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Forteo—Cont.

Overdose management—There is no specific antidote for teriparatide. Treatment of suspected overdose should include discontinuation of FORTEO, monitoring of serum calcium and phosphorus, and implementation of appropriate supportive measures, such as hydration.

DOSAGE AND ADMINISTRATION

FORTEO should be administered as a subcutaneous injection into the thigh or abdominal wall. The recommended dosage is 20 mcg once a day.

FORTEO should be administered initially under circumstances in which the patient can sit or lie down if symptoms of orthostatic hypotension occur (*see* PRECAUTIONS, Information for the Patient).

FORTEO is a clear and colorless liquid. Do not use if solid particles appear or if the solution is cloudy or colored. The FORTEO pen should not be used past the stated expiration date.

No data are available on the safety or efficacy of intravenous or intramuscular injection of FORTEO.

The safety and efficacy of FORTEO have not been evaluated beyond 2 years of treatment. Consequently, use of the drug for more than 2 years is not recommended.

INSTRUCTIONS FOR PEN USE

Patients and caregivers who administer FORTEO should receive appropriate training and instruction on the proper use of the FORTEO pen from a qualified health professional. It is important to read, understand, and follow the instructions in the FORTEO pen User Manual for priming the pen and dosing. Failure to do so may result in inaccurate dosing. Each FORTEO pen can be used for up to 28 days after the first injection. After the 28-day use period, discard the FORTEO pen, even if it still contains some unused solution. Never share a FORTEO pen.

STORAGE

The FORTEO pen should be stored under refrigeration at 2° to 8°C (36° to 46°F) at all times. Recap the pen when not in use to protect the cartridge from physical damage and light. During the use period, time out of the refrigerator should be minimized; the dose may be delivered immediately following removal from the refrigerator.

Do not freeze. Do not use FORTEO if it has been frozen.

HOW SUPPLIED

The FORTEO pen is available in the following package size:

One 3 mL prefilled pen delivery device — NDC 0002-8971-01 (MS8971)

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Manufactured by Lilly France S.A.S.
F-67640 Fegersheim, France
for Eli Lilly and Company
Indianapolis, IN 46285, USA
www.lilly.com

Medication Guide

FORTEO™

Generic name: teriparatide (rDNA origin) injection

Read this information carefully before you start taking FORTEO (for-TAY-o) to learn about the benefits and risks of FORTEO. Before beginning therapy, read the FORTEO pen User Manual for information on how to use the pen to inject your medicine. Read the information you get with FORTEO each time you get a refill, in case something has changed. Talk with your health care provider if there is something you do not understand or if you want to learn more about FORTEO.

What is the most important information I should know about FORTEO?

As part of drug testing, teriparatide, the active ingredient in FORTEO, was given to rats for a significant part of their lifetime. **In these studies, teriparatide caused some rats to develop osteosarcoma, a bone cancer.** Osteosarcoma in humans is a serious but very rare cancer. Osteosarcoma occurs in about 4 out of every million older adults each year. **It is not known if humans treated with FORTEO also have a higher chance of getting osteosarcoma.**

FORTEO is approved for use in both men and postmenopausal (after the "change of life") women with osteoporosis who are at high risk for having broken bones (fractures) from osteoporosis.

Before starting treatment, talk with your doctor about the possible benefits and risks of FORTEO so you can decide if it is right for you.

What is Osteoporosis?

Osteoporosis is a disease in which the bones become thin and weak, increasing the chance of having a broken bone. Osteoporosis usually causes no symptoms until a fracture happens. The most common fractures are in the spine (backbone). They can shorten height, even without causing pain. Over time, the spine can become curved or deformed and the body bent over. Fractures from osteoporosis can also happen in almost any bone in the body, for example, the wrist, rib, or hip. Once you have had a fracture, the chance for more fractures greatly increases.

The following risk factors increase your chance of getting fractures from osteoporosis:

- past broken bones from osteoporosis
- very low bone mineral density (BMD)
- frequent falls
- limited movement, such as using a wheelchair
- medical conditions likely to cause bone loss, such as some kinds of arthritis
- medicines that may cause bone loss, for example: seizure medicines (such as phenytoin), blood thinners (such as heparin), steroids (such as prednisone), or high doses of vitamins A or D.

What is FORTEO?

FORTEO is a prescription medicine used to treat osteoporosis by forming new bone. FORTEO is the brand name for teriparatide, which is the same as the active part of a natural hormone called parathyroid hormone or "PTH." FORTEO forms new bone, increases bone mineral density and bone strength, and as a result, reduces the chance of getting a fracture. In a study of postmenopausal (after the "change of life") women with osteoporosis, FORTEO reduced the number of fractures of the spine and other bones. The effect on fractures has not been studied in men.

FORTEO is approved for use in both men and postmenopausal women with osteoporosis who are at high risk for having fractures. FORTEO can be used by people who have had a fracture related to osteoporosis, or who have multiple risk factors for fracture (See "What is osteoporosis?"), or who cannot use other osteoporosis treatments.

Who should not use FORTEO?

Do not use FORTEO if you:

- have Paget's disease of the bone
- have unexplained high levels of alkaline phosphatase in your blood, which means you might have Paget's disease. If you are not sure, ask your doctor.
- are a child or growing adult
- have ever been diagnosed with bone cancer or other cancers that have spread (metastasized) to your bones
- have had radiation therapy involving your bones
- have certain bone diseases. If you have a bone disease, tell your doctor.
- have too much calcium in your blood (hypercalcemia)
- are pregnant or nursing
- have had an allergic reaction to FORTEO or one of its ingredients (See the ingredients section at the end of this Medication Guide)
- have trouble injecting yourself and do not have someone who can help you.

FORTEO should not be used to prevent osteoporosis or to treat patients who are not considered to be at high risk for fracture.

Tell your health care provider and pharmacist about all the medicines you are taking when you start taking FORTEO, and if you start taking a new medicine after you start FORTEO treatment. Tell them about all medicines you get with prescriptions and without prescriptions, as well as herbal or natural remedies. Your doctor and pharmacist need this information to help keep you from taking a combination of products that may harm you.

How should I take FORTEO?

- Take FORTEO once a day for as long as your doctor prescribes it for you. Use of FORTEO for more than 2 years is not recommended. Your health care professional (doctor, nurse, or pharmacist) should teach you how to use the FORTEO pen (prefilled delivery device). (See the User Manual for written instructions on how to use the FORTEO pen.)
- Some patients get dizzy or get a fast heartbeat after the first few doses. For the first few doses, inject FORTEO where you can sit or lie down right away if you get dizzy.
- Inject FORTEO once each day in your thigh or abdomen (lower stomach area).
- You can take FORTEO with or without food or drink.
- You can take FORTEO at any time of the day. To help you remember to take FORTEO, take it at about the same time each day.
- Do not use FORTEO if it has solid particles in it, or if it is cloudy or colored. It should be clear and colorless.
- Do not use FORTEO after the expiration date printed on the pen and pen packaging.
- Throw away any FORTEO pen that you started using more than 28 days earlier, even if it still has medicine in it (See the User Manual).
- Inject FORTEO shortly after you take the pen out of the refrigerator. Recap the pen and put it back into the refrigerator right after use (See the User Manual).
- If you forget or are unable to take FORTEO at your usual time, take it as soon as possible on that day. Do not take more than one injection in the same day.
- Talk with your health care provider about other ways you can help your osteoporosis, such as exercise, diet, supplements, and reducing or stopping your use of tobacco and alcohol. If your health care provider recommends calcium and vitamin D supplements, you can take them at the same time as FORTEO.

What are the possible side effects of FORTEO?

Most side effects are mild and include dizziness and leg cramps. If you become lightheaded or have fast heartbeats after your injection, sit or lie down until you feel better. If you do not feel better, call your health care provider before continuing treatment.

Contact your health care provider if you have continuing nausea, vomiting, constipation, low energy, or muscle weakness. These may be signs there is too much calcium in your blood.

These are not all the possible side effects of FORTEO. For more information, ask your health care provider or pharmacist.

Your health care provider may take samples of blood and urine during treatment to check your response to FORTEO. Also, your health care provider may ask you to have follow-up tests of bone mineral density.

How should I store FORTEO?

- Keep your FORTEO pen in the refrigerator at 36° to 46°F (2° to 8°C).
- Do not freeze the pen. Do not use FORTEO if it has been frozen.
- You can use your FORTEO pen for up to 28 days after the first injection from the pen.
- Throw away the pen properly (See the User Manual) after 28 days of use, even if it is not completely empty.
- Recap the pen after each use (See the User Manual) to protect from physical damage.

General information about using FORTEO safely and effectively

Medicines are sometimes prescribed for conditions that are not mentioned in Medication Guides. Do not use FORTEO for a condition for which it was not prescribed. Do not give FORTEO to other people, even if they have the same condition you have.

This Medication Guide summarizes the most important information about FORTEO. If you would like more information, talk with your doctor, nurse, or pharmacist. You can ask your pharmacist or health care provider for information about FORTEO that is written for health care professionals. You can also call Lilly toll free at 1-866-4FORTEO (1-866-436-7836).

Ingredients

In addition to the active ingredient teriparatide, inactive ingredients are glacial acetic acid, sodium acetate (anhydrous), mannitol, Metacresol, and Water for Injection. In addition, hydrochloric acid solution 10% and/or sodium hydroxide solution 10% may have been added to adjust product pH.

This Medication Guide has been approved by the US Food and Drug Administration.

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Indianapolis, IN 46285, USA
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PA 9241 FSAMP

Shown in Product Identification Guide, page 322

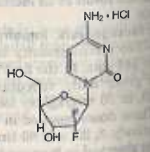
GEMZAR®

[jĕm-zar]
(Gemcitabine HCl)
FOR INJECTION

DESCRIPTION

Gemzar® (gemcitabine HCl) is a nucleoside analogue that exhibits antitumor activity. Gemcitabine HCl is 2'-deoxy-2',2'-difluorocytidine monohydrochloride (β-isomer).

The structural formula is as follows:



The empirical formula for gemcitabine HCl is $C_9H_{11}F_2N_3O_4$ • HCl. It has a molecular weight of 299.66.

Gemcitabine HCl is a white to off-white solid. It is soluble in water, slightly soluble in methanol, and practically insoluble in ethanol and polar organic solvents.

The clinical formulation is supplied in a sterile form for intravenous use only. Vials of Gemzar contain either 200 mg or 1 g of gemcitabine HCl (expressed as free base) formulated with mannitol (200 mg or 1 g, respectively) and sodium acetate (12.5 mg or 62.5 mg, respectively) as a sterile lyophilized powder. Hydrochloric acid and/or sodium hydroxide may have been added for pH adjustment.

CLINICAL PHARMACOLOGY

Gemcitabine exhibits cell phase specificity, primarily killing cells undergoing DNA synthesis (S-phase) and also blocking the progression of cells through the G1/S-phase boundary. Gemcitabine is metabolized intracellularly by nucleoside kinases to the active diphosphate (dFdCDP) and triphosphate (dFdCTP) nucleosides. The cytotoxic effect of gemcitabine is attributed to a combination of two actions of the diphosphate and the triphosphate nucleosides, which leads to inhibition of DNA synthesis. First, gemcitabine diphosphate inhibits ribonucleotide reductase, which is responsible for catalyzing the reactions that generate the deoxynucleoside triphosphates for DNA synthesis. Inhibition of this enzyme by the diphosphate nucleoside causes a reduction in the concentrations of deoxynucleotides, including dCTP. Second, gemcitabine triphosphate competes with dCTP for incorporation into DNA. The reduction in the intracellular concentration of dCTP (by the action of the diphosphate) enhances the incorporation of gemcitabine triphosphate into DNA

...nucleotide). After the gemcitabine nucleotide is incorporated into DNA, only one additional nucleotide is added to the growing DNA strands. After this addition, there is inhibition of further DNA synthesis. DNA polymerase epsilon is unable to remove the gemcitabine nucleotide and repair the growing DNA strands (masked chain termination). In CEM T lymphoblastoid cells, gemcitabine induces internucleosomal DNA fragmentation, one of the characteristics of programmed cell death.

Gemcitabine demonstrated dose-dependent synergistic activity with cisplatin *in vitro*. No effect of cisplatin on gemcitabine triphosphate accumulation or DNA double-strand breaks was observed. *In vivo*, gemcitabine showed activity in combination with cisplatin against the LX-1 and CALU-6 human lung xenografts, but minimal activity was seen with the NCI-H460 or NCI-H520 xenografts. Gemcitabine was synergistic with cisplatin in the Lewis lung murine xenograft. Sequential exposure to gemcitabine 4 hours before cisplatin produced the greatest interaction.

Human Pharmacokinetics—Gemcitabine disposition was studied in 5 patients who received a single 1000 mg/m^2/30 minute infusion of radiolabeled drug. Within one (1) week, 92% to 98% of the dose was recovered, almost entirely in the urine. Gemcitabine (<10%) and the inactive uracil metabolite, 2'-deoxy-2',2'-difluorouridine (dFdU), accounted for 90% of the excreted dose. The metabolite dFdU is also found in plasma. Gemcitabine plasma protein binding is negligible.

The pharmacokinetics of gemcitabine were examined in 353 patients, about 2/3 men, with various solid tumors. Pharmacokinetic parameters were derived using data from patients treated for varying durations of therapy given weekly with periodic rest weeks and using both short infusions (<70 minutes) and long infusions (70 to 285 minutes). The total Gemzar dose varied from 500 to 3600 mg/m^2.

Gemcitabine pharmacokinetics are linear and are described by a 2-compartment model. Population pharmacokinetic analyses of combined single and multiple dose studies showed that the volume of distribution of gemcitabine was significantly influenced by duration of infusion and gender. Clearance was affected by age and gender. Differences in either clearance or volume of distribution based on patient characteristics or the duration of infusion result in changes in half-life and plasma concentrations. Table 1 shows plasma clearance and half-life of gemcitabine following short infusions for typical patients by age and gender.

Table 1: Gemcitabine Clearance and Half-Life for the "Typical" Patient

Age	Clearance Men (L/hr/m^2)	Clearance Women (L/hr/m^2)	Half-Life[a] Men (min)	Half-Life[a] Women (min)
29	92.2	69.4	42	49
45	75.7	57.0	48	57
65	55.1	41.5	61	73
79	40.7	30.7	79	94

[a] Half-life for patients receiving a short infusion (<70 min).

Gemcitabine half-life for short infusions ranged from 32 to 94 minutes, and the value for long infusions varied from 245 to 638 minutes, depending on age and gender, reflecting a greatly increased volume of distribution with longer infusions. The lower clearance in women and the elderly results in higher concentrations of gemcitabine for any given dose. The volume of distribution was increased with infusion length. Volume of distribution of gemcitabine was 50 L/m^2 following infusions lasting <70 minutes, indicating that gemcitabine, after short infusions, is not extensively distributed into tissues. For long infusions, the volume of distribution rose to 370 L/m^2, reflecting slow equilibration of gemcitabine within the tissue compartment.

The maximum plasma concentrations of dFdU (inactive metabolite) were achieved up to 30 minutes after discontinuation of the infusions and the metabolite is excreted in urine without undergoing further biotransformation. The metabolite did not accumulate with weekly dosing, but its elimination is dependent on renal excretion, and could accumulate with decreased renal function.

The effects of significant renal or hepatic insufficiency on the disposition of gemcitabine have not been assessed.

The active metabolite, gemcitabine triphosphate, can be extracted from peripheral blood mononuclear cells. The half-life of the terminal phase for gemcitabine triphosphate from mononuclear cells ranges from 1.7 to 19.4 hours.

Drug Interactions—When gemcitabine (1250 mg/m^2 on Days 1 and 8) and cisplatin (75 mg/m^2 on Day 1) was administered in NSCLC patients, the clearance of gemcitabine on Day 1 was 128 L/hr/m^2 and on Day 8 was 107 L/hr/m^2. The clearance of cisplatin in the same study was reported to be 3.94 mL/min/m^2 with a corresponding half-life of 134 hours (*see Drug Interactions under* **PRECAUTIONS**).

CLINICAL STUDIES

Non-Small Cell Lung Cancer (NSCLC)—Data from 2 randomized clinical studies (657 patients) support the use of Gemzar in combination with cisplatin for the first-line treatment of patients with locally advanced or metastatic NSCLC.

Gemzar plus cisplatin versus cisplatin: This study was conducted in Europe, the US, Canada in 522 patients with inoperable Stage IIIA, IIIB, or IV NSCLC who had not received prior chemotherapy. Gemzar 1000 mg/m^2 was administered on Days 1, 8, and 15 of a 28-day cycle with cisplatin 100 mg/m^2 administered on Day 1 of each cycle. Single-agent cisplatin 100 mg/m^2 was administered on Day 1 of each 28-day cycle. The primary endpoint was survival. Patient demographics are shown in Table 2. An imbalance with regard to histology was observed with 48% of patients on the cisplatin arm and 37% of patients on the Gemzar plus cisplatin arm having adenocarcinoma.

The Kaplan-Meier survival curve is shown in Figure 1. Median survival time on the Gemzar plus cisplatin arm was 9.0 months compared to 7.6 months on the single-agent cisplatin arm (Logrank p=0.008, two-sided). Median time to disease progression was 5.2 months on the Gemzar plus cisplatin arm compared to 3.7 months on the cisplatin arm (Logrank p=0.009, two-sided). The objective response rate on the Gemzar plus cisplatin arm was 26% compared to 10% with cisplatin (Fisher's Exact p<0.0001, two-sided). No difference between treatment arms with regard to duration of response was observed.

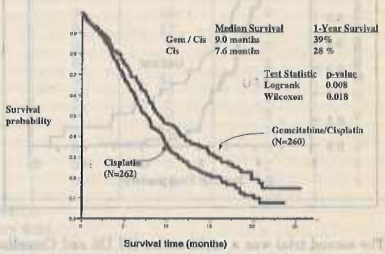
Gemzar plus cisplatin versus etoposide plus cisplatin: A second, multi-center, study in Stage IIIB or IV NSCLC randomized 135 patients to Gemzar 1250 mg/m^2 on Days 1 and 8, and cisplatin 100 mg/m^2 on Day 1 of a 21-day cycle or to etoposide 100 mg/m^2 I.V. on Days 1, 2, and 3 and cisplatin 100 mg/m^2 on Day 1 on a 21-day cycle (Table 2).

There was no significant difference in survival between the two treatment arms (Logrank p=0.18, two-sided). The median survival was 8.7 months for the Gemzar plus cisplatin arm versus 7.0 months for the etoposide plus cisplatin arm. Median time to disease progression for the Gemzar plus cisplatin arm was 5.0 months compared to 4.1 months on the etoposide plus cisplatin arm (Logrank p=0.015, two-sided). The objective response rate for the Gemzar plus cisplatin arm was 33% compared to 14% on the etoposide plus cisplatinarm (Fisher's Exact p=0.01, two-sided).

Quality of Life (QOL): QOL was a secondary endpoint in both randomized studies. In the Gemzar plus cisplatin versus cisplatin study, QOL was measured using the FACT-L, which assessed physical, social, emotional and functional well-being, and lung cancer symptoms. In the study of Gemzar plus cisplatin versus etoposide plus cisplatin, QOL was measured using the EORTC QLQ-C30 and LC13, which assessed physical and psychological functioning and symptoms related to both lung cancer and its treatment. In both studies no significant differences were observed in QOL between the Gemzar plus cisplatin arm and the comparator arm.

Figure 1

Kaplan-Meier Survival Curve in Gemzar plus Cisplatin versus Cisplatin NSCLC Study (N=522)



[See table 2 at left]

Pancreatic Cancer—Data from 2 clinical trials evaluated the use of Gemzar in patients with locally advanced or metastatic pancreatic cancer. The first trial compared Gemzar to 5-Fluorouracil (5-FU) in patients who had received no prior chemotherapy. A second trial studied the use of Gemzar in pancreatic cancer patients previously treated with 5-FU or a 5-FU-containing regimen. In both studies, the first cycle of Gemzar was administered intravenously at a dose of 1000 mg/m^2 over 30 minutes once weekly for up to 7 weeks (or until toxicity necessitated holding a dose) followed by a week of rest from treatment with Gemzar. Subsequent cycles consisted of injections once weekly for 3 consecutive weeks out of every 4 weeks.

The primary efficacy parameter in these studies was "clinical benefit response," which is a measure of clinical improvement based on analgesic consumption, pain intensity, performance status, and weight change. Definitions for improvement in these variables were formulated prospectively during the design of the 2 trials. A patient was considered a clinical benefit responder if either:

i) the patient showed a ≥50% reduction in pain intensity (Memorial Pain Assessment Card) or analgesic consumption, or a 20-point or greater improvement in performance status (Karnofsky Performance Scale) for a period of at least 4 consecutive weeks, without showing any sustained worsening in any of the other parameters. Sustained worsening was defined as 4 consecutive weeks with either any increase in pain intensity or analgesic consumption or a 20-point decrease in performance status occurring during the first 12 weeks of therapy.

OR:

ii) the patient was stable on all of the aforementioned parameters, and showed a marked, sustained weight gain (≥7% increase maintained for ≥4 weeks) not due to fluid accumulation.

The first study was a multi-center (17 sites in US and Canada), prospective, single-blinded, two-arm, randomized, comparison of Gemzar and 5-FU in patients with locally advanced or metastatic pancreatic cancer who had received no prior treatment with chemotherapy. 5-FU was administered intravenously at a weekly dose of 600 mg/m^2 for 30 minutes. The results from this randomized trial are shown in Table 3. Patients treated with Gemzar had statistically significant increases in clinical benefit response, survival, and time to disease progression compared to 5-FU. The Kaplan-Meier curve for survival is shown in Figure 2. No confirmed objective tumor responses were observed with either treatment.

[See table 3 at top of next page]

Continued on next page

Table 2: Randomized Trials of Combination Therapy with Gemzar plus Cisplatin in NSCLC

Trial	28-day Schedule[a]			21-day Schedule[b]		
Treatment Arm	Gemzar/ Cisplatin	Cisplatin		Gemzar/ Cisplatin	Cisplatin/ Etoposide	
Number of patients Male Female	260 182 78	262 186 76		69 64 5	66 61 5	
Median age, years Range	62 36 to 88	63 35 to 79		58 33 to 76	60 35 to 75	
Stage IIIA Stage IIIB Stage IV	7% 26% 67%	7% 23% 70%		N/A 48% 52%	N/A 52% 49%	
Baseline KPS[c] 70 to 80 Baseline KPS[c] 90 to 100	41% 57%	44% 55%		45% 55%	52% 49%	
Survival Median, months (95% C.I.) months	9.0 8.2, 11.0	7.6 6.6, 8.8	p=0.008	8.7 7.8, 10.1	7.0 6.0, 9.7	p=0.18
Time to Disease Progression Median, months (95% C.I.) months	5.2 4.2, 5.7	3.7 3.0, 4.3	p=0.009	5.0 4.2, 6.4	4.1 2.4, 4.5	p=0.015
Tumor Response	26%	10%	p<0.0001[d]	33%	14%	p=0.01[d]

[a] 28-day schedule—Gemzar plus cisplatin: Gemzar 1000 mg/m^2 on Days 1, 8, and 15 and cisplatin 100 mg/m^2 on Day 1 every 28 days; Single-agent cisplatin: cisplatin 100 mg/m^2 on Day 1 every 28 days.

[b] 21-day schedule—Gemzar plus cisplatin: Gemzar 1250 mg/m^2 on Days 1 and 8 and cisplatin 100 mg/m^2 on Day 1 every 21 days; Etoposide plus Cisplatin: cisplatin 100 mg/m^2 on Day 1 and I.V. etoposide 100 mg/m^2 on Days 1, 2, and 3 every 21 days.

[c] Karnofsky Performance Status.

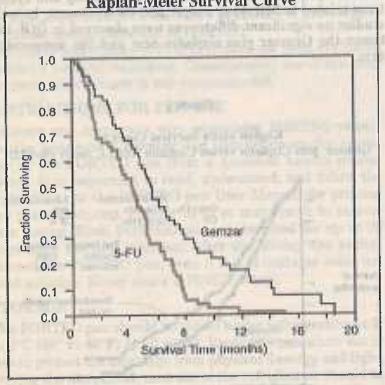
[d] Test for tumor response was calculated using the two-sided Fisher's exact test for difference in binomial proportions. All other p-values were calculated using the Logrank test for difference in overall time to an event.

N/A Not applicable.

Gemzar—Cont.

Clinical benefit response was achieved by 14 patients treated with Gemzar and 3 patients treated with 5-FU. One patient on the Gemzar arm showed improvement in all 3 primary parameters (pain intensity, analgesic consumption, and performance status). Eleven patients on the Gemzar arm and 2 patients on the 5-FU arm showed improvement in analgesic consumption and/or pain intensity with stable performance status. Two patients on the Gemzar arm showed improvement in analgesic consumption or pain intensity with improvement in performance status. One patient on the 5-FU arm was stable with regard to pain intensity and analgesic consumption with improvement in performance status. No patient on either arm achieved a clinical benefit response based on weight gain.

Figure 2
Kaplan-Meier Survival Curve



The second trial was a multi-center (17 US and Canadian centers), open-label study of Gemzar in 63 patients with advanced pancreatic cancer previously treated with 5-FU or a 5-FU-containing regimen. The study showed a clinical benefit response rate of 27% and median survival of 3.9 months.

Other Clinical Studies—When Gemzar was administered more frequently than once weekly or with infusions longer than 60 minutes, increased toxicity was observed. Results of a Phase 1 study of Gemzar to assess the maximum tolerated dose (MTD) on a daily × 5 schedule showed that patients developed significant hypotension and severe flu-like symptoms that were intolerable at doses above 10 mg/m^2. The incidence and severity of these events were dose-related. Other Phase 1 studies using a twice-weekly schedule reached MTDs of only 65 mg/m^2 (30-minute infusion) and 150 mg/m^2 (5-minute bolus). The dose-limiting toxicities were thrombocytopenia and flu-like symptoms, particularly asthenia. In a Phase 1 study to assess the maximum tolerated infusion time, clinically significant toxicity, defined as myelosuppression, was seen with weekly doses of 300 mg/m^2 at or above a 270-minute infusion time. The half-life of gemcitabine is influenced by the length of the infusion (*see* **CLINICAL PHARMACOLOGY**) and the toxicity appears to be increased if Gemzar is administered more frequently than once weekly or with infusions longer than 60 minutes (*see* **WARNINGS**).

INDICATIONS AND USAGE

Therapeutic Indications

Non-Small Cell Lung Cancer—Gemzar is indicated in combination with cisplatin for the first-line treatment of patients with inoperable, locally advanced (Stage IIIA or IIIB), or metastatic (Stage IV) non-small cell lung cancer.

Pancreatic Cancer—Gemzar is indicated as first-line treatment for patients with locally advanced (nonresectable Stage II or Stage III) or metastatic (Stage IV) adenocarcinoma of the pancreas. Gemzar is indicated for patients previously treated with 5-FU.

CONTRAINDICATION

Gemzar is contraindicated in those patients with a known hypersensitivity to the drug (*see Allergic under* **ADVERSE REACTIONS**).

WARNINGS

Caution—Prolongation of the infusion time beyond 60 minutes and more frequent than weekly dosing have been shown to increase toxicity (*see* **CLINICAL STUDIES**).

Hematology—Gemzar can suppress bone marrow function as manifested by leukopenia, thrombocytopenia, and anemia (*see* **ADVERSE REACTIONS**), and myelosuppression is usually the dose-limiting toxicity. Patients should be monitored for myelosuppression during therapy. *See* **DOSAGE AND ADMINISTRATION** for recommended dose adjustments.

Pulmonary—Pulmonary toxicity has been reported with the use of Gemzar. In cases of severe lung toxicity, Gemzar therapy should be discontinued immediately and appropriate supportive care measures instituted (*see Pulmonary under* **Single-Agent Use** *and under* **Post-marketing experience** in **ADVERSE REACTIONS** section).

Table 3: Gemzar Versus 5-FU in Pancreatic Cancer

	Gemzar	5-FU	
Number of patients Male Female	63 34 29	63 34 29	
Median age Range	62 years 37 to 79	61 years 36 to 77	
Stage IV disease	71.4%	76.2%	
Baseline KPS[a] ≤70	69.8%	68.3%	
Clinical benefit response	22.2% (N[c]=14)	4.8% (N=3)	p=0.004
Survival Median 6-month probability[b] 9-month probability[b] 1-year probability[b] Range 95% C.I. of the median	5.7 months (N=30) 46% (N = 14) 24% (N = 9) 18% 0.2 to 18.6 months 4.7 to 6.9 months	4.2 months (N=19) 29% (N = 4) 5% (N = 2) 2% 0.4 to 15.1+ months 3.1 to 5.1 months	p=0.0009
Time to Disease Progression Median Range 95% C.I. of the median	2.1 months 0.1+ to 9.4 months 1.9 to 3.4 months	0.9 months 0.1 to 12.0+ months 0.9 to 1.1 months	p = 0.0013

[a] Karnofsky Performance Status.
[b] Kaplan-Meier estimates.
[c] N=number of patients.
+ No progression at last visit; remains alive.
The p-value for clinical benefit response was calculated using the two-sided test for difference in binomial proportions; other p-values were calculated using the Logrank test for difference in overall time to an event.

Table 4: Selected WHO-Graded Adverse Events in Patients Receiving Single-Agent Gemzar
WHO Grades (% incidence)

	All Patients[a]			Pancreatic Cancer Patients[b]			Discontinuations (%)[c]
	All Grades	Grade 3	Grade 4	All Grades	Grade 3	Grade 4	All Patients
Laboratory[d]							
Hematologic							<1
Anemia	68	7	1	73	8	2	<1
Leukopenia	62	9	<1	64	8	1	<1
Neutropenia	63	19	6	61	17	7	-
Thrombocytopenia	24	4	1	36	7	<1	<1
Hepatic							<1
ALT	68	8	2	72	10	1	
AST	67	6	2	78	12	5	
Alkaline Phosphatase	55	7	2	77	16	4	
Bilirubin	13	2	<1	26	6	2	
Renal							<1
Proteinuria	45	<1	0	32	<1	0	
Hematuria	35	<1	0	23	0	0	
BUN	16	0	0	15	0	0	
Creatinine	8	<1	0	6	0	0	
Non-laboratory[e]							
Nausea and Vomiting	69	13	1	71	10	2	<1
Pain	48	9	<1	42	6	<1	<1
Fever	41	2	0	38	2	0	<1
Rash	30	<1	0	28	<1	0	<1
Dyspnea	23	3	<1	10	0	<1	0
Constipation	23	1	<1	31	3	<1	0
Diarrhea	19	1	0	30	3	0	<1
Hemorrhage	17	<1	<1	4	2	<1	<1
Infection	16	1	<1	10	2	<1	0
Alopecia	15	<1	0	16	0	0	<1
Stomatitis	11	<1	0	10	<1	0	<1
Somnolence	11	<1	<1	11	2	<1	0
Paresthesias	10	<1	0	10	<1	0	

Grade based on criteria from the World Health Organization (WHO).
[a] N=699-974; all patients with laboratory or non-laboratory data.
[b] N=161-241; all pancreatic cancer patients with laboratory or non-laboratory data.
[c] N=979.
[d] Regardless of causality.
[e] Table includes non-laboratory data with incidence for all patients ≥10%. For approximately 60% of the patients laboratory events were graded only if assessed to be possibly drug-related.

Renal—Hemolytic Uremic Syndrome (HUS) and/or renal failure have been reported following one or more doses of Gemzar. Renal failure leading to death or requiring dialysis, despite discontinuation of therapy, has been rarely reported. The majority of the cases of renal failure leading to death were due to HUS (*see Renal under* **Single-Agent Use** *and under* **Post-marketing experience** in **ADVERSE REACTIONS** section).

Hepatic—Serious hepatotoxicity, including liver failure and death, has been reported very rarely in patients receiving Gemzar alone or in combination with other potentially hepatotoxic drugs (*see Hepatic under* **Single-Agent Use** *and under* **Post-marketing experience** in **ADVERSE REACTIONS** section).

Pregnancy—Pregnancy Category D. Gemzar can [illegible] harm when administered to a pregnant woman. [illegible] bine is embryotoxic causing fetal malformations [illegible] ate, incomplete ossification) at doses of 1.5 mg/kg/day [illegible] mice (about 1/200 the recommended human dose [illegible] mg/m^2 basis). Gemcitabine is fetotoxic causing fetal [illegible] mations (fused pulmonary artery, absence of gall bl[illegible] doses of 0.1 mg/kg/day in rabbits (about 1/600 the [illegible] mended human dose on a mg/m^2 basis). Embryo[illegible] characterized by decreased fetal viability, reduced fe[illegible] sizes, and developmental delays. There are no [illegible] Gemzar in pregnant women. If Gemzar is used [illegible] pregnancy, or if the patient becomes pregnant [illegible] Gemzar, the patient should be apprised of the [illegible] hazard to the fetus.

PRECAUTIONS

General—Patients receiving therapy with Gemzar should be monitored closely by a physician experienced in the use of cancer chemotherapeutic agents. Most adverse events are reversible and do not need to result in discontinuation, although doses may need to be withheld or reduced. There was a greater tendency in women, especially older women, not to proceed to the next cycle.

Laboratory Tests—Patients receiving Gemzar should be monitored prior to each dose with a complete blood count (CBC), including differential and platelet count. Suspension or modification of therapy should be considered when marrow suppression is detected (*see* **DOSAGE AND ADMINISTRATION**).

Laboratory evaluation of renal and hepatic function should be performed prior to initiation of therapy and periodically thereafter (see **WARNINGS**).

Carcinogenesis, Mutagenesis, Impairment of Fertility—Long-term animal studies to evaluate the carcinogenic potential of Gemzar have not been conducted. Gemcitabine induced forward mutations *in vitro* in a mouse lymphoma (L5178Y) assay and was clastogenic in an *in vivo* mouse micronucleus assay. Gemcitabine was negative when tested in the Ames, *in vivo* sister chromatid exchange, and *in vivo* chromosomal aberration assays, and did not cause unscheduled DNA synthesis *in vitro*. Gemcitabine I.P. doses of 0.4 mg/kg/day (about 1/700 the human dose on a mg/m^2 basis) in male mice had an effect on fertility with moderate to severe hypospermatogenesis, decreased fertility, and decreased implantations. In female mice, fertility was not affected but maternal toxicities were observed at 1.5 mg/kg/day I.V. (about 1/200 the human dose on a mg/m^2 basis) and embryotoxicity or embryolethality was observed at 0.25 mg/kg/day I.V. (about 1/1300 the human dose on a mg/m^2 basis).

Pregnancy—Category D. *See* **WARNINGS**.

Nursing Mothers—It is not known whether Gemzar or its metabolites are excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions from Gemzar in nursing infants, the mother should be warned and a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother and the potential risk to the infant.

Elderly Patients—Gemzar clearance is affected by age (*see* **CLINICAL PHARMACOLOGY**). There is no evidence, however, that unusual dose adjustments, (i.e., other than those already recommended in the **DOSAGE AND ADMINISTRATION** section) are necessary in patients over 65, and in general, adverse reaction rates in the single-agent safety database of 979 patients were similar in patients above and below 65. Grade 3/4 thrombocytopenia was more common in the elderly.

Gender—Gemzar clearance is affected by gender (*see* **CLINICAL PHARMACOLOGY**). In the single-agent safety database (N=979 patients), however, there is no evidence that unusual dose adjustments (i.e., other than those already recommended in the **DOSAGE AND ADMINISTRATION** section) are necessary in women. In general, in single-agent studies of gemcitabine, adverse reaction rates were similar in men and women, but women, especially older women, were more likely not to proceed to a subsequent cycle and to experience Grade 3/4 neutropenia and thrombocytopenia.

Pediatric Patients—Gemzar has not been studied in pediatric patients. Safety and effectiveness in pediatric patients have not been established.

Patients with Renal or Hepatic Impairment—Gemzar should be used with caution in patients with preexisting renal impairment or hepatic insufficiency. Gemzar has not been studied in patients with significant renal or hepatic impairment.

Drug Interactions—No specific drug interaction studies have been conducted. For information on the pharmacokinetics of Gemzar and cisplatin in combination, *see Drug Interactions under* **CLINICAL PHARMACOLOGY** section.

Radiation Therapy—Safe and effective regimens for the administration of Gemzar with therapeutic doses of radiation have not yet been determined.

ADVERSE REACTIONS

Gemzar has been used in a wide variety of malignancies, both as a single-agent and in combination with other cytotoxic drugs. The following discussion focuses on single-agent use where the effects of Gemzar can be most readily determined and on the specific combination use that is the basis for its use in NSCLC.

Single-Agent Use: Myelosuppression is the principal dose-limiting toxicity with Gemzar therapy. Dosage adjustments for hematologic toxicity are frequently needed and are described in the **DOSAGE AND ADMINISTRATION** section.

Data in Table 4 are based on 979 patients receiving Gemzar as a single-agent administered weekly as a 30-minute infusion for treatment of a wide variety of malignancies. The Gemzar starting doses ranged from 800 to 1,250 mg/m^2. Data are also shown for the subset of patients with pancreatic cancer treated in 5 clinical studies. The frequencies of grades and severe (WHO Grade 3 or 4) adverse events were generally similar in the single-agent safety database of 979 patients and the subset of patients with pancreatic cancer. Adverse reactions reported in the single-agent safety database resulted in discontinuation of Gemzar therapy in about 10% of patients. In the comparative trial in pancreatic cancer, the discontinuation rate for adverse reactions was 14.3% for the gemcitabine arm and 4.8% for the 5-FU arm.

Table 5: Selected WHO-Graded Adverse Events from Comparative Trial of Gemzar and 5-FU in Pancreatic Cancer
WHO Grades (% incidence)

	Gemzar[a]			5-FU[b]		
	All Grades	Grade 3	Grade 4	All Grades	Grade 3	Grade 4
Laboratory[c]						
Hematologic						
Anemia	65	7	3	45	0	0
Leukopenia	71	10	0	15	2	0
Neutropenia	62	19	7	18	2	3
Thrombocytopenia	47	10	0	15	2	0
Hepatic						
ALT	72	8	2	38	0	0
AST	72	10	2	52	2	0
Alkaline Phosphatase	71	16	0	64	10	3
Bilirubin	16	2	2	25	6	3
Renal						
Proteinuria	10	0	0	2	0	0
Hematuria	13	0	0	0	0	0
BUN	8	0	0	10	0	0
Creatinine	2	0	0	0	0	0
Non-laboratory[d]						
Nausea and Vomiting	64	10	3	58	5	0
Pain	10	2	0	7	0	0
Fever	30	0	0	16	0	0
Rash	24	0	0	13	0	0
Dyspnea	6	0	0	3	0	0
Constipation	10	3	0	11	2	0
Diarrhea	24	2	0	31	5	0
Hemorrhage	0	0	0	2	0	0
Infection	8	0	0	3	2	0
Alopecia	18	0	0	16	0	0
Stomatitis	14	0	0	15	0	0
Somnolence	5	2	0	7	2	0
Paresthesias	2	0	0	2	0	0

Grade based on criteria from the World Health Organization (WHO).
[a] N=58-63; all Gemzar patients with laboratory or non-laboratory data.
[b] N=61-63; all 5-FU patients with laboratory or non-laboratory data.
[c] Regardless of causality.
[d] Non-laboratory events were graded only if assessed to be possibly drug-related.

[See table 4 at top of previous page]
[See table 5 above]

Hematologic—In studies in pancreatic cancer myelosuppression is the dose-limiting toxicity with Gemzar, but <1% of patients discontinued therapy for either anemia, leukopenia, or thrombocytopenia. Red blood cell transfusions were required by 19% of patients. The incidence of sepsis was less than 1%. Petechiae or mild blood loss (hemorrhage), from any cause, was reported in 16% of patients; less than 1% of patients required platelet transfusions. Patients should be monitored for myelosuppression during Gemzar therapy and dosage modified or suspended according to the degree of hematologic toxicity (*see* **DOSAGE AND ADMINISTRATION**).

Gastrointestinal—Nausea and vomiting were commonly reported (69%) but were usually of mild to moderate severity. Severe nausea and vomiting (WHO Grade 3/4) occurred in <15% of patients. Diarrhea was reported by 19% of patients, and stomatitis by 11% of patients.

Hepatic—In clinical trials, Gemzar was associated with transient elevations of one or both serum transaminases in approximately 70% of patients, but there was no evidence of increasing hepatic toxicity with either longer duration of exposure to Gemzar or with greater total cumulative dose. Serious hepatotoxicity, including liver failure and death, has been reported very rarely in patients receiving Gemzar alone or in combination with other potentially hepatotoxic drugs (*see Hepatic under* **Post-marketing experience**).

Renal—In clinical trials, mild proteinuria and hematuria were commonly reported. Clinical findings consistent with the Hemolytic Uremic Syndrome (HUS) were reported in 6 of 2429 patients (0.25%) receiving Gemzar in clinical trials. Four patients developed HUS on Gemzar therapy, 2 immediately post-therapy. The diagnosis of HUS should be considered if the patient develops anemia with evidence of microangiopathic hemolysis, elevation of bilirubin or LDH, reticulocytosis, severe thrombocytopenia, and/or evidence of renal failure (elevation of serum creatinine or BUN). Gemzar therapy should be discontinued immediately. Renal failure may not be reversible even with discontinuation of therapy and dialysis may be required (*see Renal under* **Post-marketing experience**).

Fever—The overall incidence of fever was 41%. This is in contrast to the incidence of infection (16%) and indicates that Gemzar may cause fever in the absence of clinical infection. Fever was frequently associated with other flu-like symptoms and was usually mild and clinically manageable.

Rash—Rash was reported in 30% of patients. The rash was typically a macular or finely granular maculopapular pruritic eruption of mild to moderate severity involving the trunk and extremities. Pruritus was reported for 13% of patients.

Pulmonary—In clinical trials, dyspnea, unrelated to underlying disease, has been reported in association with Gemzar therapy. Dyspnea was occasionally accompanied by bronchospasm. Pulmonary toxicity has been reported with the use of Gemzar (*see Pulmonary under* **Post-marketing experience**). The etiology of these effects is unknown. If such effects develop, Gemzar should be discontinued. Early use of supportive care measures may help ameliorate these conditions.

Edema—Edema (13%), peripheral edema (20%), and generalized edema (<1%) were reported. Less than 1% of patients discontinued due to edema.

Flu-like Symptoms—"Flu syndrome" was reported for 19% of patients. Individual symptoms of fever, asthenia, anorexia, headache, cough, chills, and myalgia were commonly reported. Fever and asthenia were also reported frequently as isolated symptoms. Insomnia, rhinitis, sweating, and malaise were reported infrequently. Less than 1% of patients discontinued due to flu-like symptoms.

Infection—Infections were reported for 16% of patients. Sepsis was rarely reported (<1%).

Alopecia—Hair loss, usually minimal, was reported by 15% of patients.

Neurotoxicity—There was a 10% incidence of mild paresthesias and a <1% rate of severe paresthesias.

Extravasation—Injection-site related events were reported for 4% of patients. There were no reports of injection site necrosis. Gemzar is not a vesicant.

Allergic—Bronchospasm was reported for less than 2% of patients. Anaphylactoid reaction has been reported rarely. Gemzar should not be administered to patients with a known hypersensitivity to this drug (*see* **CONTRAINDICATION**).

Cardiovascular—During clinical trials, 2% of patients discontinued therapy with Gemzar due to cardiovascular events such as myocardial infarction, cerebrovascular acci-

Continued on next page

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