Gemcitabine is an Antineoplastic Agent; Antimetabolite. It is used to treat some cancers.

Pre-Authorization Criteria:

**Breast cancer:** First-line treatment of metastatic breast cancer (in combination with paclitaxel) after failure of adjuvant chemotherapy which contained an anthracycline, e.g. doxycyclinic (unless contraindicated);

**Non-small cell lung cancer (NSCLC):** First-line treatment of inoperable, locally-advanced (stage IIIA or IIIB) or metastatic (stage IV) NSCLC (in combination with cisplatin);

**Ovarian cancer:** Treatment of advanced ovarian cancer (in combination with carboplatin) that has relapsed at least 6 months following completion of platinum-based chemotherapy;

**Pancreatic cancer:** First-line treatment of locally-advanced (nonresectable stage II or III) or metastatic (stage IV) pancreatic adenocarcinoma

VCHCP requires that Gemcitabine be prescribed by an Oncologist.

**Dosing: Adult**

Details concerning dosing in combination regimens should also be consulted.

**Note:** Prolongation of the infusion time >60 minutes and administration more frequently than once weekly have been shown to increase toxicity.

**Pancreatic cancer, locally advanced or metastatic:** I.V.: Initial: 1000 mg/m² over 30 minutes once weekly for up to 7 weeks followed by 1 week rest; then
once weekly for 3 weeks out of every 4 weeks

_Dose escalation:_ Patients who complete an entire cycle of therapy may have the dose in subsequent cycles increased by 25% as long as the absolute granulocyte count (AGC) nadir is $>1500$/mm$^3$, platelet nadir is $>100,000$/mm$^3$, and nonhematologic toxicity is less than WHO Grade 1. If the increased dose is tolerated (with the same parameters) the dose in subsequent cycles may again be increased by 20%.

**Pancreatic cancer, advanced (unlabeled dosing/combinations):** I.V.: 1000 mg/m$^2$ over 30 minutes weekly for up to 7 weeks followed by 1 week rest; then weekly for 3 weeks out of every 4 weeks (in combination with erlotinib) (Moore, 2007) or 1000 mg/m$^2$ over 30 minutes days 1, 8, and 15 every 4 weeks (in combination with capecitabine) (Cunningham, 2009) or 1000 mg/m$^2$ over 30 minutes days 1 and 15 every 4 weeks (in combination with cisplatin) (Heinemann, 2006) or 1000 mg/m$^2$ infused at 10 mg/m$^2$/minute every 2 weeks (in combination with oxaliplatin) (Louvet, 2005)

**Nonsmall cell lung cancer, locally advanced or metastatic (in combination with cisplatin):** I.V.: 1000 mg/m$^2$ over 30 minutes days 1, 8, and 15; repeat cycle every 28 days or 1250 mg/m$^2$ over 30 minutes days 1 and 8; repeat cycle every 21 days

**Breast cancer, metastatic (AGC should be $\geq1500$/mm$^3$ and platelets $\geq100,000$/mm$^3$ prior to each cycle):** I.V.: 1250 mg/m$^2$ over 30 minutes days 1 and 8; repeat cycle every 21 days (in combination with paclitaxel) or (unlabeled dosing) as a single agent: 800 mg/m$^2$ over 30 minutes days 1, 8, and 15 of a 28-day treatment cycle (Carmichael, 1995)

**Ovarian cancer, advanced (AGC should be $\geq1500$/mm$^3$ and platelets $\geq100,000$/mm$^3$ prior to each cycle):** I.V.: 1000 mg/m$^2$ over 30 minutes days 1 and 8; repeat cycle every 21 days (in combination with carboplatin)

**Biliary tract cancer, advanced (unlabeled use):** I.V.: 1000 mg/m$^2$ over 30
minutes days 1 and 8; repeat cycle every 21 days (in combination with cisplatin) (Valle, 2010) or 1000 mg/m² over 30 minutes days 1 and 8; repeat cycle every 21 days (in combination with capecitabine) (Knox, 2005) or 1000 mg/m² infused at 10 mg/m²/minute over 100 minutes every 2 weeks (in combination with oxaliplatin) (Andre, 2004)

**Bladder cancer (unlabeled use):**

*Advanced or metastatic:* I.V.: 1000 mg/m² over 30-60 minutes days 1, 8, and 15; repeat cycle every 4 weeks (in combination with cisplatin) (von der Maase, 2000)

*Transitional cell carcinoma:* Intravesicular instillation: 2000 mg (in 100 mL NS; retain for 1 hour) twice weekly for 3 weeks; repeat cycle every 4 weeks for at least 2 cycles (Dalbagni, 2006)

**Cervical cancer, recurrent or persistent (unlabeled use):** I.V.: 1000 mg/m² days 1 and 8; repeat cycle every 21 days (in combination with cisplatin) (Monk, 2009) or 1250 mg/m² over 30 minutes days 1 and 8; repeat cycle every 21 days (in combination with cisplatin) (Burnett, 2000) or 800 mg/m² over 30 minutes days 1, 8, and 15; repeat cycle every 28 days (as a single-agent) (Schilder, 2005)

**Head and neck cancer, nasopharyngeal (unlabeled use):** I.V.: 1000 mg/m² over 30 minutes days 1, 8, and 15 every 4 weeks (Zhang, 2008)

**Hodgkin lymphoma, relapsed (unlabeled use):** I.V.: 1000 mg/m² (800 mg/m² for post-transplant patients) over 30 minutes days 1 and 8; repeat cycle every 21 days (in combination with vinorelbine and doxorubicin liposomal) (Bartlett, 2007) or 800 mg/m² days 1 and 4; repeat cycle every 21 days (in combination with ifosfamide, mesna, vinorelbine, and prednisolone) (Santoro, 2007)

**Malignant pleural mesothelioma (unlabeled use; in combination with cisplatin):** I.V.: 1000 mg/m² over 30 minutes days 1, 8 and 15 every 4 weeks for
up to 6 cycles (Nowak, 2002) or 1250 mg/m² over 30 minutes days 1 and 8 every 3 weeks for up to 6 cycles (van Haarst, 2002)

**Non-Hodgkin lymphoma, refractory (unlabeled use):** I.V.: 1000 mg/m² over 30 minutes days 1 and 8; repeat cycle every 21 days (in combination with cisplatin and dexamethasone) (Crump, 2004) or 1000 mg/m² every 15-21 days (in combination with oxaliplatin and rituximab) (Lopez, 2008)

**Sarcoma (unlabeled uses):** I.V.:

_Ewing's sarcoma, refractory:_ 675 mg/m² over 90 minutes days 1 and 8; repeat cycle every 21 days (in combination with docetaxel) (Navid, 2008)

_Osteosarcoma, refractory:_ 675 mg/m² over 90 minutes days 1 and 8; repeat cycle every 21 days (in combination with docetaxel) (Navid, 2008) or 1000 mg/m² weekly for 7 weeks followed by 1 week rest; then weekly for 3 weeks out of every 4 weeks (Merimsky, 2000)

_Soft tissue sarcoma, advanced:_ I.V.: 800 mg/m² over 90 minutes days 1 and 8; repeat cycle every 21 days (in combination with vinorelbine) (Dileo, 2007) or 675 mg/m² over 90 minutes days 1 and 8; repeat cycle every 21 days (in combination with docetaxel) (Leu, 2004) or 900 mg/m² over 90 minutes days 1 and 8; repeat cycle every 21 days (in combination with docetaxel) (Maki, 2007)

**Small cell lung cancer, refractory or relapsed (unlabeled use):** I.V.: 1000-1250 mg/m² over 30 minutes days 1, 8, and 15 every 4 weeks (as a single agent) (Masters, 2003)

**Testicular cancer, refractory germ cell (unlabeled use):** I.V.: 1000 mg/m² over 30 minutes days 1 and 8 every 3 weeks (in combination with oxaliplatin) (Kohlmannsberger, 2004; Pectasides, 2004) or 1250 mg/m² over 30 minutes days 1 and 8 every 3 weeks (in combination with oxaliplatin) (De Giorgi, 2006) or 1000 mg/m² over 30 minutes days 1, 8 and 15 every 4 weeks for up to 6 cycles
(in combination with paclitaxel) (Hinton, 2002)

**Unknown-primary, adenocarcinoma (unlabeled use):** I.V.: 1250 mg/m² days 1 and 8 every 3 weeks (in combination with cisplatin) (Culine, 2003) or 1000 mg/m² over 30 minutes days 1 and 8 every 3 weeks (in combination with docetaxel) for up to 6 cycles (Pouessel, 2004)

**Uterine cancer (unlabeled use):** I.V.: 900 mg/m² over 90 minutes days 1 and 8 every 3 weeks (in combination with docetaxel) (Hensley, 2008) or 1000 mg/m² over 30 minutes days 1, 8, and 15 every 4 weeks (Look, 2004)

**Dosing: Pediatric**

(For additional information see "Gemcitabine: Pediatric drug information")

Details concerning dosing in combination regimens should also be consulted. **Note:** Prolongation of the infusion time >60 minutes and administration more frequently than once weekly have been shown to increase toxicity. Refer to specific references for ages of populations studied):

**Germ cell tumor, refractory (unlabeled use):** I.V.: 1000 mg/m² over 30 minutes days 1, 8, and 15 every 4 weeks (in combination with paclitaxel) for up to 6 cycles (Hinton, 2002)

**Hodgkin lymphoma, relapsed (unlabeled use):** I.V.: 1000 mg/m² over 100 minutes days 1 and 8; repeat cycle every 21 days (in combination with vinorelbine) (Cole; 2009) or 800 mg/m² days 1 and 4; repeat cycle every 21 days (in combination with ifosfamide, mesna, vinorelbine, and prednisolone) (Santoro, 2007)

**Sarcomas (unlabeled use):** I.V.: 

Ewing's sarcoma, refractory: 675 mg/m² over 90 minutes days 1 and 8; repeat cycle every 21 days (in combination with docetaxel) (Navid, 2008)

Osteosarcoma, refractory: 675 mg/m² over 90 minutes days 1 and 8; repeat cycle
every 21 days (in combination with docetaxel) (Navid, 2008) or 1000 mg/m² weekly for 7 weeks followed by 1 week rest; then weekly for 3 weeks out of every 4 weeks (Merimsky, 2000)

**Dosing: Geriatric**
Refer to adult dosing.

**Dosage Forms: U.S.**
Excipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, powder for reconstitution: 200 mg, 1 g, 2 g

Gemzar®: 200 mg, 1 g

Injection, solution: 38 mg/mL (5.26 mL, 26.3 mL, 52.6 mL)

**Administration**
Infuse over 30 minutes; for unlabeled uses, infusion times may vary (refer to specific references). **Note:** Prolongation of the infusion time >60 minutes has been shown to increase toxicity. Gemcitabine has been administered at a fixed-dose rate (FDR) infusion rate of 10 mg/m²/minute (unlabeled); prolonged infusion times increase the accumulation of the active metabolite, gemcitabine triphosphate, optimizing the pharmacokinetics (Ko, 2006; Tempero, 2003). Patients who receive gemcitabine FDR experience more grade 3/4 hematologic toxicity (Ko, 2006; Poplin, 2009).

For intravesicular (bladder) instillation, gemcitabine was diluted in 50-100 mL normal saline; patients were instructed to retain in the bladder for 1 hour (Addeo, 2010; Dalbaghi, 2006)

**WARNINGS / PRECAUTIONS**
Concerns related to adverse effects:

Bone marrow suppression: May cause bone marrow suppression (leukopenia, thrombocytopenia, and anemia); myelosuppression is generally the dose-limiting toxicity. Monitor blood counts; dosage adjustments are frequently required.

Fever: May cause fever in the absence of clinical infection.

Hemolytic uremic syndrome: Hemolytic uremic syndrome (and/or renal failure) has been reported; monitor for evidence of microangiopathic hemolysis (elevation of bilirubin or LDH, reticulocytosis, severe thrombocytopenia, and/or renal failure).

Hepatotoxicity: Serious hepatotoxicity (including liver failure and death) has been reported (when alone or used in combination with other hepatotoxic medications); use with caution in patients with hepatic impairment (history of cirrhosis, hepatitis, or alcoholism) or in patients with hepatic metastases; may lead to exacerbation of hepatic impairment. Dose adjustments may be considered with elevated bilirubin.

Pulmonary toxicity: Pulmonary toxicity has been observed; discontinue if severe and institute supportive measures.

Disease-related concerns:

Renal impairment: Use with caution in patients with pre-existing renal impairment.

DRUG Interactions
(For additional information: Launch Lexi-Interact™ Drug Interactions Program)

BCG: Immunosuppressants may diminish the therapeutic effect of BCG. Risk X: Avoid combination
Bleomycin: Gemcitabine may enhance the adverse/toxic effect of Bleomycin. The risk of pulmonary toxicity may be increased. **Risk D: Consider therapy modification**

Coccidioidin Skin Test: Immunosuppressants may diminish the diagnostic effect of Coccidioidin Skin Test. **Risk C: Monitor therapy**

Denosumab: May enhance the adverse/toxic effect of Immunosuppressants. Specifically, the risk for serious infections may be increased. **Risk C: Monitor therapy**

Echinacea: May diminish the therapeutic effect of Immunosuppressants. **Risk D: Consider therapy modification**

Fluorouracil: Gemcitabine may increase the serum concentration of Fluorouracil. **Risk C: Monitor therapy**

Fluorouracil (Systemic): Gemcitabine may increase the serum concentration of Fluorouracil (Systemic). **Risk C: Monitor therapy**

Fluorouracil (Topical): Gemcitabine may increase the serum concentration of Fluorouracil (Topical). **Risk C: Monitor therapy**

Leflunomide: Immunosuppressants may enhance the adverse/toxic effect of Leflunomide. Specifically, the risk for hematologic toxicity such as pancytopenia, agranulocytosis, and/or thrombocytopenia may be increased. Management: Consider not using a leflunomide loading dose in patients receiving other immunosuppressants. Patients receiving both leflunomide and another immunosuppressant should be monitored for bone marrow suppression at least monthly. **Risk D: Consider therapy modification**
Natalizumab: Immunosuppressants may enhance the adverse/toxic effect of Natalizumab. Specifically, the risk of concurrent infection may be increased. **Risk X: Avoid combination**

Pimecrolimus: May enhance the adverse/toxic effect of Immunosuppressants. **Risk X: Avoid combination**

Roflumilast: May enhance the immunosuppressive effect of Immunosuppressants. **Risk D: Consider therapy modification**

Sipuleucel-T: Immunosuppressants may diminish the therapeutic effect of Sipuleucel-T. **Risk C: Monitor therapy**

Tacrolimus (Topical): May enhance the adverse/toxic effect of Immunosuppressants. **Risk X: Avoid combination**

Trastuzumab: May enhance the neutropenic effect of Immunosuppressants. **Risk C: Monitor therapy**

Vaccines (Inactivated): Immunosuppressants may diminish the therapeutic effect of Vaccines (Inactivated). **Risk C: Monitor therapy**

Vaccines (Live): Immunosuppressants may enhance the adverse/toxic effect of Vaccines (Live). Vaccinial infections may develop. Immunosuppressants may diminish the therapeutic effect of Vaccines (Live). Management: Avoid use of live organism vaccines with immunosuppressants; live-attenuated vaccines should not be given for at least 3 months after immunosuppressants. **Risk X: Avoid combination**

Vitamin K Antagonists (eg, warfarin): Antineoplastic Agents may enhance the anticoagulant effect of Vitamin K Antagonists. Antineoplastic Agents may diminish the anticoagulant effect of Vitamin K Antagonists. **Risk C: Monitor therapy**
REFERENCES


Cisplatin in Patients With Recurrent or Refractory Aggressive Histology B-Cell Non-Hodgkin Lymphoma: A Phase II Study by the National Cancer Institute of Canada Clinical Trials Group (NCIC-CTG)," *Cancer*, 2004, 101(8):1835-42. [PubMed 15386331]


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