NEW ZEALAND DATA SHEET

1. PRODUCT NAME

Gemcitabine Ebewe injection vials

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Gemcitabine Ebewe containing 10 mg/mL gemcitabine hydrochloride in vial containing 200 mg, 500 mg or 1000 mg of gemcitabine.

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.

For the full list of excipients, see Section 6.1 List of excipients.

3. PHARMACEUTICAL FORM

Gemcitabine Ebewe is a sterile, clear, colourless, solution for intravenous use.

4. CLINICAL PARTICULARS

4.1. THERAPEUTIC 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.

4.2. DOSE AND METHOD OF ADMINISTRATION

Dosage

Standard Dosing

Non-Small Cell Lung Cancer: (Single-agent Use): Adults - the recommended dose of gemcitabine is 1000 mg/m^2, 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 over used a four-week schedule.

The three-week schedule used gemcitabine 1250 mg/m^2, 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/m^2, 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/m^2, 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/m^2, 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/m^2, 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/m^2 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/m^2.

Breast Cancer: (Combination Use): Adults- gemcitabine in combination with paclitaxel is recommended using paclitaxel (175 mg/m^2) administered on Day 1 over approximately 3 hours as an intravenous infusion, followed by gemcitabine (1250 mg/m^2) 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 (x10^6/L) prior to initiation of gemcitabine + paclitaxel combination.

Ovarian Cancer: (Combination use): Adults- Gemcitabine in combination with carboplatin is recommended using gemcitabine 1000 mg/m^2 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.

Dose Adjustments

Haematological Toxicity: 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.

Patients receiving gemcitabine should have an absolute granulocyte count of at least 1.5 (x 10^9/L) and a platelet count of $\geq$ 100 (x 10^9/L) prior to initiation of a cycle. Dose modifications of gemcitabine Day 8 and/or Day 15 for haematological toxicity should be performed according

to the guidelines below (Table 1, Table 2 and Table 3).

Gemcitabine monotherapy or in combination with cisplatin:

Table 1. Dose modification of Gemcitabine on Day 8 and/or Day 15 for Gemcitabine monotherapy or in combination with Cisplatin

Absolute granulocyte count ($\times 10^9$/L)		Platelet ($\times 10^9$/L)	count % of full dose
> 1.0	and	> 100	100
0.5 to 1.0	to	50 to 100	75
< 0.5	to	< 50	Hold*
* Treatment may be reinstated on Day 1 of the next cycle.			

Gemcitabine in combination with paclitaxel:

Table 2. Dose modification of Gemcitabine on Day 8 for Gemcitabine in combination with Paclitaxel

Absolute granulocyte count ($\times 10^9$/L)		Platelet ($\times 10^9$/L)	% of Day 1 Gemcitabine dose
> 1.2	and	> 75	100
1.0 - < 1.2	or	50 - 75	75
0.7 - < 1.0	and	$\geq$ 50	50
< 0.7	or	< 50	Hold*
* Treatment may be reinstated on Day 1 of the next cycle.			

Gemcitabine in combination with carboplatin:

Table 3. Dose modification of Gemcitabine on Day 8 for Gemcitabine in combination with Carboplatin

Absolute granulocyte count ($\times 10^9$/L)		Platelet ($\times 10^9$/L)	% of Day 1 Gemcitabine dose
$\geq$ 1.5	and	$\geq$ 100	100
1.0 - < 1.5	or	75 - 99	50
< 1.0	or	< 75	Hold*
* Treatment may be reinstated on Day 1 of the next cycle.			

Other toxicity: 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.

Method of administration

Gemcitabine is for intravenous use only.

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.

Refer Section 6.4 Special precautions for storage.

Dosage adjustment in:

- Renal/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 950 mg/m^2 compared with three out of eight at 800 mg/m^2. 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 > 60 mL/minute. There are no safety or pharmacokinetic data available for this combination in patients with creatinine clearance < 60 mL/minute.

Mild to moderate renal insufficiency (GFR from 30 mL/min to 80 mL/min has no consistent, significant effect on gemcitabine pharmacokinetics).

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.

- Elderly

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.

- Paediatrics

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.

4.3. 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 Section 4.6 Fertility, pregnancy and lactation – Use in pregnancy).

4.4. SPECIAL WARNINGS AND PRECAUTIONS FOR USE

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 (see Sections 4.2 Dose and method of administration and 4.8 Undesirable 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

Severe rarely fatal pulmonary effects, such as pulmonary oedema and acute respiratory distress syndrome (ARDS) have been reported as less common or rare. Reports of haemolytic uraemic syndrome (HUS), capillary leak syndrome (CLS) and posterior reversible encephalopathy syndrome (PRES) with potentially severe consequences have been reported in patients receiving gemcitabine as single agent or in combination with other chemotherapeutic agents. These events can be related to vascular endothelial injury possibly induced by gemcitabine. 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 anti-seizure therapy, if PRES develops during therapy (see Section 4.8 Undesirable effects).

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.

Skin and Subcutaneous Tissue Disorders

Severe cutaneous adverse reactions (SCARs) including Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), and acute generalised exanthematous pustulosis (AGEP), which can be life-threatening or fatal, have been reported in association with gemcitabine treatment. Patients should be advised of the signs and symptoms and monitored closely for skin reactions. If signs and symptoms suggestive of these reactions appear, gemcitabine should be withdrawn immediately.

Use in hepatic impairment

See Section 4.2 Dose and method of 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.

Use in the elderly

No data available.

Paediatric use

See Section 4.2 Dose and method of administration.

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.

Effects on 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 Section 4.2 Dose and method of 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 Section 4.8 Undesirable 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 Section 4.8 Undesirable effects). Serious cases of thrombotic micro-angiopathy other than HUS have been reported with gemcitabine. Gemcitabine treatment should be withdrawn if there is any sign of micro-angiopathic haemolytic anaemia, such as rapidly falling haemoglobin levels with simultaneous thrombocytopenia, elevation of serum bilirubin, serum creatinine, urea or lactate dehydrogenase (LDH). Renal failure may be irreversible despite withdrawal of the gemcitabine treatment and may require dialysis.

4.5. INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Reports of posterior reversible encephalopathy syndrome (PRES) with potentially severe consequences have been reported in patients receiving gemcitabine as a single agent or in combination with other chemotherapeutic agents, including oxaliplatin, bevacizumab and cisplatin (see Section 4.4 Special warnings and precautions for use).

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/m^2 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 cm^3). 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/m^2, four times) and cisplatin (80 mg/m^2, 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.

4.6. FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

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

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/m^2/day IV respectively, administered during the period of organogenesis) have shown teratogenicity and embryotoxicity. Peri- and post-natal studies in mice at doses up to 4.5 mg/m^2/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.

4.7. 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.

4.8. UNDESIRABLE 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 Section 4.4 Special warnings and precautions for use). Dose limiting adverse effects are reductions in platelet, leucocyte and granulocyte counts (see Section 4.2 Dose and method of administration – Dose reduction).

Slightly higher frequencies of serious adverse events were observed in females, reflecting the gender differences in pharmacokinetic parameters (see Section 5.2 Pharmacokinetic properties). 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.

Previous therapy with cytotoxic agents appears to increase the frequency and severity of the leukopenia, granulocytopenia, and thrombocytopenia. Thrombocythemia is also commonly reported but no patients were discontinued for this event.

Haemtological Toxicity (see Section 4.4 Special warnings and precautions for use)

Because gemcitabine is a bone marrow suppressant, anaemia, leukopenia, and thrombocytopenia can occur as a result of administration of gemcitabine. Myelosuppression is usually mild to moderate and is more pronounced for the granulocyte count. While two-thirds of patients experience some anaemia, only 7% have haemoglobin levels drop below 8 g/100 mL. While 19% of patients received transfusions, only 0.2% of patients discontinued because of anaemia. The white blood cell (WBC) count is depressed in 61% of patients, however only

9% of patients experience WBC count below 2000 cells/mm^3 and only 0.1% discontinued for leukopenia. Sixty-four percent of patients have reduced granulocyte counts and almost 25% drop below 1000 cells/mm^3. Platelet counts are reduced in 21% of patients but only 5% of patients experience counts below 50,000 cells/mm^3 and only 0.4% of patients were discontinued due to thrombocytopenia. Previous therapy with cytotoxic agents appears to increase the frequency and severity of the leukopenia, granulocytopenia, and thrombocytopenia. There is no evidence of cumulative haematological toxicity. Anaemia is manageable with the use of conventional transfusions. Dose reduction or omission may be necessary for severe leukopenia or thrombocytopenia (see Section 4.2 Dose and method of administration). Rare cases of haemorrhage occurring simultaneously with thrombocytopenia have been reported, but were usually thought to be disease-related. Thrombocythemia is also commonly reported (7.5% of patients), but no patients were discontinued for this event.

Febrile neutropenia is commonly reported.

Thrombocytosis and thrombotic microangiopathy are very rarely reported.

Hepatic Toxicity (see Section 4.4 Special warnings and precautions for use)

Abnormalities of liver transaminase enzymes occur in about two-thirds of patients, but they are usually mild, non-progressive, and rarely necessitate stopping treatment. Less than 10% of patients experience elevations greater than 5 times normal and only 0.5% of patients were discontinued for abnormalities in liver function. One patient was discontinued for liver failure, but the assessment was complicated by a history of chronic alcoholism. Alanine transaminase (ALT) effects decline over time despite continued treatment. Elevations of alkaline phosphatase greater than 5 times normal occurred in 6.6% of patients but may have been due to bone disorders. Bilirubin values greater than 5 times normal were observed in 1.5% of patients, but ninety percent of patients had normal bilirubin levels.

Gastrointestinal

Nausea, and nausea accompanied by vomiting are each reported in about one-third of patients, respectively. This adverse event requires therapy in about 20% of patients, is rarely dose-limiting, and is easily manageable with standard antiemetics. Only 0.9% of patients report intractable vomiting and only 0.9% of patients discontinued due to nausea and vomiting. Diarrhoea and stomatitis are commonly reported. Diarrhoea (transient to tolerable) was reported by 7% of patients. Intolerable diarrhoea requiring therapy was reported in 0.5% of patients. No patients discontinued treatment because of diarrhoea.

Renal Toxicity (see Section 4.4 Special warnings and precautions for use)

Genito-Urinary

Mild proteinuria and haematuria are reported in approximately half the patients, but are rarely clinically significant, and are not usually associated with any change in serum creatinine or blood urea nitrogen. However, a few cases (0.6% of patients) of renal failure of uncertain aetiology have been reported hence gemcitabine should be used with caution in patients with impaired renal function (see Section 4.4 Special warnings and precautions for use). Rare cases (0.4%) of possible haemolytic uraemic syndrome have been reported. Cumulative renal toxicity has not been observed.

Pulmonary Toxicity (see Section 4.4 Special warnings and precautions for use)

Dyspnoea occurring within hours following gemcitabine injection is reported by approximately

10% of patients. This dyspnoea is usually mild and short-lived, rarely dose-limiting, and usually abates spontaneously without any specific therapy. The mechanism of this toxicity is unknown and the relationship to gemcitabine is not clear. Only 0.6% of patients discontinued due to dyspnoea and only 0.1% of these were believed to be medicine-related. Interstitial pneumonitis has been reported infrequently.

Allergic Toxicity

A rash is seen in approximately 25% of patients and is associated with pruritus in about 10% of patients. The rash is usually mild, not dose-limiting, and responds to local therapy. Desquamation, vesiculation, and ulceration have been reported rarely. Discontinuations for cutaneous toxicity were reported for only 0.3% of patients. Gemcitabine is well tolerated during the infusion with only a few cases of injection site reaction reported. Gemcitabine does not appear to be a vesicant. There have been no reports of injection site necrosis. Bronchospasm is usually mild and transient, but parenteral therapy may be required. Gemcitabine should not be administered to patients with a known hypersensitivity to the medicine (see Section 4.3 Contraindications).

Neurotoxicity (see Section 4.4 Special warnings and precautions for use)

Mild to moderate somnolence occurs in approximately 10% of patients. Only 0.1% of patients discontinued for somnolence. Asthenia is frequently reported with other flu symptoms (see Flu Symptoms) but is also reported as an isolated symptom. Asthenia was cause for discontinuation by 1.4% of patients. Paresthesias are reported in 3.4% of patients, but only 0.2% report these as severe.

Flu Symptoms

An entity resembling influenza is reported by approximately 20% of patients. This is usually mild, short-lived, and rarely dose-limiting with 1.5% of patients reporting this to be severe. Fever, headache, back pain, chills, myalgia, asthenia and anorexia are the most commonly reported symptoms. Cough, rhinitis, malaise, sweating and insomnia are also commonly reported. Fever and asthenia are also reported frequently as isolated symptoms. The mechanism of this toxicity is unknown. Reports received indicate that paracetamol may produce symptomatic relief. Only 0.1% of patients reported discontinuation because of the flu symptoms. The percentages of patients who discontinued for fever, malaise or myalgia are reported as 0.4%, 0.3% and 0.1%, respectively.

Oedema/Peripheral Oedema

Oedema/peripheral oedema is reported by approximately 30% of patients. Some cases of facial oedema have also been reported. Pulmonary oedema was reported infrequently (1%). Oedema/peripheral oedema is usually mild to moderate, rarely dose-limiting, is sometimes reported as painful and is usually reversible after stopping gemcitabine treatment. The mechanism of this toxicity is unknown. However, it was not associated with any evidence of cardiac, renal or hepatic failure. Oedema resulted in the discontinuation of 0.7% of patients.

Alopecia

Overall, 86.7% of patients had no hair loss at all. Minimal to moderate hair loss was reported by 13% of patients. Only 0.5% of patients reported complete but reversible alopecia.

Other Adverse Effects

The following adverse effects are also reported. Oral toxicity mainly described as soreness or erythema occurred in 7% of patients, however, this only required a liquid diet in 0.2% of patients. Mild constipation is reported by 6% of patients. A few cases of hypotension have been reported with only 0.1% of patients discontinued for this event. Irrespective of medicine causality, some cases of myocardial infarction, congestive heart failure, and arrhythmia have been reported in studies. Radiation toxicity has been reported (see Section 4.5 Interactions with other medicines and other forms of interactions). Hypersensitivity: anaphylactoid reaction has been reported very rarely.

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 4.

Table 4.

	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%

Gemcitabine plus paclitaxel

An increase was seen in the following grade 3 and 4 events (gemcitabine + paclitaxel versus paclitaxel alone) as shown in Table 5.

Table 5.

	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 6.

Table 6.

	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.

Post-marketing experience

(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: Leukopenia, thrombocytopenia, anaemia, (neutropenia grade 3 = 19.3%; grade 4 = 6%).
Common: Febrile neutropenia.
Very rare: Thrombocytosis, thombotic microangiopathy.

Immune system disorders
Very rare: Anaphylactoid reaction (see Section 4.3 Contraindications).

Nervous system disorders
Common: Insomnia, somnolence.
Uncommon: Cerebrovascular accident.
Very rare: Posterior reversible encephalopathy syndrome (PRES) (see Section 4.4 Special warnings and precautions for use).

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

Vascular disorders
Rare: Hypotension.
Very rare: Clinical signs of peripheral vasculitis, gangrene and capillary leak syndrome (see Section 4.4 Special warnings and precautions for use).

Respiratory, thoracic and mediastinal disorders
Very common: Dyspnoea.
Uncommon: Pulmonary oedema; bronchospasm; interstitial pneumonitis (see Section 4.4 Special warnings and precautions for use).

Rare: Acute respiratory distress syndrome (ARDS) (see Section 4.4 Special warnings and precautions for use).
Frequency not known: Pulmonary eosinophilia

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 Section 4.4 Special warnings and precautions for use).
Common: Increased bilirubin (see Section 4.4 Special warnings and precautions for use).
Uncommon: Serious hepatotoxicity (including liver failure and death).
Rare: Elevation of gamma-glutamyl transferase (GGT).

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.
Frequency not known: Pseudocellulitis, Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), acute generalised exanthematous pustulosis (AGEP).

Musculoskeletal and connective tissue disorders
Common: Back pain.

Renal and urinary disorders
Very common: Mild proteinuria, haematuria.
Rare: Renal failure, haemolytic uraemic syndrome (see Section 4.4 Special warnings and precautions for use).

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 Section 4.5 Interactions with other medicines and other forms of interactions).

Genito-urinary system
Very common: Mild proteinuria, haematuria.
Rare: Renal failure. 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.

Reporting suspected adverse effects

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions https://pophealth.my.site.com/carmreportnz/s/

4.9. OVERDOSE

There is no antidote for overdosage of gemcitabine. Single doses as high as 5.7 g/m^2 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.

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

5. PHARMACOLOGICAL PROPERTIES

5.1. PHARMACODYNAMIC PROPERTIES

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

Mechanism of action

Gemcitabine Ebewe is a nucleoside analogue that exhibits antitumour activity.

Gemcitabine exhibits significant cytotoxic 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 progression of cells through the GI/S-phase boundary. *In vitro* the cytotoxic action of gemcitabine is both concentration and time dependent.

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 and have excellent antitumour activity against a broad range of mouse tumours.

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-potentiation). 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.

Clinical trials

Non-Small Cell Lung Cancer (NSCLC):

Single-agent use: Four phase II single agent studies were conducted with the primary endpoint being tumour response and a secondary measure of symptomatic improvement. The studies were conducted using gemcitabine doses from 800 - 1250 mg/m^2 as a single agent. The three major studies conducted resulted in uniform response rates from 19.7 - 22.5% of evaluable patients and from 17.9 - 20.5% on an intent to treat based analysis after assessment by external peer review boards. The median response duration was 7.6 to 12.7 months, while the overall median survival (for responders and non responders) was from 8.1 to 9.2 months. The major study conducted had 3 patients (2%) achieve complete response and 30 patients (20%) experience partial response out of 151 patients. The fourth trial which was much smaller, with only a total of 34 patients. The mean effective patient dose in this smaller trial was 741 mg/m^2 which was lower than that in the 3 major studies ($\geq$ 960 mg/m^2), with a tendency towards dose reduction rather than dose incrementing. A response rate of 1 patient (3.2%) out of 31 evaluable patients was observed. The following shows an integrated summary of adverse events (events that occurred in $\geq$ 2 % of patients without causality assessment) for the 4 pivotal trials (n = 360): dyspnoea = 7.5% (27), anaemia = 6.9% (25), fever = 4.2% (15), nausea = 3.9% (14), vomiting = 3.3% (12), carcinoma of lung = 3.1% (11), pain = 2.5% (9), pneumonia = 2.5% (9), dehydration = 2.2% (8), pleural effusion = 2.2% (8) and discontinuation due to progressive disease = 53.6% (193).

Combination use: A total of 522 patients were enrolled in a phase III randomised trial to receive gemcitabine plus cisplatin (GC) (260) or single agent cisplatin (262) over a 4-week schedule. The median survival was 9.1 months (95% CI 8.3 to 10.6 months) for the GC-treated patients, which was significantly superior to cisplatin-treated patients [7.6 months (95% CI 6.5 to 8.2 months)] (p = 0.0040). The estimate of median time to disease progression was 5.6 months (95% CI of 4.6 to 6.1 months) for GC-treated patients, which was significantly superior to cisplatin-treated patients [3.7 months (95% CI 3.3 to 4.2 months)] (p = 0.0013). The overall response rate was 30.4% for GC- treated patients and 11.1% for patients treated with single agent cisplatin (p < 0.0001).

A total of 135 patients were enrolled in a phase III randomised trial to receive GC (69) or cisplatin plus etoposide (66) over a 3-week schedule. The median survival was 8.7 months (95% CI 7.7 to 10.2 months) for the GC arm and 7.2 months (95% CI 6.1 to 9.8 months) for the patients treated with cisplatin plus etoposide, which was not significantly different. The estimate of median time to disease progression was 6.9 months (95%CI of 5.0 to 8.1 months) for GC-treated patients, which was significantly superior to cisplatin plus etoposide treated patients [4.3 months (95% CI 3.5 to 4.7 months)] (p = 0.0147). The overall response rate (intent-to-treat) was 40.6% for GC-treated patients and 21.2% for patients treated with cisplatin plus etoposide (p = 0.0167).

Pancreatic Cancer:

Data from two clinical trials evaluated the use of gemcitabine in patients with locally advanced or metastatic pancreatic cancer. The first trial compared gemcitabine to 5-Fluorouracil in patients who had received no prior chemotherapy. A second trial studied the use of gemcitabine in pancreatic cancer patients previously treated with 5-Fluorouracil or a 5-Fluorouracil

containing regimen.

The primary efficacy parameter in these studies was clinical benefit response. Clinical benefit response is a measure of symptomatic improvement. When these studies were being conducted, a standard validated quality of life instrument was not available for the assessment of patients with pancreatic cancer. Clinical benefit 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 two trials. A patient was considered a clinical responder if either:

i) the patient showed a > 50% reduction in pain intensity (Memorial Pain Assessment) or analgesic consumption, or a twenty point or greater improvement in performance status (Karnofsky Performance Scale) for a period of at least four consecutive weeks, without showing any sustained worsening in any of the other parameters. Sustained worsening was defined as four consecutive weeks with either an 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 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 multicenter, prospective, single-blinded, two arm, randomised comparison of Gemcitabine and 5-Fluorouracil in patients with locally advanced or metastatic pancreatic cancer who had received no prior treatment with chemotherapy. 5-Fluorouracil was administered intravenously at a weekly dose of 600 mg/m2 for 30 minutes. The results for this randomised trial are shown in Table 7. Compared to 5-Fluorouracil, patients treated with gemcitabine had statistically significant increase in symptomatic improvement, survival and time to progressive disease (23.8% vs 4.8%).

Table 7. Summary of Gemcitabine vs. 5-Fluorouracil in pancreatic cancer

	Gemcitabine	**5-Fluorouracil**	
Number of patients	63	63	Total: 126
Stage IV disease	71.4%	76.2%	
Baseline KPS ≤ 70	69.8%	68.3%	
Clinical Response	23.8% (n=15)	4.8% (n=3_	p=0.0022
Survival			p=0.0009
Median	5.7 months	4.2 months	
6 month probability	46% (n=30)	29% (n=19)	
9 month probability	24% (n=14)	5% (n=4)	
1 year probability	18% (n=9)	2% (n=2)	
Range	0.2-18.6 months	0.4 to 15.1+ months	
Time to progressive disease			p=0.0013
Median	2.1 months	0.9 months	
Range	0.1+ to 9.4 months	0.1 to 12.0+ months	
+ = no progression of disease at last visit, still alive			

The second trial was a multicenter, open-label study of 63 patients with advanced pancreatic cancer previously treated with 5-Fluorouracil or a 5-Fluorouracil containing regimen. In this study, 27% of the 63 patients who had failed 5-Fluorouracil combinations showed, with gemcitabine a clinical benefit response and a median survival of 3.8 months.

Bladder cancer:

A total of 405 patients were randomised in a phase III trial to receive gemcitabine plus cisplatin (GC) or MVAC (methotrexate, vinblastine, adriamycin, cisplatin). Two hundred patients received GC (gemcitabine 1000 mg/m^2 on Days 1, 8 and 15; cisplatin 70 mg/m^2 on Day 2) administered intravenously over a 28-day period or MVAC (methotrexate, 30 mg/m^2 on Days 1, 15 and 22; vinblastine 3 mg/m^2 on Days 2, 15 and 22; adriamycin 30 mg/m^2 on Day 2; cisplatin 70 mg/m^2 on Day 2) administered intravenously over a 28-day period. The median overall survival was 12.8 months (95% CI 12.0 to 15.3 months) for patients treated with GC and 14.8 months (95% CI 13.2 to 17.2 months) for MVAC-treated patients, which was not statistically significantly different. The probability of surviving beyond 12 months was estimated as 57% for the GC arm and 62% for the MVAC arm. Median time to progressive disease was 7.4 months (95% CI 6.6 to 8.1 months) for GC- treated patients and 7.6 months (95% CI 6.7 to 9.1 months) for MVAC-treated patients, which was not statistically significantly different. The independently reviewed, overall response rate was 49.4%, (95% CI 41.7%-57.1%) in the GC arm and 45.7 % (95% CI 37.7 to 53.7) in the MVAC arm (p = 0.512). The median duration of response was 9.6 months (95% CI 8.0 to 10.8 months) for GC-treated patients and 10.7 months (95% CI 9.4 to 12.6 months) for MVAC-treated patients, which was not statistically significantly different.

Phase II trials were conducted using single agent gemcitabine, administered at doses of 1200 or 1250 mg/m^2 given weekly for 3 out of every 4 weeks. The response rates were 23% (95% CI 9.6 - 41.2%), 24% (95% CI 11.8 - 41.1%) and 22% (95% CI 9.8 - 38.2%). The median survivals were 9.3 months (95% CI 4.9 - 14.9 months), 12.5 months (95% CI 9.4 - 14.6 months) and 7.9 months (95% CI 5.8 - 11.6 months).

Breast cancer:

Data from a pivotal study support the use of gemcitabine in combination with paclitaxel for the treatment of patients with unresectable, locally recurrent or metastatic breast cancer who have relapsed following adjuvant anthracycline based chemotherapy. In this multicentre, open-label, randomised Phase III study, a total of 529 female patients with unresectable, recurrent or metastatic breast cancer were randomised to receive gemcitabine plus paclitaxel (GT) combination therapy (n = 266) or paclitaxel (T) monotherapy (n = 263). In the GT arm gemcitabine (1250 mg/m^2) was administered intravenously over 30 to 60 minutes on Days 1 and 8 of a 21-day cycle and paclitaxel (175 mg/m^2) was administered intravenously over 3 hours before gemcitabine on Day 1 of a 21-day cycle. In the T arm paclitaxel (175 mg/m^2) was administered intravenously over 3 hours on Day 1 of a 21-day cycle. Patients were included in the trial if they had relapsed after receiving either one anthracycline-based chemotherapy in the adjuvant/neoadjuvant setting or a non-anthracycline-based regimen in the adjuvant/neoadjuvant setting if use of an anthracycline was clinically contraindicated.

The study objectives were to compare overall survival time to documented disease progression (TtDDP), progression-free survival (PFS), response rates, duration of response and toxicities between patients treated with gemcitabine plus paclitaxel combination therapy and those treated with paclitaxel monotherapy.

The primary endpoint of the planned interim analysis was time to documented progression of disease (TtDPD). Patients who died without evidence of disease progression were excluded from this analysis. Estimates of median TtDPD were 5.4 months (95% CI, 4.6 to 6.1 months) on the GT therapy arm and 3.5 months (95% CI, 2.9 to 4.0 months) on the T arm using the earlier of the dates of disease progression, derived from either the investigator's or the

independent reviewers' assessment. The difference between the two treatment arms was statistically significant (p = 0.0013). GT also significantly improved progression-free survival by a similar amount. This endpoint accounts for not only patients with documented disease progression but also patients who died without evidence of progression.

Median Overall Survival analysis showed statistically significant improvement in the gemcitabine plus paclitaxel arm compared with the paclitaxel alone arm, as demonstrated by a longer median survival (18.6 versus 15.8 months, with hazard ratio of 0.82 (95% confidence interval [CI], 0.67 to 1.00, log- rank p = 0.05).

The overall response rates, according to the investigator assessment were 39.3% (95% CI, 33.5% to 45.2%) on the GT arm and 25.6% (95% CI, 20.3% to 30.9%) on the T arm, which was statistically significant (p = 0.0007). Overall best study response as determined by independent review for a subset of 382 patients (72% of total patients) confirmed that GT-treated patients had statistically significant improvement in overall response compared with patients treated with T monotherapy.

There were no significant treatment differences in the patient-assessed quality-of-life measures, Brief Pain Inventory and Rotterdam Symptom Checklist.

Ovarian cancer:

A total of 356 patients with advanced epithelial ovarian cancer who had failed first-line platinum-containing therapy at least 6 months after treatment discontinuation were randomised to receive gemcitabine plus carboplatin (GCb) (178) or carboplatin (Cb) (178). Patients received either GCb (gemcitabine 1000 mg/m^2 on Days 1 and 8 and carboplatin administered after gemcitabine on Day 1 with a target AUC of 4.0 mg/mL) or Cb (target AUC of 5.0 mg/mL administered on Day 1) every 21 days until disease progression or until a maximum of six cycles of treatment had been given.

Patients on the GCb arm had a statistically significant improvement in Time to Progressive Disease (TtPD) compared with those on the Cb arm (hazard ratio, 0.72; 95% CI, 0.57 to 0.90; log-rank p-value = 0.0038) with a median TtPD of 8.6 months (95% CI, 8.0 to 9.7 months) on the GCb arm versus 5.8 months (95% CI, 5.2 to 7.1 months) on the Cb arm. Patients on the GCb arm had a statistically significant improvement in Time to Treatment Failure (TtTF) compared with those on the Cb arm (hazard ratio 0.74, 95% CI, 0.60 to 0.92; log-rank p-value = 0.0072). The median TtTF was 7.0 months (95% CI, 5.8 to 8.1 months) on the GCb arm and 4.8 months (95% CI, 4.1 to 5.6 months) on the Cb arm.

Median overall survival was 18.0 months (95% CI, 16.2-20.2) for GCb arm and 17.3 months (95% CI, 15.2-19.3) for the Cb arm (hazard ratio 0.96, 95% CI 0.75 - 1.23). The trial was not powered to detect an effect on overall survival and treatments received after completion of study therapy were not balanced between arms.

5.2. PHARMACOKINETIC PROPERTIES

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/m^2 that were infused from 0.4 to 1.2 hours.

Absorption

Peak Plasma Concentrations (obtained within 5 minutes of the end of the infusion): 3.2 to 45.5 micrograms/mL.

Distribution

Volume of Distribution of the Central Compartment: 12.4 L/m^2 for women and 17.5 L/m^2 for men (inter-individual variability was 91.9%). Volume of Distribution of the Peripheral Compartment: 47.4 L/m^2. The volume of the peripheral compartment was not sensitive to gender. Plasma Protein Binding: negligible.

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/m^2/30 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/m^2/30 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/m^2): 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/m^2 (range 11 to 22 L/m^2).

Mean steady state volume of distribution (Vss): 150 L/m^2 (range 96 to 228 L/m^2).

Tissue distribution: extensive.

Excretion

Systemic Clearance: ranged from 29.2 L/hr/m^2 to 92.2 L/hr/m^2 depending on gender and age (inter-individual variability was 52.2%). These effects result in inter-patient differences in the plasma concentration of gemcitabine and its rate of elimination from the systemic circulation

(reflected by differences in half life). 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/m^2 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/m^2. 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.

Mean apparent clearance: 2.5 L/hr/m^2 (range 1 to 4 L/hr/m^2).

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.

5.3. 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.

Genotoxicity

Cytogenetic damage has been produced by gemcitabine in an *in vivo* assay. Gemcitabine induced forward mutation *in vitro* in a mouse lymphoma (L5178Y) assay.

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.

Carcinogenicity

Long-term duration animal studies have not been conducted to evaluate the carcinogenic potential of gemcitabine.

Reproductive and developmental toxicity

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 (see Section 4.6 Fertility, pregnancy and lactation).

6. PHARMACEUTICAL PARTICULARS

6.1. LIST OF EXCIPIENTS

Gemcitabine Ebewe also contains sodium acetate, sodium hydroxide (for pH adjustment), and water for injections.

6.2. INCOMPATIBILITIES

The compatibility with other medicines has not been studied.

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.

6.3. SHELF LIFE

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

6.4. SPECIAL PRECAUTIONS FOR STORAGE

If storage is necessary, hold below 25°C (do not refrigerate or freeze) for not more than 24 hours.

6.5. NATURE AND CONTENTS OF CONTAINER

200 mg in 20 mL (single glass vial)

500 mg in 50 mL (single glass vial)

1000 mg in 100 mL (single glass vial)

6.6. SPECIAL PRECAUTIONS FOR DISPOSAL

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.

Discard any unused portion within 24 hours of preparation. Gemcitabine Ebewe should not be refrigerated, as crystallisation may occur.

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

7. MEDICINE SCHEDULE

Prescription Only Medicine

8. SPONSOR

Sandoz New Zealand Limited
12 Madden Street
Auckland 1010
New Zealand
Telephone: 0800 726 369

9. DATE OF FIRST APPROVAL

04 December 2008

10. DATE OF REVISION OF THE TEXT

18 October 2024

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
All	Minor editorial changes
4.4	Addition of SCARs (SJS, TEN and AGEP) warning
4.5	Addition of PRES warning
4.8	Addition of post-marketing adverse drug reactions: Pulmonary eosinophilia, pseudocellulitis and AGEP Update to new ADR reporting website