

Data Sheet

GEMCITABINE EBEWE

Gemcitabine (as hydrochloride) 200mg/20mL, 500mg/50mL and 1000mg/100mL injection vials

Name of the medicine

Gemcitabine hydrochloride

Description

Gemcitabine hydrochloride is 2'-deoxy-2',2'-difluorocytidine monohydrochloride (β -isomer). The empirical formula for gemcitabine hydrochloride is $C_9H_{11}F_2N_3O_4 \cdot HCl$. It has a molecular weight of 299.66.

Gemcitabine is a white to off-white solid. Gemcitabine is an acidic compound. The free base is soluble in water, slightly soluble in methanol, and practically insoluble in ethanol and polar organic solvents.

Gemcitabine Ebewe is a sterile, clear, colourless, solution containing 10mg/mL gemcitabine hydrochloride in vial containing 200mg, 500mg or 1000mg of gemcitabine for intravenous use.

In addition to the active ingredient gemcitabine hydrochloride, Gemcitabine Ebewe also contains sodium acetate, sodium hydroxide (for pH adjustment), and water for injections.

Pharmacology

Pharmacodynamics

Gemcitabine Ebewe is a nucleoside analogue that exhibits antitumour activity.

Gemcitabine (dFdC) is metabolised intracellularly by nucleoside kinases to the active diphosphate (dFdCDP) and triphosphate (dFdCTP) nucleosides. The cytotoxic action of gemcitabine appears to be due to inhibition of DNA synthesis by two actions of dFdCDP and dFdCTP. First, dFdCDP inhibits ribonucleotide reductase which is uniquely responsible for catalysing the reactions that generate the deoxynucleoside triphosphates for DNA synthesis. Inhibition of this enzyme by dFdCDP causes a reduction in the concentrations of deoxynucleosides in general, and especially in that of dCTP. Secondly, dFdCTP competes with dCTP for incorporation into DNA. Likewise, a small amount of gemcitabine may also be incorporated into RNA. Thus, the reduction in the intracellular concentration of dCTP potentiates the incorporation of dFdCTP into DNA (self-potential). DNA polymerase epsilon is essentially unable to remove gemcitabine and 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 then appears to induce the programmed cellular death process known as apoptosis.

Pharmacokinetics

The pharmacokinetics of gemcitabine have been examined in 353 patients in seven studies. The 121 women and 232 men ranged in age from 29 to 79 years. Of these patients, approximately 45% had non-small cell lung cancer and 35% were diagnosed with pancreatic cancer. The following pharmacokinetic parameters were obtained for doses ranging from 500 to 2,592 mg/m² that were infused from 0.4 to 1.2 hours.

Peak Plasma Concentrations (obtained within 5 minutes of the end of the infusion): 3.2 to 45.5 micrograms/mL. Volume of Distribution of the Central Compartment: 12.4 L/m² for women and 17.5 L/m² for men (inter-individual variability was 91.9%). Volume of Distribution of the Peripheral Compartment: 47.4 L/m². The volume of the peripheral compartment was not sensitive to gender. Plasma Protein Binding: negligible. Systemic Clearance: ranged from 29.2 L/hr/m² to 92.2 L/hr/m² depending on gender and age (inter-individual 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 1000 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: 2 to 7 L/hr/m². Half-Life: 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 metabolised 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.

dFdCTP Kinetics

This metabolite can be found in peripheral blood mononuclear cells and the information below refers to these cells. Half-life of terminal elimination: 0.7 to 12 hours. Intracellular concentrations increase in proportion to gemcitabine doses of 35 to 350 mg/m²/30 min, which give steady state concentrations of 0.4 to 5 micrograms/mL. At gemcitabine plasma concentrations above 5 micrograms/mL, dFdCTP levels do not increase, suggesting that the formation is saturable in these cells. Parent plasma concentrations following a dose of 1000 mg/m²/30 min are greater than 5 micrograms/mL for approximately 30 minutes after the end of the infusion, and greater than 0.4 micrograms/mL for an additional hour.

dFdU Kinetics

Peak plasma concentrations 3 to 15 minutes after end of 30-minute infusion (1000 mg/m²): 28 to 52 micrograms/mL. Trough concentration following once weekly dosing: 0.07 to 1.12 micrograms/mL, with no apparent accumulation. Triphasic plasma concentration versus time

curve, mean half-life of terminal phase: 65 hours (range 33 to 84 hr). Formation of dFdU from parent compound: 91% to 98%.

Mean volume of distribution of central compartment: 18 L/m² (range 11 to 22 L/m²). Mean steady state volume of distribution (V_{ss}): 150 L/m² (range 96 to 228 L/m²). Tissue distribution: extensive. Mean apparent clearance: 2.5 L/hr/m² (range 1 to 4 L/hr/m²). Urinary excretion: all.

Overall Elimination: amount recovered in one week: 92% to 98%, of which 99% is dFdU, 1% of the dose is excreted in faeces.

Indications

Non-Small Cell Lung Cancer: Gemcitabine Ebewe, alone or in combination with cisplatin, is indicated for the first line treatment of patients with locally advanced or metastatic non-small cell lung cancer.

Pancreatic Cancer: Gemcitabine Ebewe is indicated for treatment of patients with locally advanced or metastatic adenocarcinoma of the pancreas. Gemcitabine Ebewe is indicated for patients with 5-FU refractory pancreatic cancer. Patients treated with Gemcitabine Ebewe may derive improvement in survival, significant clinical benefit, or both.

Bladder Cancer: gemcitabine is indicated for the treatment of patients with bladder cancer.

Breast Cancer: Gemcitabine Ebewe, in combination with paclitaxel, is indicated for the first line treatment of patients with unresectable, locally recurrent or metastatic breast cancer who have relapsed following adjuvant/neoadjuvant chemotherapy, containing anthracycline, unless clinically contraindicated.

Ovarian Cancer: Gemcitabine Ebewe in combination with carboplatin, is indicated for the treatment of patients with recurrent epithelial ovarian carcinoma who have relapsed following platinum-based therapy.

Contraindications

Gemcitabine is contraindicated in those patients with a known hypersensitivity to the medicine or any of the excipients in the medicinal product.

Gemcitabine is contraindicated in pregnancy (see Precautions)

Warnings and Precautions

Prolongation of the infusion time and increased dosing frequency have been shown to increase toxicity. Gemcitabine can suppress bone marrow function as manifested by leukopenia, thrombocytopenia and anaemia. However, myelosuppression is short-lived and usually does not result in dose reductions and rarely in discontinuation (*see* Dosage and Administration and Adverse Effects-Haematological).

General

Patients receiving therapy with gemcitabine must be monitored closely. Laboratory facilities should be available to monitor patient status. Treatment for a patient compromised by medicine toxicity may be required.

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.

Pulmonary

Interstitial pneumonitis together with pulmonary infiltrates has been seen in less than 1% of the patients. In such cases, Gemcitabine Ebewe treatment must be stopped. Steroids may relieve the symptoms in such situations. Severe rarely fatal pulmonary effects, such as pulmonary oedema, interstitial pneumonitis and acute respiratory distress syndrome (ARDS) have been reported as less common or rare. In such cases, cessation of Gemcitabine Ebewe treatment is necessary. Starting supportive treatment at an early stage may improve the situation.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term duration animal studies have not been conducted to evaluate the carcinogenic potential of gemcitabine. Cytogenetic damage has been produced by gemcitabine in an *in vivo* assay. Gemcitabine induced forward mutation *in vitro* in a mouse lymphoma (L5178Y) assay. Gemcitabine causes a reversible, dose- and schedule-dependent hypospermatogenesis in male mice. Although animal studies have shown an effect of gemcitabine on male fertility, no effect has been demonstrated on female fertility. 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.

Use in Pregnancy and Lactation

Pregnancy

Category D. Because of the potential for abnormalities with cytotoxic therapy, particularly during the first trimester, gemcitabine must not be used during pregnancy. Studies in experimental animals (mice and rabbits at doses up to 4.5 and 1.6 mg/m²/day IV respectively, administered during the period of organogenesis) have shown teratogenicity and embryotoxicity. Peri- and postnatal studies in mice at doses up to 4.5 mg/m²/day have shown retarded physical development in the offspring. Women of childbearing age receiving gemcitabine should be advised to avoid becoming pregnant, and to inform the treating physician immediately should this occur.

Use in Lactation

It is not known whether gemcitabine is excreted in human milk and adverse effects on the suckling child cannot be excluded. However, studies in lactating rats have shown gemcitabine and/or its metabolites in the milk 10 minutes after an IV dose to the dam. The use of gemcitabine should be avoided in nursing women because of the potential hazard to the infant.

Usage in Children

See Dosage and administration

Patients with Renal and Hepatic Impairment - *see* Dosage and Administration

Gemcitabine should be used with caution in patients with impaired renal function or hepatic insufficiency. No studies have been done in patients with significant renal or hepatic impairment. The patient must be advised of the lack of information in patients with significant renal or hepatic impairment.

Effects on the 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

Radiotherapy

Concurrent (given together or less than or equal to 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. Pre-clinical and clinical studies have shown that gemcitabine has radiosensitising activity.

In a single trial, where gemcitabine at a dose of 1000 mg/m² was administered concurrently for up to 6 consecutive weeks with therapeutic thoracic radiation to patients with non-small cell lung cancer, 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 (median treatment volumes 4795 cm³). Studies done subsequently have suggested that it is feasible to administer gemcitabine at lower doses with concurrent radiotherapy with predictable toxicity, such as a phase II study in non-small cell lung cancer. Thoracic radiation doses of 66Gy were administered 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 tumour types.

Radiation injury has been reported on targeted tissues (e.g. oesophagitis, colitis, and pneumonitis) in association with both concurrent and non-concurrent use of gemcitabine.

When given in combination with paclitaxel, cisplatin or carboplatin, the pharmacokinetics of gemcitabine were not altered. Gemcitabine had no effect on paclitaxel pharmacokinetics.

Live vaccinations. Yellow fever vaccine and other live attenuated vaccines are not recommended in patients treated with gemcitabine, due to the risk of systemic, possible fatal disease particularly in immunosuppressed patients.

Sequential (given >7 days apart)

Available information does not indicate any enhanced toxicity with administration of gemcitabine in patients who received prior radiation, other than radiation recall. Data suggest that gemcitabine can be started after the acute effects of radiation have resolved or at least one week after radiation. Available information does not indicate any enhanced toxicity from radiation therapy following gemcitabine exposure.

Laboratory Tests

Therapy should be started cautiously in patients with compromised bone marrow function. As with other oncolytics, the possibility of cumulative bone marrow suppression when using combination or sequential chemotherapy should be considered.

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 medicine-induced marrow depression is detected (*see* Dosage and Administration). However myelosuppression is short lived and usually does not result in dose reduction and rarely in discontinuation. For guidelines regarding dose modifications see Dosage and Administration.

Peripheral blood counts may continue to fall after the medicine is stopped. Laboratory evaluation of renal and hepatic functions should be performed periodically.

Raised liver transaminases (aspartate aminotransferase (AST) and / alanine aminotransferase (ALT)) and alkaline phosphatase are seen in approximately 60% of the patients. These increases are usually mild, transient and not progressive, and seldom lead to cessation of treatment (see Adverse Effects). Increased bilirubin (WHO toxicity degrees 3 and 4) was observed in 2.6% of the patients. Gemcitabine should be given with caution to patients with impaired hepatic function.

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 insufficiency.

A few cases of renal failure, including haemolytic uraemic syndrome have been reported (see Adverse Effects). Gemcitabine should be administered with caution to patients with impaired renal function. Gemcitabine Ebewe treatment should be withdrawn if there is any sign of microangiopathic haemolytic anaemia, such as rapidly falling haemoglobin levels with simultaneous thrombocytopenia, elevation of serum bilirubin, serum creatinine, urea or LDH. Renal failure may be irreversible despite withdrawal of the Gemcitabine Ebewe treatment and may require dialysis.

Adverse Effects

The most commonly reported adverse medicine reactions associated with Gemcitabine Ebewe treatment include nausea with or without vomiting; raised liver transaminases (AST/ALT) and alkaline phosphatase, reported in approximately 60% of patients; proteinuria and haematuria reported in approximately 50% of patients; dyspnoea reported in 10 to 40% of patients (highest incidence in lung cancer patients); and allergic skin rashes, which occur in approximately 25% of patients and are associated with itching in 10% of patients.

The frequency and severity of the adverse effects are affected by the dose, infusion rate and intervals between doses (see Precautions). Dose limiting adverse effects are reductions in platelet, leucocyte and granulocyte counts (see Dosage and Administration, Dose reduction).

Slightly higher frequencies of serious adverse events were observed in females, reflecting the gender differences in pharmacokinetic parameters (see Pharmacology, Pharmacokinetics). However, the pattern was inconsistent, with some events being more frequently reported for males than females. In analysis of World Health Organization (WHO) toxicity no important differences were observed, although slightly higher frequencies of haematological toxicity were found in females.

(Frequencies. *Very common*: greater than or equal to 10%; *common*: greater than or equal to 1% and < 10%; *uncommon*: greater than or equal to 0.1% and < 1%; *rare*: greater than or equal to 0.01% and < 0.1%; *very rare*: < 0.01%.)

Blood and lymphatic system disorders

Very common: Leucopenia, thrombocytopenia, anaemia, (neutropenia grade 3 = 19.3%; grade 4 = 6%).

Common: Febrile neutropenia.

Very rare: Thrombocytosis.

Immune system disorders

Very rare: Anaphylactoid reaction (see Contraindications).

Nervous system disorders

Common: Insomnia, somnolence.

Uncommon: Cerebrovascular accident.

Cardiac disorders

Rare: Myocardial infarction, heart failure, arrhythmia (predominantly supraventricular in nature).

Vascular disorders

Rare: Hypotension.

Very rare: Clinical signs of peripheral vasculitis and gangrene.

Respiratory, thoracic and mediastinal disorders

Very common: Dyspnoea.

Uncommon: Pulmonary oedema; bronchospasm; interstitial pneumonitis (see Precautions).

Rare: ARDS (see Precautions).

Gastrointestinal disorders

Very common: Nausea, vomiting.

Common: Diarrhoea, constipation, stomatitis and ulceration of the mouth.

Very rare: Ischaemic colitis.

Hepatobiliary disorders

Very common: Elevation of liver transaminases (AST/ALT) and alkaline phosphatase (see Precautions).

Common: Increased bilirubin (see Precautions).

Uncommon: Serious hepatotoxicity (including liver failure and death).

Rare: Elevation of gamma-glutamyl transferase (GCT).

Skin and subcutaneous tissue disorders

Very common: Allergic skin rash, frequently associated with pruritus.

Common: Alopecia, ulceration of mucous membrane of the mouth, itching.

Rare: Scaling, vesicle and sore formation, ulceration.

Very rare: Severe skin reactions including desquamation and bullous skin eruptions, Toxic epidermal necrolysis, Stevens-Johnson syndrome.

Musculoskeletal and connective tissue disorders

Common: Back pain.

Renal and urinary disorders

Very common: Mild proteinuria, haematuria.

Rare: Renal failure, haemolytic uraemic syndrome (see Precautions).

General disorders and administration site conditions

Very common: Oedema/ peripheral oedema, influenza-like symptoms; most commonly fever, headache, back pain, shivering, muscle pain, asthenia and anorexia. Cough, rhinitis, perspiration, malaise and sleeping difficulties have also been reported.

Common: Fever, asthenia.

Rare: Injection site reactions (mainly mild in nature).

Very rare: Facial oedema.

Injury, poisoning and procedural complications

Radiation toxicity and radiation recall (see Interactions).

Gemcitabine plus cisplatin

An increase was seen in the following grade 3 and 4 events (gemcitabine + cisplatin versus MVAC (methotrexate, vinblastine, doxorubicin and cisplatin)) as shown in Table 2.

Table 2

	Gemcitabine + cisplatin		MVAC	
	Grade 3	Grade 4	Grade 3	Grade 4
Haematological toxicity				
Haemoglobin	24%	4%	16%	2%
Platelets	29%	29%	8%	13%
Nonhaematological toxicity				
Diarrhoea	3%	0	8%	1%
Infection	2%	1%	10%	5%

Nausea and vomiting	22%	0	19%	2%
Stomatitis	1%	0	18%	4%

MVAC = methotrexate, vinblastine, Adriamycin, cisplatin

Gemcitabine plus paclitaxel

An increase was seen in the following grade 3 and 4 events (gemcitabine + paclitaxel versus paclitaxel alone) as shown in Table 3.

Table 3

	Gemcitabine + paclitaxel		Paclitaxel	
	Grade 3	Grade 4	Grade 3	Grade 4
Haematological toxicity				
Haemoglobin	5.7%	1.1%	1.9%	0.4%
Neutrophils/granulocytes	31.3%	17.2%	4.2%	6.6%
Platelets	5.3%	0.4%	0	0
Nonhaematological toxicity				
Diarrhoea	3.1%	0	1.9%	0
Fatigue	5.7%	0.8%	1.2%	0.4%
Febrile neutropenia	4.6%	0.4%	1.2%	0

Gemcitabine plus carboplatin

An increase was seen in the following grade 3 and 4 events (gemcitabine + carboplatin versus carboplatin alone) as shown in Table 4.

Table 4

	Gemcitabine+carboplatin		Carboplatin	
	Grade 3	Grade 4	Grade 3	Grade 4
Haematological toxicity				
Haemoglobin	22.3%	5.1%	5.7%	2.3%
Neutrophils	41.7%	28.6%	10.9%	1.1%
Platelets	30.3%	10.3%	4.6%	1.1%
Nonhaematological toxicity				
Febrile neutropenia	1.1%	0	0	0
Haemorrhage	1.8%	0	0	0
Infection without neutropenia	0.6%	0	0	0

Toxicity

In repeat dose studies of up to six months' duration in mice and dogs, the principal finding was haemopoietic suppression. These effects were related to the cytotoxic properties of the medicine and were reversible when treatment was withdrawn. The degree of the effect was schedule and dose dependent.

Dosage and Administration

Gemcitabine is for intravenous use only.

Standard Dosing

Non-Small Cell Lung Cancer:(Single-agent Use): Adults - the recommended dose of gemcitabine is 1000 mg/m², given by 30-minute intravenous infusion. This should be repeated once weekly for three weeks, followed by a one-week rest period. This four-week cycle is then repeated. Dosage reduction with each cycle or within a cycle may be applied based upon the amount of toxicity experienced by the patient.

Non-Small Cell Lung Cancer: (Combination Use): Adults- gemcitabine in combination with cisplatin has been investigated using two dosing regimens. One regimen used a three-week schedule and the other used a four-week schedule.

The three-week schedule used gemcitabine 1250 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 amount of toxicity experienced by the patient.

The four-week schedule used gemcitabine 1000 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 amount of toxicity experienced by the patient.

Pancreatic Cancer: Adults - the recommended dose of gemcitabine is 1000 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 amount of toxicity experienced by the patient.

Bladder Cancer: (Single agent use): Adults - the recommended dose of gemcitabine is 1250 mg/m², given by 30-minute intravenous infusion. The dose should be given on days 1, 8 and 15 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 amount of toxicity experienced by the patient.

Bladder Cancer: (Combination use): Adults - the recommended dose for gemcitabine is 1000 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 amount of toxicity experienced by the patient. A clinical trial showed more myelosuppression when cisplatin was used in doses of 100 mg/m².

Breast Cancer: (Combination Use): Adults- 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 (1250 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 amount of toxicity experienced by the patient. Patients should have an absolute granulocyte count of at least 1,500 (x10⁶/L) prior to initiation of gemcitabine + paclitaxel combination.

Ovarian Cancer: (Combination use): Adults- Gemcitabine in combination with carboplatin is recommended using gemcitabine 1000 mg/m² administered on days 1 and 8 of each 21-day cycle as a 30-minute intravenous infusion. After gemcitabine, carboplatin should be given on day 1 consistent with target AUC of 4.0 mg/mL/min. Dosage reduction with each cycle or within a cycle may be applied based upon the amount of toxicity experienced by the patient.

Monitoring, Dose Adjustment or Titration, Methods of Terminating Treatment

Patients receiving gemcitabine should be monitored prior to each dose for platelet, leukocyte and granulocyte counts and, if necessary, the dose of gemcitabine may be either reduced or withheld in the presence of haematological toxicity, according to the following scale:

Absolute granulocyte count (x 10⁶/L)	Platelet count (x 10⁶/L)	% of full dose
>1000	and >100,000	100
500 to 1000	or 50,000 to 100,000	75
<500	or <50,000	hold

Periodic physical examination and checks of renal and hepatic function should be made to detect non-haematologic toxicity. Dosage reduction with each cycle or within a cycle may be applied based on the amount of toxicity experienced by the patient. Doses should be withheld until toxicity has resolved in the opinion of the physician. Gemcitabine is well tolerated during the infusion, with only a few cases of injection site reaction reported. There have been no reports of injection site necrosis. Gemcitabine can be easily administered on an outpatient basis.

Elderly Patients

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

Renal and Hepatic Impairment

Gemcitabine should be used with caution in patients with impaired renal function or hepatic insufficiency, as there is insufficient information from clinical studies to allow clear recommendation for this patient population.

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 insufficiency. Dose reduction is recommended in patients with elevated serum bilirubin concentration because such patients are at increased risk of toxicity. In a study of cancer patients with elevated serum bilirubin concentrations (median 50 micromol/L, range 30 to 100 micromol/L) who were administered gemcitabine monotherapy, eight out of ten patients experienced toxicity at a gemcitabine dose of 950mg/m² compared with three out of eight at 800mg/m². The toxicity was mostly related to the liver.

In the same study, patients with elevated serum creatinine concentration appeared to experience increased sensitivity to gemcitabine. However, the data based on 15 patients were not sufficient to make dosing recommendations.

All combination studies involving gemcitabine and cisplatin have been performed in patients with creatinine clearance > 60mL/minute. There are no safety or pharmacokinetic data available for this combination in patients with creatinine clearance < 60mL/minute.

Clinical findings consistent with the haemolytic uremic syndrome (HUS) were rarely reported in patients receiving gemcitabine. Gemcitabine should be discontinued at the first signs of any evidence of microangiopathic haemolytic anaemia, such as rapidly falling haemoglobin 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.

Gemcitabine should be used with caution in patients with hepatic insufficiency or with impaired renal function as there is insufficient information from clinical studies to allow clear dose recommendation for this patient population.

Paediatric Use

Gemcitabine has been studied in limited Phase I and II trials in children in a variety of tumour types. These studies did not provide sufficient data to establish the efficacy and safety of gemcitabine in children.

Instructions for Use/Handling

Refer Pharmaceutical Precautions Section.

Overdosage

Contact the Poisons Information Centre on 0800 POISON or 0800 764766 for advice on management of overdose.

There is no antidote for overdosage of gemcitabine. Single doses as high as 5.7 g/m² have been administered by IV 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 should receive supportive therapy, as necessary.

Pharmaceutical Precautions

Unopened vials when stored below 25°C (do not refrigerate or freeze) have a shelf life of 24 months.

Instructions for Use/Handling

Gemcitabine Ebewe must never be given as a bolus injection. It should be administered by infusion in 0.9% sodium chloride and stored in glass, polyethylene or polyolefin containers.

Gemcitabine Ebewe contains no antimicrobial preservative. Unused portions of the undiluted solution should be discarded as soon as possible after opening. Following preparation of the

solution for infusion, it should be used as soon as practicable after preparation. If storage is necessary, hold below 25°C (do not refrigerate or freeze) for not more than 24 hours. Discard any unused portion within 24 hours of preparation. Gemcitabine Ebewe should not be refrigerated, as crystallisation may occur.

Parenteral medicines should be inspected visually for particulate matter and discolouration, prior to administration, whenever solution or container permits. Procedures for proper handling and disposal of anti-cancer medicines should be considered.

Incompatibilities

The compatibility with other medicines has not been studied.

Presentation and storage conditions

200mg in 20mL (single glass vial)
500mg in 50mL (single glass vial)
1000mg in 100mL (single glass vial)

Medicine Classification

Prescription Medicine.

Further Information

Preclinical Data

Cytotoxic Activity in Cell Culture Models

Gemcitabine exhibits significant cytotoxicity activity against a variety of cultured murine and human tumour cells. It exhibits cell phase specificity, primarily killing cells undergoing DNA synthesis (S-phase) and under certain conditions blocking the progression of cells through the G1/S-phase boundary. *In vitro* the cytotoxic action of gemcitabine is both concentration and time-dependent.

Antitumour Activity in Preclinical Models

In animal tumour models, the antitumour activity of gemcitabine is schedule-dependent. When administered daily gemcitabine causes death in animals with minimal antitumour activity. However, when an every third or fourth day dosing schedule is used, gemcitabine can be given at non-lethal doses that have excellent antitumour activity against a broad range of mouse tumours.

Preclinical Safety Data

In repeat dose studies of up to 6 months in duration in mice and dogs, the principal finding was haematopoietic suppression. These effects were related to the cytotoxic properties of the

medicine and were reversible when treatment was withdrawn. The degree of the effect was schedule and dose-dependent.

Name and Address

Pharmaco (NZ) Ltd
4 Fisher Crescent
Mt Wellington
Auckland

Date of Preparation

15 November 2011