cycle until ANC ≥ 1.5 x 10^9/L, platelets ≥ 100 x 10^9/L and non-hematologic toxicity ≤ grade 2. Discontinue if non-hematological toxicities require more than a 50% dose reduction from the starting dose.

** except nausea/vomiting or alopecia

Other treatment days within cycle:

Table 2 - Non-hematologic toxicities

Toxicity	Action (% Full dose)
Grade 3**	HOLD; restart at 50-75%*
Grade 4	Discontinue

* Treat only if non-hematologic toxicities recover to ≤ grade 2 and hematologic parameters are met on treatment day (Table 3). Discontinue if non-hematological toxicities require more than a 50% dose reduction from the starting dose.

**except nausea/vomiting, alopecia

Table 3 - Hematologic Toxicities:

Platelets on treatment day (x 10^9/L)		**ANC on treatment day (x 10^9/L)**	**Action (% Full Dose)**
>100	And	> 1	100% *
50 to 100	And/or	0.5 to 1	75% or consider omit*
<50	And/or	<0.5	Omit

* Treat only if above parameters are met on treatment day and non-hematologic toxicities ≤ grade 2.

Dosage with Hepatic Impairment:

Gemcitabine should be used with caution in patients with hepatic impairment (cirrhosis, hepatitis, alcoholism, metastases, etc.); initial dose reduction should be considered if the patient is treated, especially in hyperbilirubinemia.

Suggested:

Bilirubin (micromol/L)	**Starting dose**
> 1.2 x ULN	800 mg/m2; escalate if tolerated

Dosage with Renal Impairment:

Gemcitabine should be used with caution in patients with renal insufficiency. There is insufficient information from clinical studies to allow clear dose recommendations for this patient population. Clinical trials with cisplatin mandated CrCl ≥ 60mL/min. For patients with pre-existing renal insufficiency, the close monitoring for occurrence of hemolytic uremic syndrome is required.

Dosage in the elderly:

Decreased clearance and increased half-life occurs with increasing age; however, no dose adjustment is necessary.

Dosage based on gender:

Decreased volume of distribution and clearance are seen in women; however, no dose adjustment is necessary.

Children:

Safety and effectiveness in children have not been established.

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F - Administration Guidelines

- May dilute reconstituted drug in normal saline for IV infusion, resulting in a minimum final concentration of at least 0.1 mg/mL.
- Gemcitabine is for IV administration only and should be infused over 30 minutes.
- To prevent increased toxicity, avoid an infusion time of > 60 minutes (exception: over 90 minutes when in combination with docetaxel for soft tissue sarcomas) or dosing more frequently than once weekly

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G - Special Precautions

Contraindications:

- Patients who have a hypersensitivity to this drug or any of its components.

Other Warnings/Precautions:

- Use with extreme caution in patients with compromised bone marrow reserve.
- Use with caution in patients with hepatic impairment (including concurrent liver metastases or a previous history of hepatitis, alcoholism or liver cirrhosis) and patients with renal impairment.

- Acute shortness of breath with a temporal relationship to gemcitabine injection administration may occur.

- Patients receiving concurrent radiation while receiving the full dose gemcitabine should be closely monitored for reactions. Exacerbation of radiation therapy toxicity including potentially life-threatening esophagitis and pneumonitis, particularly in patients receiving large volumes of radiotherapy have been observed.

Pregnancy and Lactation:

- Clastogenicity: Yes
- Mutagenicity: Yes
- Embryotoxicity: Yes
- Fetotoxicity: Yes
  Gemcitabine is not recommended for use in pregnancy. Adequate contraception should be used by both sexes during treatment, and for at least 6 months (general recommendation) after the last dose.
- Excretion into breast milk: Unknown
  Breastfeeding is not recommended.
- Fertility effects: Documented in animals
  Decreased spermatogenesis and fertility in male mice.

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H - Interactions

No specific drug interaction studies have been conducted.

AGENT	EFFECT	MECHANISM	MANAGEMENT
warfarin	possible ↑ in INR and risk of bleeding	possible ↓ in metabolism and synthesis of clotting factors	Monitor INR closely and adjust warfarin dose as needed

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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.

Recommended Clinical Monitoring

Monitor Type	Monitor Frequency
CBC	Baseline and before each dose
Renal function tests	Baseline, before each cycle and as clinically indicated
Liver function tests	Baseline, before each cycle and as clinically indicated
Clinical assessment of bleeding, infection, rash, diarrhea, nausea/vomiting, edema, injection site reactions, flu-like symptoms, hemolysis, signs/symptoms of capillary leak syndrome, cardiovascular, CNS and respiratory effects	At each visit

Grade toxicity using the current NCI-CTCAE (Common Terminology Criteria for Adverse Events) version

Suggested Clinical Monitoring

Monitor Type	Monitor Frequency
Urinalysis	Baseline and as clinically indicated
INR for patient receiving warfarin	Baseline and as clinically indicated

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K - References

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May 2022 Removed NDFP forms

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L - Disclaimer

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