FONKO-GEMCITABINE

Lyophilized powder for solution for infusion

Composition:
Each vial contains
Gemcitabine HCl equivalent to Gemcitabine 200 mg

List of Excipients:
Mannitol, sodium acetate trihydrate, sodium hydroxide 1N, hydrochloric acid 1N, and water for injection.

Product Description:
White to off white lyophilized plug contained in a flint glass vial.

Pharmacodynamics:
ATC code: L01BC05
Cytotoxic activity in cell cultures
Gemcitabine shows significant cytotoxic effects against a variety of cultured murine and human tumor cells. Its action is phase-specific such that gemcitabine primarily kills cells that are undergoing DNA synthesis (S-phase) and, under certain circumstances, blocks the progression of cells at the junction of the G_1/S phase boundary. *In vitro*, the cytotoxic effect of gemcitabine is dependent on both concentration and time.

Antitumoral activity in preclinical models
In animal tumor models, antitumoral activity of gemcitabine is schedule-dependent. When gemcitabine is administered daily, high mortality among the animals but minimal antitumoral activity is observed. If, however, gemcitabine is given every third or fourth day, it can be administered in nonlethal doses with substantial antitumoral activity against a broad spectrum of mouse tumors.

Mechanism of action
Cellular metabolism and mechanism of action: gemcitabine (dFdC), which is a pyrimidine antimetabolite, is metabolized intracellularly by nucleoside kinase to the active diphosphate (dFdCDP) and triphosphate (dFdCTP) nucleosides. The cytotoxic effect of gemcitabine is due to inhibition of DNA synthesis by two mechanisms of action by dFdCDP and dFdCTP. First, dFdCDP inhibits ribonucleotide reductase, which is uniquely responsible for catalyzing the reactions that produce deoxynucleoside triphosphates (dCTP) for DNA synthesis. Inhibition of this enzyme by dFdCDP reduces the concentration of deoxynucleosides in general and, in particular, dCTP. Second, dFdCTP competes with dCTP for incorporation into DNA (self-potentiation).
Likewise, a small amount of gemcitabine may also be incorporated into RNA. Thus, the reduced intracellular concentration of dCTP potentiates the incorporation of dFdCTP into DNA. DNA polymerase epsilon lacks the ability to eliminate gemcitabine and to repair the growing DNA strands. After gemcitabine is incorporated into DNA, one additional nucleotide is added to the growing DNA strands. After this addition there is essentially a complete inhibition in further DNA synthesis (masked chain termination). After incorporation into DNA, gemcitabine appears to induce the programmed cell death process known as apoptosis.

Clinical data
Non small cell lung cancer (NSCLC)
In a randomized phase III study of 522 patients with inoperable, locally advanced, or metastatic NSCLC, gemcitabine in combination with cisplatin showed a statistically significant higher response rate than cisplatin alone (31.0% and 12.0%, respectively, $p<0.0001$). A statistically significant prolongation of the time to progression, from 3.7 to 5.6 months (log-rank $p=0.0013$) and a statistically significant prolongation of median survival from 7.6 months to 9.1 months (log-rank $p=0.0040$) was observed in patients treated with gemcitabine/cisplatin compared to patients treated with cisplatin.
In another randomized phase III study of 133 evaluable patients with stage IIIB or IV NSCLC, a combination of gemcitabine and cisplatin showed a statistically significant higher response rate than the combination of cisplatin and etoposide (40.6% and 21.9%, respectively, $p=0.0253$). A prolongation of the time to progression, from 4.6 to 7.9 months was observed in patients treated with gemcitabine/cisplatin compared to patients treated with etoposide/cisplatin.
In both studies it was found that tolerability was similar in the two treatment arms.

Pancreatic cancer
In a randomized phase III study of 126 patients with advanced or metastatic pancreatic cancer, gemcitabine showed a statistically significant higher clinical benefit response rate than 5-fluorouracil (23.8% and 4.8% respectively, $p=0.0022$). Also, a statistically significant prolongation of the time to progression from 0.9 to 2.3 months (log-rank $p<0.0002$) and a statistically significant prolongation of median survival from 4.4 to 5.7 months (log-rank $p<0.0024$) was observed in patients treated with gemcitabine compared to patients treated with 5-fluorouracil.

Bladder cancer
A randomized phase III study of 405 patients with advanced or metastatic urothelial transitional cell carcinoma showed no difference between the two treatment arms, gemcitabine/cisplatin versus methotrexate/vinblastine/adriamycin/cisplatin (MVAC), in terms of median survival (12.8 and 14.8 months respectively, $p=0.547$), time to disease progression (7.4 and 7.6 months respectively, $p=0.842$) and response rate (49.4% and 45.7% respectively, $p=0.512$). However, the combination of gemcitabine and cisplatin had a better toxicity profile than MVAC.

Breast cancer
In a randomized phase III study of 529 patients with inoperable, locally recurrent, or metastatic breast cancer with relapse after adjuvant/neoadjuvant chemotherapy, gemcitabine in combination with paclitaxel showed a statistically significant prolongation of time to documented disease progression from 3.98 to 6.14 months (log-rank $p=0.0002$) in patients treated with gemcitabine/paclitaxel compared to patients treated with paclitaxel. After 377 deaths, the overall survival was 18.6 months versus 15.8 months (log rank $p=0.0489$, HR 0.82) in patients treated with gemcitabine/paclitaxel compared to patients treated with paclitaxel and the overall response rate was 41.4% and 26.2% respectively ($p=0.0002$).

Pharmacokinetics:
Absorption
Peak plasma concentrations (obtained within 5 minutes of the end of the infusion) were 3.2 to 45.5 mcg/ml. Plasma concentrations of the parent compound following a dose of 1,000 mg/m²/30-minutes are greater than 5 mcg/ml for approximately 30-minutes after the end of the infusion, and greater than 0.4 mcg/ml for an additional hour.

Distribution
The volume of distribution of the central compartment was 12.4 l/m² for women and 17.5 l/m² for men (interindividual variability was 91.9%). The volume of distribution of the peripheral compartment was 47.4 l/m². The volume of the peripheral compartment was not sensitive to gender.
The plasma protein binding was considered to be negligible.
Half-life: this ranged from 42 to 94 minutes depending on age and gender. For the recommended dosing schedule, gemcitabine elimination should be virtually complete within 5 to 11 hours of the start of the infusion. Gemcitabine does not accumulate when administered once weekly.

Metabolism
Gemcitabine is rapidly metabolized by cytidine deaminase in the liver, kidney, blood, and other tissues. Intracellular metabolism of gemcitabine produces the gemcitabine mono, di, and triphosphates (dFdCMP, dFdCDP, and dFdCTP) of which dFdCDP and dFdCTP are considered active. These intracellular metabolites have not been detected in plasma or urine. The primary metabolite, 2'-deoxy-2', 2' difluorouridine (dFdU), is not active and is found in plasma and urine.

Elimination
Systemic clearance ranged from 29.2 to 92.2 l/hour/m² depending on gender and age (interindividual variability was 52.2%). Clearance for women is approximately 25% lower than the values for men. Although rapid, clearance for both men and women appears to decrease with age. For the recommended gemcitabine dose of 1,000 mg/m² given as a 30-minute infusion, lower clearance values for women and men should not necessitate a decrease in the gemcitabine dose.
Urinary excretion: less than 10% is excreted as unchanged drug.
Renal clearance was 2 to 7 l/hour/m².
During the week following administration, 92 to 98% of the dose of gemcitabine administered is recovered, 99% in the urine, mainly in the form of dFdU and 1% of the dose is excreted in feces.

dFdCTP kinetics
This metabolite can be found in peripheral blood mononuclear cells and the information below refers to these cells. Intracellular concentrations increase in proportion to gemcitabine doses of 35–350 mg/m²/30-minutes, which give steady state concentrations of 0.4–5 mcg/ml. At gemcitabine plasma concentrations above 5 mcg/ml, dFdCTP levels do not increase, suggesting that the formation is saturable in these cells.
Half-life of terminal elimination: 0.7–12 hours.

dFdU kinetics
Peak plasma concentrations (3–15 minutes after end of 30-minute infusion, 1,000 mg/m²): 28–52 mcg/ml. Trough concentration following once weekly dosing: 0.07–1.12 mcg/ml, with no apparent accumulation. Triphasic plasma concentration versus time curve, mean half-life of terminal phase - 65 hours (range 33–84 hours).
Formation of dFdU from parent compound: 91%–98%.
Mean volume of distribution of central compartment: 18 l/m² (range 11–22 l/m²).
Mean steady state volume of distribution (Vss): 150 l/m² (range 96–228 l/m²).
Tissue distribution: extensive.
Mean apparent clearance: 2.5 l/hour/m² (range 1–4 l/hour/m²).
Urinary excretion: all.

Gemcitabine and paclitaxel combination therapy
Combination therapy did not alter the pharmacokinetics of either gemcitabine or paclitaxel.

Renal impairment
Mild to moderate renal insufficiency (GFR from 30 to 80 ml/minute) has no consistent, significant effect on gemcitabine pharmacokinetics.

Preclinical Safety Data:
In repeat-dose studies of up to 6 months duration in mice and dogs, the principal finding was schedule and dose-dependent hematopoietic suppression which was reversible.

Gemcitabine is mutagenic in an *in vitro* mutation test and an *in vivo* bone marrow micronucleus test. Long term animal studies evaluating the carcinogenic potential have not been performed.
In fertility studies, gemcitabine caused reversible hypospermatogenesis in male mice. No effect on the fertility of females has been detected.
Evaluation of experimental animal studies has shown reproductive toxicity e.g., birth defects and other effects on the development of the embryo or fetus, the course of gestation or peri- and postnatal development.

Indications:
Non-small cell lung cancer (NSCLC)
Gemcitabine, in combination with cisplatin, is indicated as a first line treatment of patients with locally advanced (inoperable stage IIIA or IIIB) or metastatic (stage IV) NSCLC.
Gemcitabine is indicated for the palliative treatment of adult patients with locally advanced or metastatic NSCLC.

Pancreatic cancer
Gemcitabine is indicated for the treatment of adult patients with locally advanced or metastatic adenocarcinoma of the pancreas. Gemcitabine is indicated for patients with 5-FU refractory pancreatic cancer.

Bladder cancer
Gemcitabine is indicated for the treatment of advanced bladder cancer (muscle invasive stage IV tumors with or without metastases) in combination with cisplatin therapy.

Breast cancer
Gemcitabine, in combination with paclitaxel is indicated for the treatment of patients with unresectable, locally recurrent or metastatic breast cancer who have relapsed following adjuvant/neoadjuvant chemotherapy. Prior chemotherapy should have included an anthracycline unless clinically contraindicated.

Recommended Dosage:
Non-small cell lung cancer (NSCLC)
Monotherapy
The recommended dose of gemcitabine is 1,000 mg/m², given by 30-minute intravenous infusion. This should be repeated once weekly for 3 weeks, followed by a 1-week rest period. This 4-week cycle is then repeated. Dosage reduction with each cycle or within a cycle may be applied based upon the grade of toxicity experienced by the patient.

Combination use
Gemcitabine in combination with cisplatin has been investigated using two dosing regimen. One regimen used a 3-week schedule and the other used a 4-week schedule.
The 3-week schedule used gemcitabine 1,250 mg/m², given by 30-minute intravenous infusion, on days 1 and 8 of each 21-day cycle. Dosage reduction with each cycle or within a cycle may be applied based upon the grade of toxicity experienced by the patient.
The 4-week schedule used gemcitabine 1,000 mg/m², given by 30-minute intravenous infusion, on days 1, 8, and 15 of each 28-day cycle. Dosage reduction with each cycle or within a cycle may be applied based upon the grade of toxicity experienced by the patient.
Cisplatin has been used at doses between 75–100 mg/m² once every 3 or 4 weeks.

Pancreatic cancer
Monotherapy
The recommended dose of gemcitabine is 1,000 mg/m², given by 30-minute intravenous infusion. This should be repeated once weekly for up to 7 weeks, followed by a week of rest. Subsequent cycles should consist of injections once weekly for 3 consecutive weeks out of every 4 weeks. Dosage reduction with each cycle or within a cycle may be applied based upon the grade of toxicity experienced by the patient.

Bladder cancer
Combination use
The recommended dose for gemcitabine is 1,000 mg/m², given by 30-minute infusion. The dose should be given on days 1, 8, and 15 of each 28-day cycle in combination with cisplatin. Cisplatin is given at a recommended dose of 70 mg/m² on day 1 following gemcitabine or day 2 of each 28-day cycle. This 4-week cycle is then repeated. Dosage reduction with each cycle or within a cycle may be applied based upon the grade of toxicity experienced by the patient. More myelosuppression when cisplatin was used in doses of 100 mg/m².

Breast cancer
Combination use
Gemcitabine in combination with paclitaxel is recommended using paclitaxel 175 mg/m² administered on day 1 over approximately 3 hours as an intravenous infusion, followed by gemcitabine 1,250 mg/m² as a 30-minute intravenous infusion on days 1 and 8 of each 21-day cycle. Dose reduction with each cycle or within a cycle may be applied based upon the grade of toxicity experienced by the patient.

Monitoring for toxicity and dose modification due to toxicity
Dose modification due to nonhematological toxicity
Periodic physical examination and checks of renal and hepatic function should be made to detect nonhematological toxicity. Dosage reduction with each cycle or within a cycle may be applied based upon the grade of toxicity experienced by the patient. In general, for severe (grade 3 or 4) nonhematological toxicity, except nausea/vomiting, therapy with gemcitabine should be withheld or decreased depending on the judgement of the treating physician. Doses should be withheld until toxicity has resolved in the opinion of the physician.
For cisplatin and paclitaxel dosage adjustment in combination therapy, please refer to the corresponding manufacturers' prescribing information.

Dose modification due to hematological toxicity
Initiation of a cycle
For all indications, the patient must be monitored before each dose for platelet and granulocyte counts. Patients should have an absolute granulocyte count of at least 1,500 (x 10^9/l) and platelet count of 100,000 (x 10^9/l) prior to the initiation of a cycle.

Within a cycle
Dose modifications of gemcitabine within a cycle should be performed according to the following tables:

Dose modification of gemcitabine within a cycle for NSCLC, pancreatic cancer, and bladder cancer, given in monotherapy or in combination with cisplatin

Absolute granulocyte count (x 10^9/l)		Platelet count (x 10^9/l)	Percentage of standard dose of gemcitabine (%)
>1,000	and	>100,000	100
500–1,000	or	50,000–100,000	75
<500	or	<50,000	Omit dose*

*Treatment omitted will not be reinstated within a cycle before the absolute granulocyte count reaches at least 500 (x 10^9/l) and the platelet count reaches 50,000 (x 10^9/l).

Dose modification of gemcitabine within a cycle for breast cancer, given in combination with paclitaxel

Absolute granulocyte count (x 10^9/l)		Platelet count (x 10^9/l)	Percentage of standard dose of gemcitabine (%)
≥1,200	and	>75,000	100
1,000–<1,200	or	50,000–75,000	75
700–<1,000	and	≥50,000	50
<700	or	<50,000	Omit dose*

*Treatment omitted will not be reinstated within a cycle. Treatment will start on day 1 of the next cycle once the absolute granulocyte count reaches at least 1,500 (x 10^9/l) and the platelet count reaches 100,000 (x 10^9/l).

Dose modifications due to hematological toxicity in subsequent cycles, for all indications
The gemcitabine dose should be reduced to 75% of the original cycle initiation dose, in the case of the following hematological toxicities:
- Absolute granulocyte count <500 x 10^9/l for more than 5 days.
- Absolute granulocyte count <100 x 10^9/l for more than 3 days.
- Febrile neutropenia.
- Platelets <25,000 x 10^9/l.
- Cycle delay of more than 1 week due to toxicity.

Special populations
Patients with renal or hepatic impairment
Gemcitabine should be used with caution in patients with hepatic or renal impairment as there is insufficient information to allow for clear dose recommendations for this patient populations (see **Warnings and Precautions** and **Pharmacokinetics**). Dose reduction is recommended in patients with elevated serum bilirubin concentration because such patients are at increased risk of toxicity. The toxicity was mostly related to the liver. Patients with elevated serum creatinine concentration appeared to experience increased sensitivity to gemcitabine.

Elderly population (>65 years)
Gemcitabine has been well tolerated in patients over the age of 65. There is no evidence to suggest that dose adjustments, other than those already recommended for all patients, are necessary in elderly, although gemcitabine clearance and half-life are affected by age (see **Pharmacokinetics**).

Pediatric population (<18 years)
Gemcitabine is not recommended for use in children under 18 years of age due to insufficient data on safety and efficacy.

Method of administration
Gemcitabine is tolerated well during infusion and may be administered ambulant. If extravasation occurs, generally the infusion must be stopped immediately and started again in another blood vessel. The patient should be monitored carefully after the administration.

Route of Administration:
Intravenous infusion.

Contraindications:
- Hypersensitivity to the active substance or to any of the excipients.
- Breastfeeding (see **Use during Pregnancy and Lactation**).

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Last revised: dd/mm/yyyy

Warnings and Precautions:
Prolongation of the infusion time and increased dosing frequency have been shown to increase toxicity.

Hematological toxicity
Gemcitabine can suppress bone marrow function as manifested by leukopenia, thrombocytopenia, and anemia. Patients receiving gemcitabine should be monitored prior to each dose for platelet, leukocyte, and granulocyte counts. Suspension or modification of therapy should be considered when drug-induced bone marrow depression is detected (see **Recommended Dosage**). However, myelosuppression is short lived and usually does not result in dose reduction and rarely in discontinuation. Peripheral blood counts may continue to deteriorate after gemcitabine administration has been stopped. In patients with impaired bone marrow function, the treatment should be started with caution.
As with other cytotoxic treatments, the risk of cumulative bone-marrow suppression must be considered when gemcitabine treatment is given together with other chemotherapy.

Hepatic and renal impairment
Gemcitabine should be used with caution in patients with hepatic or renal function impairment as there is insufficient information to allow clear dose recommendation for this patient population (see **Recommended Dosage**).
Administration of gemcitabine in patients with concurrent liver metastases or a pre-existing medical history of hepatitis, alcoholism, or liver cirrhosis may lead to exacerbation of the underlying hepatic impairment.
Laboratory evaluation of renal and hepatic function (including virological tests) should be performed periodically.

Concomitant radiotherapy
Concomitant radiotherapy (given together or ≤7 days apart): toxicity has been reported (see **Interactions with Other Medicines and Other Forms of Interaction** for details and recommendations for use).

Live vaccinations
Yellow fever vaccine and other live attenuated vaccines are not recommended in patients treated with gemcitabine (see **Interactions with Other Medicines and Other Forms of Interaction**).

Posterior reversible encephalopathy syndrome (PRES)
Reports of PRES with potentially severe consequences have been reported in patients receiving gemcitabine as single agent or in combination with other chemotherapeutic agents. Acute hypertension and seizure activity were reported in most gemcitabine patients experiencing PRES, but other symptoms such as headache, lethargy, confusion, and blindness could also be present. Diagnosis is optimally confirmed by magnetic resonance imaging (MRI). PRES was typically reversible with appropriate supportive measures. Gemcitabine should be permanently discontinued and supportive measures implemented, including blood pressure control and antiseizure therapy, if PRES develops during therapy.

Cardiovascular
Due to the risk of cardiac and/or vascular disorders with gemcitabine, particular caution must be exercised with patients presenting a history of cardiovascular events.

Capillary leak syndrome
Capillary leak syndrome has been reported in patients receiving gemcitabine as single agent or in combination with other chemotherapeutic agents (see **Adverse Effects**). The condition is usually treatable if recognized early and managed appropriately, but fatal cases have been reported. The condition involves systemic capillary hyperpermeability during which fluid and proteins from the intravascular space leak into the interstitium. The clinical features include generalized edema, weight gain, hypoalbuminemia, severe hypotension, acute renal impairment, and pulmonary edema. Gemcitabine should be discontinued and supportive measures implemented if capillary leak syndrome develops during therapy. Capillary leak syndrome can occur in later cycles and has been associated in the literature with acute respiratory distress syndrome.

Pulmonary
Pulmonary effects, sometimes severe (such as pulmonary edema, interstitial pneumonitis, or acute respiratory distress syndrome (ARDS)) have been reported in association with gemcitabine therapy. If such effects develop, consideration should be made to discontinuing gemcitabine therapy. Early use of supportive care measure may help ameliorate the condition.

Renal
Hemolytic uremic syndrome (HUS)
Clinical findings consistent with the HUS were rarely reported in patients receiving gemcitabine (see **Adverse Effects**). HUS is a potentially life-threatening disorder. Gemcitabine should be discontinued at the first signs of any evidence of microangiopathic hemolytic anemia, such as rapidly falling hemoglobin with concomitant thrombocytopenia, elevation of serum bilirubin, serum creatinine, blood urea nitrogen, or LDH. Renal failure may not be reversible with discontinuation of therapy and dialysis may be required.

Sodium
FONKO-GEMCITABINE lyophilized powder for solution for infusion 200 mg contains 4.66 mg (<1 mmol) sodium per vial i.e. essentially sodium free.

Effects on ability to drive and use machines
No studies on the effects on the ability to drive and use machines have been performed. However, gemcitabine has been reported to cause mild to moderate somnolence, especially in combination with alcohol consumption. Patients should be cautioned against driving or operating machinery until it is established that they do not become somnolent.

Interactions with Other Medicines and Other Forms of Interaction:
No specific drug interaction studies have been performed (see **Pharmacokinetics**).

Radiotherapy
Concurrent (given together or ≤7 days apart)
Toxicity associated with this multimodality therapy is dependent on many different factors, including dose of gemcitabine, frequency of gemcitabine administration, dose of radiation, radiotherapy planning technique, the target tissue, and target volume. Gemcitabine has radiosensitizing activity. Where gemcitabine at a dose of 1,000 mg/m² was administered concurrently for up to 6 consecutive weeks with therapeutic thoracic radiation to patients with NSCLC, significant toxicity in the form of severe, and potentially life threatening mucositis, especially esophagitis, and pneumonitis was observed, particularly in patients receiving large volumes of radiotherapy. It is feasible to administer gemcitabine at lower doses with concurrent radiotherapy with predictable toxicity, such as in NSCLC, where thoracic radiation doses of 66 Gy were applied conconitantly with an administration with gemcitabine (600 mg/m², four times) and cisplatin (80 mg/m² twice) during 6 weeks. The optimum regimen for safe administration of gemcitabine with therapeutic doses of radiation has not yet been determined in all tumor types.

Nonconcurrent (given >7 days apart)
Analysis of the data does not indicate any enhanced toxicity when gemcitabine is administered more than 7 days before or after radiation, other than radiation recall. Gemcitabine can be started after the acute effects of radiation have resolved or at least one week after radiation.
Radiation injury has been reported on targeted tissues (e.g., esophagitis, colitis, and pneumonitis) in association with both concurrent and nonconcurrent use of gemcitabine.

Others
Yellow fever and other live attenuated vaccines are not recommended due to the risk of systemic, possibly fatal, disease, particularly in immunosuppressed patients.

Use during Pregnancy and Lactation:
Pregnancy
There are no adequate data from the use of gemcitabine in pregnant women. This substance should not be used during pregnancy unless clearly necessary. Women should be advised not to become pregnant during treatment with gemcitabine and to warn their attending physician immediately, should this occur after all.

Lactation
It is not known whether gemcitabine is excreted in human milk and adverse effects on the suckling child cannot be excluded. Breastfeeding must be discontinued during gemcitabine therapy.

Fertility
Gemcitabine caused hypospermatogenesis in male mice. Therefore, men being treated with gemcitabine are advised not to father a child during and up to 6 months after treatment and to seek further advice regarding cryoconservation of sperm prior to treatment because of the possibility of infertility due to therapy with gemcitabine.

Adverse Effects:
The most commonly reported adverse drug reactions associated with gemcitabine treatment include: nausea with or without vomiting, raised liver transaminases (AST/ALT) and alkaline phosphatase; proteinuria and hematuria; dyspnea (highest incidence in lung cancer patients); allergic skin rashes and are associated with itching.

The frequency and severity of the adverse reactions are affected by the dose, infusion rate, and intervals between doses (see **Warnings and Precautions**). Dose-limiting adverse reactions are reductions in thrombocyte, leukocyte, and granulocyte counts (see **Recommended Dosage**).

Frequencies are defined as:
- Very common (≥1/10)
- Common (≥1/100 to <1/10)
- Uncommon (≥1/1,000 to <1/100)
- Rare (≥1/10,000 to <1/1,000)
- Very rare (<1/10,000)
- Not known (cannot be estimated from available data)

The following list of adverse effects within each frequency grouping is presented in order of decreasing seriousness.
Infections and infestations
- *Common:* infections.
- *Not known:* sepsis.

Blood and lymphatic system disorders
- *Very common:* leukopenia (neutropenia grade 3 and 4), bone-marrow suppression is usually mild to moderate and mostly affects the granulocyte count (see **Recommended Dosage** and **Warnings and Precautions**), thrombocytopenia, anemia.
- *Common:* febrile neutropenia.
- *Very rare:* thrombocytosis, thrombotic microangiopathy.

Immune system disorders
- *Very rare:* anaphylactoid reaction.

Metabolism and nutrition disorders
- *Common:* anorexia.

Nervous system disorders
- *Common:* headache, insomnia, somnolence.
- *Uncommon:* cerebrovascular accident.
- *Very rare:* posterior reversible encephalopathy syndrome (see **Warnings and Precautions**).

Cardiac disorders
- *Uncommon:* arrhythmias, predominantly supraventricular in nature, heart failure.
- *Rare:* myocardial infarction.

Vascular disorders
- *Rare:* clinical signs of peripheral vasculitis and gangrene, hypotension.
- *Very rare:* capillary leak syndrome (see **Warnings and Precautions**).

Respiratory, thoracic, and mediastinal disorders
- *Very common:* dyspnea (usually mild and passes rapidly without treatment).
- *Common:* cough, rhinitis.
- *Uncommon:* interstitial pneumonitis (see **Warnings and Precautions**), bronchospasm (usually mild and transient but may require parenteral treatment).
- *Rare:* pulmonary edema, acute respiratory distress syndrome (see **Warnings and Precautions**).

Gastrointestinal disorders
- *Very common:* vomiting, nausea.
- *Common:* diarrhea, stomatitis and ulceration of the mouth, constipation.
- *Very rare:* ischemic colitis.

Hepatobiliary disorders
- *Very common:* elevation of liver transaminases (AST and ALT) and alkaline phosphatase.
- *Common:* increased bilirubin.
- *Uncommon:* serious hepatotoxicity, including liver failure and death.
- *Rare:* increased gamma-glutamyl transferase (GGT).

Skin and subcutaneous tissue disorders
- *Very common:* allergic skin rash frequently associated with pruritus, alopecia.
- *Common:* itching, sweating.
- *Rare:* severe skin reactions, including desquamative and bullous skin eruptions, ulceration, vesicle and sore formation, scaling.
- *Very rare:* toxic epidermal necrolysis, Stevens-Johnson syndrome.
- *Not known:* pseudocellulitis.

Musculoskeletal and connective tissue disorders
- *Common:* back pain, myalgia.

Renal and urinary disorders
- *Very common:* hematuria, mild proteinuria.
- *Uncommon:* renal failure (see **Warnings and Precautions**), hemolytic uremic syndrome (see **Warnings and Precautions**).

General disorders and administration site conditions
- *Very common:* influenza-like symptoms (the most common symptoms are fever, headache, chills, myalgia, asthenia, and anorexia). Cough, rhinitis, malaise, perspiration, and sleeping difficulties have also been reported. Edema/peripheral edema including facial edema. Edema is usually reversible after stopping treatment.
- *Common:* fever, asthenia, chills.
- *Rare:* injection site reactions (mainly mild in nature).

Injury, poisoning, and procedural complications
- *Rare:* radiation toxicity (see **Interactions with Other Medicines and Other Forms of Interaction**), radiation recall.

Combination use in bladder cancer
The adverse effects of combination use in bladder cancer are as follows:
- Anemia
- Thrombocytopenia
- Nausea and vomiting
- Diarrhea
- Infection
- Stomatitis.

Combination use in breast cancer
The frequency of grade 3 and 4 hematological toxicities, particularly neutropenia, increases when gemcitabine is used in combination with paclitaxel. However, the increase in these adverse effects is not associated with an increased incidence of infections or hemorrhagic events. Fatigue and febrile neutropenia occur more frequently when gemcitabine is used in combination with paclitaxel. Fatigue, which is not associated with anemia, usually resolves after the first cycle.
The adverse effects of combination use in breast cancer are as follows:
- Anemia
- Thrombocytopenia
- Neutropenia
- Febrile neutropenia
- Fatigue
- Diarrhea
- Motor neuropathy
- Sensory neuropathy.

Overdose and Treatment:
There is no known antidote for overdose of gemcitabine. Doses as high as 5,700 mg/m² have been administered by intravenous infusion over 30-minutes every 2 weeks with clinically acceptable toxicity. In the event of suspected overdose, the patient should be monitored with appropriate blood counts and receive supportive therapy, as necessary.

Incompatibilities:
This medicinal product must not be mixed with other medicinal products except those mentioned in **Instructions for Use and Handling and Disposal**.

Shelf Life After Reconstitution:
FONKO-GEMCITABINE lyophilized powder for solution for infusion 200 mg is chemically and physically stable during in-use stability study in 0.9% NaCl for up to 24 hours at a concentration 38 mg/ml stored at 30±2°C, in an appropriately controlled aseptic environment. From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at room temperature, unless reconstitution (and further dilution, if applicable) has taken place in controlled and validated aseptic conditions. Solutions of reconstituted gemcitabine should not be refrigerated, as crystallization may occur.

Instructions for Use and Handling and Disposal:
Handling
The normal safety precautions for cytostatic agents must be observed when preparing and disposing of the infusion solution. Handling of the solution for infusion should be done in a safety box and protective coats and gloves should be used. If no safety box is available, the equipment should be supplemented with a mask and protective glasses.
If the preparation comes into contact with the eyes, this may cause serious irritation. The eyes should be rinsed immediately and thoroughly with water. If there is lasting irritation, a doctor should be consulted. If the solution is spilled on the skin, rinse thoroughly with water.

Instructions for reconstitution (and further dilution, if performed)
The only approved diluent for reconstitution of gemcitabine sterile powder is sodium chloride 9 mg/ml (0.9%) solution for injection (without preservatives). Due to solubility considerations, the maximum concentration for gemcitabine upon reconstitution is 40 mg/ml. Reconstitution at concentrations greater than 40 mg/ml may result in incomplete dissolution, and should be avoided.
- Use aseptic technique during the reconstitution and any further dilution of gemcitabine for intravenous infusion administration.
- To reconstitute, add 5 ml of sterile sodium chloride 9 mg/ml (0.9%) solution for injection, without preservative, to the 200 mg vial. The total volume after reconstitution is 5.26 ml. This yields a gemcitabine concentration of 38 mg/ml, which includes accounting for the displacement volume of the lyophilized powder. Shake to dissolve. Further dilution with sterile sodium chloride 9 mg/ml (0.9%) solution for injection, without preservative can be done. Reconstituted solution is clear, colorless to light straw-colored, free from visible particles.
- Parenteral medicinal products should be inspected visually for particulate matter and discoloration prior to administration. If particulate matter is observed, do not administer.

Any unused product or waste material should be disposed of in accordance with local requirements.

Presentation and Registration Number:
1 vial x 200 mg (10 ml USP Type I clear glass vial with chlorobutyl rubber stopper and flip off 20 mm blue aluminium seal); SINXXXXXX

ON MEDICAL PRESCRIPTION ONLY.

STORE AT TEMPERATURES BELOW 30°C.

RETAIN IN THE ORIGINAL PACKAGE.

CYTOTOXIC DRUG

Manufactured by
PT FONKO INTERNATIONAL PHARMACEUTICALS
Kawasan Industri Jababeka II
Jl. Industri Selatan V Blok PP No. 7
Cikarang Selatan
Bekasi-Indonesia

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