DRUG NAME: Gemcitabine

SYNONYM(S): gemcitabine hydrochloride, difluorodeoxycytidine, 2’,2’-difluorodeoxycytidine, dFdC, LY 188011

COMMON TRADE NAME(S): GEMZAR®

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.¹ 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.²³ Gemcitabine is a radiation-sensitizing agent.³ It is cell-cycle phase specific (S and G1/S-phases).³

PHARMACOKINETICS:

<table>
<thead>
<tr>
<th>Interpatient variability</th>
<th>3- to 4-fold interpatient and intrapatient variability⁴</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral absorption</td>
<td>no information found</td>
</tr>
</tbody>
</table>

**Distribution**

- widely distributed into tissues; also present in ascitic fluid.⁵
- cross blood brain barrier? no information found
- volume of distribution
  - IV infusion < 70 min: 50 L/m²
  - IV infusion 70-285 min: 370 L/m²
- plasma protein binding < 10%³

**Metabolism**

Metabolized intracellularly by nucleoside kinases to active metabolites dFdCDP and dFdCTP; also metabolized intracellularly and extracellularly by cytidine deaminase to inactive metabolite difluorodeoxouridine (dFdU).³⁴

- 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/m² given over 30 minutes.³
- 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/m² (male)
  - 31-69 L/h/m² (female)

**Gender**

decreased volume of distribution and clearance in women

**Elderly**

decreased clearance and increased half-life with increasing age

Adapted from reference² unless specified otherwise.
USES:

*Primary uses:
- Lung cancer, non-small cell
- Pancreatic cancer
- Bladder cancer

*Other uses:
- Breast cancer
- Cervical Cancer
- Head and neck cancer
- Lung cancer, small cell
- Lymphoma, cutaneous T-cell
- Lymphoma, Hodgkin's disease
- Mesothelioma
- Ovarian cancer

*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.

*Fertility: Decreased spermatogenesis and fertility in male mice.

*Pregnancy: FDA Pregnancy Category D. There is positive evidence of human fetal risk, but the benefits from use in pregnant women may be acceptable despite the risk (e.g., 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.

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.

<table>
<thead>
<tr>
<th>ORGAN SITE</th>
<th>SIDE EFFECT</th>
</tr>
</thead>
<tbody>
<tr>
<td>allergy/immunology</td>
<td>allergic reaction (4%, severe 0.2%)²¹</td>
</tr>
<tr>
<td>blood/bone marrow</td>
<td>anemia (68%, severe 8%)</td>
</tr>
<tr>
<td>febrile neutropenia</td>
<td>leukopenia (62%, severe 9%)</td>
</tr>
<tr>
<td></td>
<td>neutropenia (63%, severe 25%); nadir 7-10 days, recovery within 7 days²²</td>
</tr>
<tr>
<td>cardiovascular (arrhythmia)</td>
<td>cardiac arrhythmia (2%, severe 0.2%)²¹</td>
</tr>
<tr>
<td>cardiovascular (general)</td>
<td>edema/peripheral edema (28%, severe 3%)²³</td>
</tr>
<tr>
<td>coagulation</td>
<td>hemolytic uremic syndrome (0.3%); see paragraph following Side Effects table</td>
</tr>
<tr>
<td>constitutional symptoms</td>
<td>asthenia (42%, severe 2%)²¹</td>
</tr>
<tr>
<td>ORGAN SITE</td>
<td>SIDE EFFECT</td>
</tr>
<tr>
<td>------------</td>
<td>-------------</td>
</tr>
<tr>
<td></td>
<td>Clinically important side effects are in <strong>bold, italics</strong></td>
</tr>
<tr>
<td></td>
<td>fever (37%, severe &lt;1%); see paragraph following Side Effects table</td>
</tr>
<tr>
<td>dermatology/skin</td>
<td>extravasation hazard: irritant²⁴-²⁹</td>
</tr>
<tr>
<td></td>
<td>alopecia (14%)</td>
</tr>
<tr>
<td></td>
<td>injection site reactions (4%); see paragraph following Side Effects table</td>
</tr>
<tr>
<td></td>
<td>skin rash (25%, severe &lt;1%); see paragraph following Side Effects table</td>
</tr>
<tr>
<td>gastrointestinal</td>
<td>emetogenic potential: low moderate³¹</td>
</tr>
<tr>
<td></td>
<td>constipation (8%, severe &lt;1%)</td>
</tr>
<tr>
<td></td>
<td>diarrhea (12%, severe &lt;1%)</td>
</tr>
<tr>
<td></td>
<td>nausea and vomiting (64%, severe 18%)</td>
</tr>
<tr>
<td></td>
<td>stomatitis (8%, severe &lt;1%)</td>
</tr>
<tr>
<td>hemorrhage</td>
<td>hematuria (31%, severe &lt;1%)</td>
</tr>
<tr>
<td>hepatic</td>
<td>elevated alkaline phosphatase (55%, severe 9%); see paragraph following Side Effects table</td>
</tr>
<tr>
<td></td>
<td>elevated AST (67%, severe 9%); see paragraph following Side Effects table</td>
</tr>
<tr>
<td></td>
<td>elevated ALT (68%, severe 10%); see paragraph following Side Effects table</td>
</tr>
<tr>
<td></td>
<td>elevated bilirubin (13%, severe 2%); see paragraph following Side Effects table</td>
</tr>
<tr>
<td>infection</td>
<td>infection (9%, severe 1%)</td>
</tr>
<tr>
<td>neurology</td>
<td>decreased level of consciousness (9%, severe &lt;1%)</td>
</tr>
<tr>
<td></td>
<td>peripheral neuropathy (3%)³²</td>
</tr>
<tr>
<td>pain</td>
<td>pain (16%, severe 1%)</td>
</tr>
<tr>
<td>pulmonary</td>
<td>dyspnea (8%, severe 1%); see paragraph following Side Effects table</td>
</tr>
<tr>
<td>renal/genitourinary</td>
<td>elevated BUN (16%, severe 0%)</td>
</tr>
<tr>
<td></td>
<td>elevated creatinine (7%, severe &lt;1%)</td>
</tr>
<tr>
<td></td>
<td>proteinuria (36%, severe &lt;1%)</td>
</tr>
<tr>
<td>syndromes</td>
<td>flu-like symptoms (19%, severe 1%); see paragraph following Side Effects table</td>
</tr>
<tr>
<td>vascular</td>
<td>digital ischemia; see paragraph following Side Effects table</td>
</tr>
<tr>
<td></td>
<td>peripheral vasculitis (&lt;1%); see paragraph following Side Effects table</td>
</tr>
</tbody>
</table>

Adapted from reference² 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.³³ 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).³⁵-³⁸ Refer to protocol by which patient is being treated for direction regarding duration of infusion.

**Hemolytic uremic syndrome** has been infrequently reported² 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.³⁹ 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.³ Therefore, patients with impaired renal function should be monitored closely while being treated with gemcitabine.²,²¹
**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.²,²¹

**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.² These symptoms are usually mild and transient, and rarely dose-limiting. The use of acetaminophen may provide symptomatic relief.²¹

**Injection site reactions** are reported in 4% of patients. Extravasation of gemcitabine does not cause tissue necrosis.³⁰ Anecdotally BC Cancer nurses have reported frequent injection site reactions to gemcitabine infusion. Although no further specific published reports have been identified, more recent practice guidelines have either reclassified gemcitabine as an irritant or noted its ability to cause a chemical phlebitis.²⁰ Therefore, it has been proposed to reclassify gemcitabine as an irritant. See BC Cancer Policy Number III-20 Prevention and Management of Extravasation of Chemotherapy.

**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.² The symptoms are manifested as progressive dyspnea, tachypnea, hypoxemia and pulmonary infiltrates on chest radiograph that are sometimes accompanied by fever and cough.³⁰,⁴¹ 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.⁴⁰,⁴¹ Management of pulmonary toxicities consists of discontinuation of gemcitabine and early supportive care with bronchodilators, corticosteroids, diuretics, and/or oxygen.²,⁴⁰-⁴² Although pulmonary toxicities may be reversible with treatment, fatal recurrence of severe pulmonary symptoms was reported in one patient upon rechallenge with gemcitabine.⁴⁰

**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.²,³² If needed, antihistamines such as diphenhydramine can be used.³²

**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.³³,⁴³-⁴⁵

### INTERACTIONS:

<table>
<thead>
<tr>
<th>AGENT</th>
<th>EFFECT</th>
<th>MECHANISM</th>
<th>MANAGEMENT</th>
</tr>
</thead>
<tbody>
<tr>
<td>warfarin⁴⁶</td>
<td>increased anticoagulant effect of warfarin</td>
<td>possibly decreased metabolism of warfarin and decreased hepatic synthesis of clotting factors</td>
<td>monitor INR carefully during and for 1-2 months after gemcitabine therapy; adjust warfarin dose as needed</td>
</tr>
</tbody>
</table>

### SUPPLY AND STORAGE:

**Injection:** Accord Healthcare Inc. supplies gemcitabine hydrochloride as 1000 mg, and 2000 mg vials of sterile lyophilized powder. Store at room temperature.⁴⁷
Pfizer Canada / Hospira Healthcare Corporation supplies gemcitabine as 200 mg, 1000 mg, and 2000 mg vials of ready-to-use preservative-free aqueous solution in a concentration of 38 mg/mL. Refrigerate. 48

Sandoz Canada Inc. supplies gemcitabine as 200 mg, 1000 mg, and 2000 mg vials of ready-to-use preservative-free aqueous solution in a concentration of 40 mg/mL. Refrigerate. 49

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: Solutions of reconstituted gemcitabine should not be refrigerated as crystallization may occur. 33

Compatibility: consult detailed reference

PARENTERAL ADMINISTRATION:

<table>
<thead>
<tr>
<th>Method</th>
<th>BC Cancer administration guideline noted in <strong>bold, italics</strong></th>
</tr>
</thead>
<tbody>
<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>
</tbody>
</table>
| **Intermittent infusion** | • over 30 min<sup>33</sup>; can also be given over 60 min<sup>6,10,12</sup>  
                        | • over greater than 60 minutes using a fixed dose rate (FDR) of 10 mg/m²/min<sup>50,51</sup> |
| Continuous infusion     | investigational, has been used in clinical trials at lower dosages (100 mg/m²) over 24 h<sup>52,53</sup> |
| Intraperitoneal         | no information found                                         |
| Intrapleural            | no information found                                         |
| Intrathecal             | no information found                                         |
| Intra-arterial          | no information found                                         |
| **Intravesical**        | solutions are retained for 1-2 h after instillation          |

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:**

**Intravenous:**

<table>
<thead>
<tr>
<th>Cycle length:</th>
<th>BC Cancer usual dose noted in <strong>bold, italics</strong></th>
</tr>
</thead>
</table>
| 2 weeks<sup>6,56</sup> | 2500 mg/m² (range 1250-2500 mg/m²) IV for one dose on day 1  
                        | (total dose per cycle 2500 mg/m² [range 1250-2500 mg/m²]) |
3 weeks\textsuperscript{2,20}: 1250 mg/m\textsuperscript{2} (range 800-1250 mg/m\textsuperscript{2}) IV for one dose on days 1 and 8
(total dose per cycle 2500 mg/m\textsuperscript{2} [range 1600-2500 mg/m\textsuperscript{2}])

4 weeks\textsuperscript{2,22,59}: 1000 mg/m\textsuperscript{2} (range 500-1250 mg/m\textsuperscript{2}) IV for one dose on days 1, 8 and 15
(total dose per cycle 3000 mg/m\textsuperscript{2} [range 1500-3750 mg/m\textsuperscript{2}])

8 weeks\textsuperscript{2,32}: 1000 mg/m\textsuperscript{2} (range 500-1000 mg/m\textsuperscript{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/m\textsuperscript{2} [range 3500-7000 mg/m\textsuperscript{2}])

3 weeks\textsuperscript{50,51}: 900 mg/m\textsuperscript{2} (range 750-1200 mg/m\textsuperscript{2}) IV for one dose on days 1 and 8
(total dose per cycle 1800 mg/m\textsuperscript{2} [range 1500-2400 mg/m\textsuperscript{2}])

**Intravesical:**
- **Induction:** 1000-2000 mg instilled intravesically once to twice weekly\textsuperscript{54-57,60} for 3 to 6 weeks
  (total dose per cycle 3000-24,000 mg)
- **Maintenance:** 1000-2000 mg instilled intravesically once monthly\textsuperscript{54-56,61} for up to 10 doses, starting 6 weeks after induction
  (total dose per cycle 10,000-20,000 mg)

**Concurrent with radiation:** investigational, 100-400 mg/m\textsuperscript{2} IV once daily every week\textsuperscript{62,63}

**Dosage in myelosuppression:** modify according to protocol by which patient is being treated; if no guidelines available, refer to Appendix "Dosage Modification for Myelosuppression"

**Dosage in renal failure:** No dosing recommendation available. However, caution should be used in patients with renal dysfunction.\textsuperscript{64}

**Dosage in hepatic failure:** 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\textsuperscript{2} with total bilirubin > 27 μmol/L.\textsuperscript{64} Dosage adjustment for increased bilirubin does not appear to be necessary in regimens using fixed dose rate infusion of gemcitabine.\textsuperscript{65}

**Dosage in dialysis:** no information found

**Children:** safety and effectiveness in children have not been established
REFERENCES:

36. Pollera CF, Ceribelli A, Crecco M, et al. Prolonged infusion gemcitabine: a clinical phase I study at low- (300 mg/m2) and high-dose (875 mg/m2) levels. Invest New Drugs 1997;15(2):115-121.