NEW ZEALAND DATA SHEET

1. PRODUCT NAME

DBL™ Gemcitabine Injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Gemcitabine hydrochloride 43.3 mg/mL (equivalent to gemcitabine 38 mg/mL). Each vial contains gemcitabine hydrochloride. DBL Gemcitabine Injection contains no antimicrobial agent or preservatives.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for Injection.

DBL Gemcitabine Injection is a clear, colourless to light straw-coloured solution for intravenous use.

Gemcitabine hydrochloride is a white to off-white powder. 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.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Non-Small Cell Lung Cancer: gemcitabine, 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 is indicated for treatment of patients with locally advanced or metastatic adenocarcinoma of the pancreas. Gemcitabine is indicated for patients with 5-FU refractory pancreatic cancer. Patients treated with gemcitabine 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, 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, 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

DBL Gemcitabine Injection is for intravenous use only. It contains no antimicrobial agent or preservative. Product is for single use in one patient only. Discard any residue.

For instructions on reconstitution of the medicine before administration, see section 6.6.

Dosage

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 other 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 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 1500 (x 10^6/L) prior to initiation of gemcitabine and 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 a 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.

Patients receiving gemcitabine should have an absolute granulocyte count of at least 1.5 (x 10^9/L) and a platelet count of ≥ 100 (x 10^9/L) prior to initiation of a cycle. Dose modifications of gemcitabine on Day 8 and/or Day 15 for haematological toxicity should be performed according to the guidelines below (Tables 1-3).

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 (x 10^9/L)		**Platelet count (x 10^9/L)**	**% of full dose**
>1.0	and	>100	100
0.5 to 1.0	or	50 to 100	75
< 0.5	or	< 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 (x 10^9/L)		**Platelet Count (x 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	≥ 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 Count ($\times 10^9$/L)**	**% of Day 1 Gemcitabine Dose**
≥ 1.5	and	≥ 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.

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 dose recommendation for this patient population.

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 µmol/L, range 30 - 100 µmol/L) who were administered gemcitabine monotherapy, 8 out of 10 patients experienced toxicity at a gemcitabine dose of 950 mg/m^2 compared with 3 out of 8 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 was not sufficient to make dosing recommendations.

All combination studies involving gemcitabine and cisplatin have been performed in patients with creatinine clearance > 60 mL/min. 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.

Paediatric Population

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 section 6.4.

4.3 Contraindications

Gemcitabine is contraindicated in:

- Patients with a known hypersensitivity to the medicine or any of the excipients in the medicinal product.
- Pregnancy and breastfeeding (see section 4.6).

4.4 Special warnings and precautions for use

Warnings

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 section 4.2 and section 4.8).

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. In such cases, cessation of DBL Gemcitabine Injection treatment is necessary. Starting supportive treatment at an early stage may improve the situation (see section 4.8).

Interstitial pneumonitis together with pulmonary infiltrates has been seen in less than 1% of the patients. In such cases, DBL Gemcitabine Injection 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.

Precautions

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.

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). 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). Increased bilirubin (WHO toxicity degrees 3 and 4) was observed in 2.6% of the patients. DBL Gemcitabine Injection 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). Serious cases of thrombotic micro-angiopathy other than HUS have been reported with gemcitabine. DBL Gemcitabine Injection 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 DBL Gemcitabine Injection treatment and may require dialysis.

Patients with Renal and Hepatic Impairment - see section 4.2

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.

Paediatric Population

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.

4.5 Interaction with other medicines and other forms of interaction

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).

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 oesophagitis, 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.

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.

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.

4.6 Fertility, pregnancy and lactation

Fertility

Gemcitabine caused a dose and schedule dependent hypospermatogenesis in male mice (0.9 mg/m^2/day or 10.5 mg/m^2 weekly administration intraperitoneally (IP)). Although animal studies have shown an effect of gemcitabine on male fertility (1.5 mg/m^2/day IP or 30 mg/m^2 IP weekly), no effect has been seen on female fertility (up to 4.5 mg/m^2/day IV).

Pregnancy

Category D[1]

Cytotoxic agents can produce spontaneous abortion, foetal loss and birth defects. 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.

Lactation

It is not known whether gemcitabine is excreted in human milk, 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 machinery

Gemcitabine has been reported to cause mild to moderate somnolence. Patients should be cautioned against driving or operating machinery until it is established that they do not become somnolent.

4.8 Undesirable effects

Haematological Toxicity - see section 4.4

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,

[1] Drugs which have caused, are suspected to have caused or may be expected to cause, an increased incidence of human fetal malformations or irreversible damage. These drugs may also have adverse pharmacological effects. Accompanying texts should be consulted for further details.

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). 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

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

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). 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

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).

Neurotoxicity - see section 4.4

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). 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 vs MVAC (methotrexate, vinblastine, doxorubicin, and cisplatin)) as follows:

Table 4	**Gemcitabine + Cisplatin**		**MVAC**	
Haematological toxicity	**Grade 3**	**Grade 4**	**Grade 3**	**Grade 4**
Haemoglobin	24%	4%	16%	2%
Platelets	29%	29%	8%	13%
Non-haematological 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, doxorubicin, and cisplatin				

Gemcitabine plus paclitaxel: An increase was seen in the following Grade 3 and 4 events (gemcitabine + paclitaxel vs. paclitaxel alone) as follows:

Table 5	**Gemcitabine + Paclitaxel**		**Paclitaxel**	
Haematological toxicity	**Grade 3**	**Grade 4**	**Grade 3**	**Grade 4**
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%
Non-haematological 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 vs. carboplatin alone) as follows:

Table 6	**Gemcitabine + Carboplatin**		**Carboplatin**	
Haematological toxicity	**Grade 3**	**Grade 4**	**Grade 3**	**Grade 4**
Haemoglobin	22.3%	5.1%	5.7%	2.3%

Table 6		Gemcitabine + Carboplatin		Carboplatin	
	Neutrophils	41.7%	28.6%	10.9%	1.1%
	Platelets	30.3%	10.3%	4.6%	1.1%
Non-haematological 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 6 months duration in mice and dogs, the principal finding was haematopoietic suppression. These effects were related to the cytotoxic properties of the drug and were reversible when treatment was withdrawn. The degree of the effect was schedule and dose-dependent.

Post-marketing experience

Respiratory:

Very common: Dyspnoea

Uncommon: Pulmonary oedema, bronchospasm, interstitial pneumonitis (see section 4.4)

Rare: Acute respiratory distress syndrome (ARDS) (see section 4.4)

Frequency not known: Pulmonary eosinophilia

Genito-Urinary System:

Very common: Mild proteinuria, haematuria

Rare: Renal failure. Clinical findings consistent with the haemolytic uraemic 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 even with discontinuation of therapy, and dialysis may be required.

Blood and Lymphatic System Disorders:

Very common: Leukopenia, thrombocytopenia, anaemia (Neutropenia Grade 3 = 19.3%; Grade 4 = 6%)

Common: Febrile neutropenia

Very rare: Thrombocytosis, thrombotic microangiopathy

Immune System Disorders:

Very rare: Anaphylactoid reactions

Nervous System Disorders:

Common: Somnolence

Very rare: Posterior reversible encephalopathy syndrome (PRES) (see section 4.4)

Cardiovascular:

Rare: Heart failure, myocardial infarct, arrhythmias (predominantly supraventricular in nature)

Vascular:

Rare: Hypotension

Very rare: Clinical signs of peripheral vasculitis, gangrene and capillary leak syndrome (see section 4.4).

Gastrointestinal Disorders:

Very common: Nausea and vomiting

Common: Diarrhoea and constipation

Frequency not known: stomatitis.

Hepatobiliary Disorders:

Very common: Elevation of liver transaminases (AST/ALT) and alkaline phosphatase (see section 4.4).

Common: Increased bilirubin (see section 4.4).

Rare: Elevation of gamma-glutamyl transferase (GGT)

Skin and Appendages:

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).

General Disorders and Administration Site Conditions:

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

Common: Fever, asthenia

Very rare: Facial oedema

Injury, Poisoning, and Procedural Complications:

Radiation toxicity and radiation recall reactions have been reported (see section 4.4).

Reporting of suspected adverse reactions

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

Mechanism of action

Gemcitabine 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 efficacy and safety

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/m^2 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 to 18.6 months	0.4 to 15.1+ months	

Table 7: Summary of Gemcitabine vs. 5-Fluorouracil in Pancreatic Cancer			
	Gemcitabine	**5-Fluorouracil**	
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 2592 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) ranged from 3.2 to 45.5 mcg/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 was negligible. 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. The mean renal clearance is 2 - 7 $L/hr/m^2$ with less than 10% excreted as unchanged drug. 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.

Biotransformation

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 - 12 hours.

Intracellular concentrations increase in proportion to gemcitabine doses of 35 - 350 mg/m^2/30 min, which give steady state concentrations of 0.4 - 5 mcg/mL. At gemcitabine plasma concentrations above 5 mcg/mL, dFdCTP levels do not increase, suggesting that the formation is saturable in these cells. Parent plasma concentrations following a dose of 1000 mg/m^2/30 min are greater than 5 mcg/mL for approximately 30 minutes after the end of the infusion, and greater than 0.4 mcg/mL for an additional hour.

***dFdU Kinetics**:* Peak plasma concentrations (3 - 15 minutes after end of 30-minute infusion, 1000 mg/m^2): 28 - 52 mcg/mL.

Trough concentration following once weekly dosing: 0.07 - 1.12 mcg/mL, with no apparent accumulation.

Triphasic plasma concentration versus time curve, mean half life of terminal phase - 65 hours (range 33 - 84 hours).

Formation of dFdU from parent compound: 91% - 98%.

Mean volume of distribution of central compartment: 18 L/m^2 (range 11 - 22 L/m^2).

Mean steady state volume of distribution (V_{ss}): 150 L/m^2 (range 96 - 228 L/m^2).

Tissue distribution: extensive.

Elimination

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

Urinary excretion: all.

Amount recovered in one week: 92% - 98%, of which 99% is dFdU, 1% of the dose is excreted in faeces.

5.3 Preclinical safety data

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 G_1/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.

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.

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).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

- Hydrochloric acid
- Sodium hydroxide
- Water for Injection

6.2 Incompatibilities

No incompatibilities have been identified, however, it is not recommended to mix gemcitabine with other medicines.

6.3 Shelf life

Vial – Solution for injection

24 months from date of manufacture stored at 2°C to 8°C (Refrigerate, do not freeze)

Solution After Reconstitution

24 hours reconstituted stored at 2°C to 8°C (Refrigerate, do not freeze)

24 hours reconstituted (not refrigerated) stored between 15°C - 30°C

6.4 Special precautions for storage

Store at 2°C to 8°C (refrigerate, do not freeze)

6.5 Nature and contents of container

DBL Gemcitabine Injection (38 mg/mL) is available in the following presentations:

200 mg/5.3 mL vial in single packs

1 g/26.3 mL vial in single packs

2 g/52.6 mL vial in single packs

6.6 Special precautions for disposal and other handling

DBL Gemcitabine Injection may be diluted with 0.9% sodium chloride or 5% glucose solution. Each vial contains a slight excess of the labelled volume to permit withdrawal and administration of the labelled volume. The appropriate amount of medicine may be administered neat or further diluted with 0.9% sodium chloride or 5% glucose solution.

Unopened vials should be stored at 2°C to 8°C.

Solutions of diluted DBL Gemcitabine Injection can be stored at 2°C to 8°C or room temperature (15°C - 30°C) and are chemically stable for up to 24 hours. In order to reduce microbiological hazard, the product should be used as soon as practicable after preparation (within 6 hours of preparation). Preparations are for single use in one patient only. Discard unused portion.

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.

7. MEDICINE SCHEDULE

Prescription Medicine

8. SPONSOR

Pfizer New Zealand Limited
P O Box 3998
Auckland, New Zealand, 1140
Toll Free Number: 0800 736 363
www.pfizermedicalinformation.co.nz

9. DATE OF FIRST APPROVAL

22 Aug 2013

10. DATE OF REVISION OF THE TEXT

26 April 2024

™ = Trademark

Summary table of changes

Section changed	Summary of new information
4.3	Addition of pregnancy and lactation contraindications for consistency with guidance from section 4.6.
4.4	Addition of SCARs (SJS, TEN and AGEP) warning.
4.8	Addition of post-marketing adverse drug reactions: SJS, TEN and AGEP. Update to new ADR reporting website.
8	Update to sponsor web address.
All	Minor editorial changes.