DBL™ GEMCITABINE INJECTION
(Gemcitabine hydrochloride)

1. NAME OF THE MEDICINE

Gemcitabine hydrochloride

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains gemcitabine hydrochloride (38 mg/mL) and the excipients, Water for Injections, hydrochloric acid and/or sodium hydroxide. DBL Gemcitabine Injection contains no microbial agent or preservatives.

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

3. PHARMACEUTICAL FORM

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

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

DBL Gemcitabine Injection is indicated:
- for treatment of patients with locally advanced or metastatic non-small cell lung cancer (NSCLC).
- for treatment of patients with locally advanced or metastatic adenocarcinoma of the pancreas.
- for treatment of patients with 5-Fluorouracil refractory pancreatic cancer.
- alone or in combination with cisplatin, is indicated for treatment of patients with bladder cancer.
- in combination with paclitaxel, for the treatment of patients with unresectable, locally recurrent or metastatic breast cancer who have relapsed following adjuvant/neoadjuvant chemotherapy. Prior chemotherapy should have included an anthracycline unless clinically contraindicated.
- in combination with carboplatin, for the treatment of patients with recurrent epithelial ovarian carcinoma, who have relapsed > 6 months following platinum-based therapy.

4.2 Dose and Method of Administration

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

Non-small cell lung cancer:
Single-agent use:
Adults: The optimum dose schedule for gemcitabine has not been determined. 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 dose omission within a cycle may be applied based upon the amount of toxicity experienced by the patient.

Combination use:
Adults: Gemcitabine in combination with cisplatin has been investigated using two dosage 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. The three-week schedule used cisplatin 75 - 100 mg/m^2 on Day 1 of each 21-day cycle, administered before the gemcitabine dose. Dosage reduction with each cycle or dose omission 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. The four-week schedule used cisplatin 75 - 100 mg/m^2 on Day 1 of each 28-day cycle, administered after the gemcitabine dose. Dosage reduction with each cycle or dose omission 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 dose omission within a cycle may be applied based upon the amount of toxicity experienced by the patient.

Bladder cancer:
In patients with bladder cancer who cannot tolerate cisplatin-based combinations, gemcitabine monotherapy should be considered a treatment option.

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 four-week cycle is then repeated. Dosage reduction with each cycle or dose omission within a cycle may be applied based upon the amount of toxicity experienced by the patient.

Combination use:
Adults: The recommended dose for gemcitabine is 1000 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 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 four-week cycle is then repeated. Dosage reduction with each cycle or dose omission 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:
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.

Ovarian cancer:
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.

Method of administration
The approved diluents for dilution of DBL Gemcitabine Injection are 0.9% Sodium Chloride Injection without preservatives and 5% glucose infusion solution. No incompatibilities have been identified, however, it is not recommended to mix gemcitabine with other medicines.

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 Injection.

Parenteral formulations should be inspected visually for particulate matter and discolouration prior to administration, whenever solution and container permit. Solutions showing evidence of particulate matter and/or discolouration should not be used.

Procedure for proper handling and disposal of anti-cancer medicines should be considered.

Dosage adjustments
Haematological Toxicity: Patients receiving gemcitabine should be monitored prior to each dose for platelet, leucocyte and granulocyte counts and, if there is evidence of toxicity, the dose of gemcitabine should be 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		**Platelet Count**	**% of full dose**

(x 10^9/L)		(x 10^9/L)	
>1.0	and	>100	100
0.5 - 1.0	or	50 - 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 (x 10^9/L)		**Platelet Count (x 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 liver and kidney function should be made to detect non-haematological toxicity. Dosage reduction with each cycle or dose omission within a cycle may be applied based upon 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.

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

Hepatic Impairment: Gemcitabine should be used with caution in patients with 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.

Elderly Patients: Gemcitabine has been well tolerated in patients over the age of 65. There is no evidence to suggest that dose adjustments are necessary in the elderly, although gemcitabine clearance and half-life are affected by age.

Children: Gemcitabine has been studied in limited Phase 1 and 2 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:

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

4.4 Special Warnings and Precautions for Use

Prolongation of the infusion time and the increased dosing frequency have been shown to increase toxicity. In common with other cytotoxic agents, gemcitabine has demonstrated the ability to suppress the bone marrow. Leucopenia, thrombocytopenia and anaemia are expected adverse events. However, myelosuppression is short lived.

Patients receiving therapy with gemcitabine must be monitored closely. Laboratory facilities should be available to monitor drug tolerance. Resources to protect and maintain a patient compromised by drug toxicity may be required.

Severe rarely fatal pulmonary effects, such as pulmonary oedema, interstitial pneumonitis and acute respiratory distress syndrome (ARDS) have been reported as less common or rare. 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 Adverse Effects (Undesirable Effects)).

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.

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

Paediatric use
Gemcitabine has been studied in limited Phase 1 and 2 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, leucocyte and granulocyte counts. Suspension or modification of therapy should be considered when drug-induced marrow depression is detected. For guidelines regarding dose modifications (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 function 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 Adverse Effects (Undesirable Effects)). 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 Adverse Effects (Undesirable Effects)). Serious cases of thrombotic micro-angiopathy other than HUS have been reported with gemcitabine. Gemcitabine should be administered with caution to patients with impaired renal function. 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.

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 ≤ 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. 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, oesophagitis and pneumonitis was observed, particularly in patients receiving large volumes of radiotherapy [median treatment volumes 4795 cm^3]. The optimum regimen for safe administration of gemcitabine with therapeutic doses of radiation has not yet been determined.

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.

4.6 Fertility, Pregnancy and Lactation

Effects on 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).

Use in pregnancy - Category D

Category D: *Drugs which have caused, are suspected to have caused or may be expected to cause, an increased incidence of human foetal malformation or irreversible damage. These drugs may also have adverse pharmacological effects.*

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

DBL Gemcitabine Injection 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 the medicine 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 Machines

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

4.8 Adverse Effects (Undesirable Effects)

The most commonly reported adverse drug reactions associated with gemcitabine treatment include: nausea with or without vomiting; raised liver transaminases (AST/ALT) and alkaline phosphatase, reported in approximately 60% of patients; proteinuria and haematuria reported in approximately 50% patients; dyspnoea reported in 10 - 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 reactions are affected by the dose, infusion rate and intervals between doses (see Section 4.4 Special Warnings and Precautions for Use). Dose-limiting adverse reactions are reductions in platelet, leucocyte and granulocyte counts (see Section 4.2 Dose and Method of Administration - *Dosage adjustments*).

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 Organisation (WHO) toxicity, no important differences were observed, although slightly higher frequencies of haematologic toxicity were found in females.

Frequencies: Very common: ≥10%; common: ≥1% and <10%; uncommon: ≥0.1% and <1%; rare: ≥0.01% and <0.1%; very rare: <0.01%.

System Organ Class:

Blood and Lymphatic System Disorders:
Very common: Leucopenia, thrombocytopenia, anaemia, (Neutropenia Grade 3 = 19.3%; Grade 4 = 6%).
Common: Febrile neutropenia.
Very rare: Thrombocytosis, thrombotic microangiopathy.

Immune System Disorders:
Very rare: Anaphylactoid reaction (see Section 4.3 Contraindications).

Nervous System Disorders:
Common: Somnolence.
Very rare: Posterior reversible encephalopathy syndrome (see Section 4.4 Special Warnings and Precautions for Use).

Cardiac Disorders:
Rare: Myocardial infarct, heart failure, arrhythmia (predominantly supraventricular in nature).

Vascular Disorders:
Rare: Hypotension.
Very rare: Peripheral vasculitis and 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: Adult 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.
Frequency not known: stomatitis.

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).
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.

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 - 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 (see Section 4.4 Special Warnings and Precautions for Use).

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%
	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
Skin and Subcutaneous Tissue Disorders:
Severe skin reactions (Stevens Johnson syndrome [SJS], toxic epidermal necrolysis [TEN], acute generalised exanthematous pustulosis [AGEP]).

Reporting suspected adverse effects
Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions.

4.9 Overdose

The symptoms of overdosage are likely to be an extension of the pharmacological actions of gemcitabine. Possible symptoms of toxicity are those listed under Section 4.8 Adverse Effects (Undesirable Effects). Haematopoietic, gastrointestinal, hepatic or renal toxicity may be seen depending on the dosage given and the physical condition of the patient. Toxicity may be delayed and life threatening (e.g. myelosuppression).

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 two 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.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Mechanism of action
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. Second, 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. 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/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	
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. Peak plasma concentrations (obtained within 5 minutes of the end of the infusion) ranged from 3.2 to 45.5 µg/mL. 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.

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. Terminal elimination half-life: 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 µg/mL. At gemcitabine plasma concentrations above 5 µg/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 µg/mL for approximately 30 minutes after the end of the infusion, and greater than 0.4 µg/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 µg/mL.
Trough concentration following once weekly dosing: 0.07 - 1.12 µg/mL, with no apparent accumulation.
Triphasic plasma concentration versus time curve, mean half life of terminal phase: 65 hours (range 33 - 84 hr).
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 (Vss): 150 L/m^2 (range 96 - 228 L/m^2).
Tissue distribution: extensive.
Mean apparent clearance: 2.5 $L/hr/m^2$ (range 1 - 4 $L/hr/m^2$).
Urinary excretion: all.

Excretion
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

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 animal studies have not been conducted to evaluate the carcinogenic potential of gemcitabine.

6. PHARMACEUTICAL PARTICULARS

6.1 List of Excipients

Hydrochloric acid
Sodium hydroxide
Water for Injections

6.2 Incompatibilities

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

6.3 Shelf Life

The expiry date can be found on the outer carton.

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

6.4 Special Precautions for Storage

Store at 2°C to 8°C. (Refrigerate. Do not freeze.)

6.5 Nature and Contents of Container

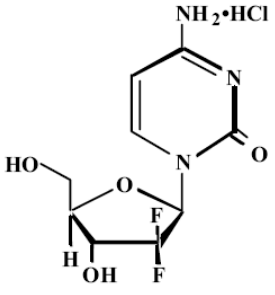
DBL Gemcitabine Injection (38 mg/mL) is a clear, colourless to light straw-coloured solution in glass vials for intravenous use that is available as:

200 mg/5.3 mL vial in single packs
1 g/26.3 mL vial in single packs

Each vial contains a slight excess of the labelled volume to permit withdrawal and administration of the labelled volume.

6.6 Physicochemical Properties

Chemical structure
Gemcitabine hydrochloride is 2'-deoxy-2', 2'-difluorocytidine monohydrochloride (beta-isomer). It has a molecular formula of $C_9H_{11}F_2N_3O_4$•HCl and molecular weight of 299.66. The chemical structure of Gemcitabine hydrochloride is shown below:



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