Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Gemcitabine 2 g Powder for Solution for Infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

One vial contains gemcitabine hydrochloride, equivalent to 2 g gemcitabine.

After reconstitution, the solution contains 38 mg/ml gemcitabine (as hydrochloride).

Excipients
Each 2 g vial contains approximately 35 mg (1.5 mmol) sodium.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Powder for solution for infusion (powder for infusion)

White to off-white plug or powder.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Bladder Cancer:
Locally advanced or metastatic bladder cancer, in combination with cisplatin.

Pancreatic Cancer:
Locally advanced or metastatic adenocarcinoma of the pancreas.

Non-Small Cell Lung Cancer:
First-line treatment of patients with locally advanced or metastatic non-small cell lung cancer, in combination with cisplatin. Gemcitabine monotherapy can be considered in elderly patients or those with performance status 2.

Ovarian Cancer:
Locally advanced or metastatic epithelial ovarian carcinoma, in combination with carboplatin, in patients with relapsed disease following a recurrence-free interval of at least 6 months after platinum-based, first line therapy.

Breast Cancer:
Unresectable, locally recurrent or metastatic breast cancer, in combination with paclitaxel, in patients experiencing a relapse after adjuvant/neoadjuvant chemotherapy. The preceding chemotherapy should have included an anthracycline, unless clinically contraindicated.

4.2 Posology and method of administration

For intravenous infusion, following reconstitution. Upon reconstitution a colourless or slightly yellow solution is produced.

Gemcitabine should only be prescribed by a physician qualified in the use of anti-cancer chemotherapy.

Bladder cancer (combination therapy):
Adults: The recommended dose for gemcitabine is 1000 mg/m^2, given as a 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 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.

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 one week rest period. Subsequent cycles should consist of gemcitabine infusions once weekly for 3 consecutive weeks out of every four weeks. 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 (monotherapy):
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 therapy):
Adults: The recommended dose of gemcitabine is 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.

Cisplatin has been used at doses between 75-100 mg/m^2 once every 3 weeks.

Ovarian cancer (combination therapy):
The recommended dose of gemcitabine, when used in combination with carboplatin, is 1000 mg/m^2, given by 30 minute intravenous infusion on days 1 and 8 of each 21 day cycle. After gemcitabine, carboplatin will be given on day 1, consistent with a target Area Under Curve (AUC) of 4.0mg/ml/min. Dosage reduction with each cycle or within a cycle may be applied, based upon the amount of toxicity experienced by the patient.

Breast cancer (combination therapy):
Adults: It is recommended that gemcitabine is used together with paclitaxel according to the following procedure:

Paclitaxel (175 mg/m^2) is intravenously infused over 3 hours on day 1, followed by gemcitabine (1250 mg/m^2) intravenously infused for 30 minutes on days 1 and 8 of each 21 day treatment cycle. Dosage reduction with each cycle or within a cycle may be applied based upon the amount of toxicity experienced by the patient. The absolute granulocyte count should be at least 1.5 x 10^9/l before treatment with the gemcitabine + paclitaxel combination.

Monitoring for toxicity and dose modification due to toxicity

Dosage adjustment due to non haematological toxicity:
Periodic physical examination and checks of renal and hepatic function should be made to detect non-haematological toxicity. Dosage reduction with each cycle or within a cycle may be applied, based upon the amount of toxicity experienced by the patient. In general, for severe (Grade 3 or 4) non-haematological toxicity, except nausea/vomiting, therapy with gemcitabine should be withheld or decreased depending on the judgement of the treating physician. Doses should be withheld until toxicity has been resolved.

For cisplatin, carboplatin, and paclitaxel dosage adjustment in combination therapy, please refer to the corresponding Summary of Product Characteristics.

Dosage adjustment in the presence of haematological toxicity:
Initiation of a cycle

For all indications, patients must be monitored before each dose for platelet and granulocyte counts. Patients should have an absolute granulocyte count of at least 1,500 (x10^6/l) and a platelet count of 100,000 (x10^6/l) prior to the administration of a cycle.

Within a cycle

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

Dose modification of gemcitabine within a cycle for bladder cancer, pancreatic cancer, and NSCLC, given in monotherapy or in combination with cisplatin			
Absolute Granulocyte Count (x 10^9/l)		**Platelet Count (x 10^9/l)**	**% of Total Dose**
> 1	and	>100	100
0.5-1	or	50-100	75
< 0.5	or	<50	Withhold*

*Withheld treatment will not be reinstated within a cycle before the absolute granulocyte count reaches at least 0.5(x 10^9/l) and the platelet count reaches 50 (x 10^9/l).

Dose modification of gemcitabine within a cycle for ovarian cancer, given in combination with carboplatin			
Absolute Granulocyte Count (x 10^9/l)		**Platelet Count (x 10^9/l)**	**% of Total Dose**
>1.5	and	>100	100
1-1.5	or	75-100	50
<1	or	<75	Withhold*

*Withheld treatment will not be reinstated within a cycle. Treatment will start on day 1 of the next cycle once the absolute granulocyte count reaches at least 1.5(x 10^9/l) and the platelet count reaches 100 (x 10^9/l) .

Dose modification of gemcitabine within a cycle for breast cancer, given in combination with paclitaxel			
Absolute Granulocyte Count (x 10^9/l)		**Platelet Count (x 10^9/l)**	**% of Total Dose**
≥1.2	and	>75	100
1-<1.2	or	50-75	75
0.7-<1	and	≥50	50
<0.7	or	<50	Withhold*

*Withheld treatment will not be reinstated within a cycle. Treatment will start on day 1 of the next cycle once the absolute granulocyte count reaches at least 1.5 (x 10^9/l) and the platelet count reaches 100 (x 10^9/l).

Dose adjustment due to haematological toxicity in subsequent cycles, for all indications

The gemcitabine dose should be reduced to 75% of the original cycle initiation dose, in the case of the following haematological toxicities:

- Absolute granulocyte count < 0.5 x 10^9/l for more than 5 days
- Absolute granulocyte count < 0.1 x 10^9/l for more than 3 days
- Febrile neutropaenia
- Platelets <25 x 10^9/l
- Cycle delay of more than one week due to toxicity

Method of administration
Gemcitabine is tolerated well during infusion and may be administered ambulant. If extravasation occurs, generally the infusion must be stopped immediately and started again in another blood vessel. The patient should be monitored carefully after the administration.
For instructions on reconstitution, see section 6.6

Special Populations

Patients with hepatic or renal impairment:
Gemcitabine should be used with caution in patients with hepatic or renal impairment as there is insufficient information from clinical studies to allow for clear dose recommendations for these patient populations (see sections 4.4 and 5.2).

Elderly population (>65 years):
Gemcitabine has been well tolerated in patients over the age of 65. There is no evidence to suggest that dose adjustments, other than those already recommended for all patients, are necessary in the elderly (see section 5.2).

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

4.3 Contraindications

Hypersensitivity to gemcitabine or to any of the excipients
Breast-feeding (see section 4.6)

4.4 Special warnings and precautions for use

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

Haematological toxicity
Gemcitabine can suppress bone marrow function as manifested by leucopaenia, thrombocytopaenia, and anaemia.

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 bone marrow depression is detected (see section 4.2). However, myelosuppression is short lived and usually does not result in dose reduction and rarely in discontinuation.

Peripheral blood counts may continue to deteriorate after gemcitabine administration has been stopped. In patients with impaired bone marrow function, the treatment should be started with caution. As with other cytotoxic treatments, the risk of cumulative bone-marrow suppression must be considered when gemcitabine treatment is given together with other chemotherapy.

Hepatic impairment
Administration of gemcitabine to patients with concurrent liver metastases or a pre-existing medical history of hepatitis, alcoholism or cirrhosis of the liver may result in exacerbation of the underlying liver impairment.

Laboratory evaluation of renal and hepatic function (including virological tests) should be performed periodically.

Gemcitabine should be used with caution in patients with hepatic insufficiency or with impaired renal function as there is insufficient information from clinical studies to allow clear dose recommendation for this patient population (see section 4.2).

Concomitant radiotherapy

Concomitant radiotherapy (given together or ≤7 days apart): Toxicity has been reported (see section 4.5 for details and recommendations for use).

Live vaccinations
Yellow fever vaccine and other live attenuated vaccines are not recommended in patients treated with gemcitabine (see section 4.5).

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

Pulmonary
Pulmonary effects, sometimes severe (such as pulmonary oedema, interstitial pneumonitis, or adult respiratory distress syndrome (ARDS), have been reported in association with gemcitabine therapy. The aetiology of these effects is unknown. If such effects develop, consideration should be given to discontinuing gemcitabine therapy. Early use of supportive care measures may help ameliorate the condition.

Renal
Clinical findings consistent with the haemolytic uraemic syndrome (HUS) were rarely reported in patients receiving gemcitabine (see section 4.8). HUS is a life-threatening disease. Treatment should be discontinued at the first signs of any evidence of micro-angiopathic haemolytic anaemia, such as rapidly falling haemoglobin levels with concurrent thrombocytopenia, elevation of serum bilirubin, serum creatinine, blood urea nitrogen or lactate dehydrogenase (LDH). Renal failure may not be reversible with discontinuation of therapy, and dialysis may be required.

Fertility
In fertility studies, gemcitabine caused hypospermatogenesis in male mice (see section 5.3). Therefore, men being treated with gemcitabine are advised not to father a child during and up to 6 months after treatment and to seek further advice regarding cryoconservation of sperm prior to treatment because of the possibility of infertility due to therapy with gemcitabine (see section 4.6).

Sodium
Gemcitabine 2 g contains 35 mg (1.5 mmol) sodium per vial. This should be taken into consideration by patients on a sodium-controlled diet.

4.5 Interaction with other medicinal products and other forms of interaction

No specific interaction studies have been performed (see section 5.2)

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.
Pre-clinical and clinical studies have shown that gemcitabine has radiosensitising activity. In a single trial, where gemcitabine at a dose of 1,000 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 4,795 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, where thoracic radiation doses of 66 Gy were applied concomitantly with an administration 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.

Non-concurrent (given >7 days apart) - Available information does not indicate any enhanced toxicity when gemcitabine is administered more than 7 days before or after 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.

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.

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

4.6 Fertility, pregnancy and lactation

Pregnancy:
There are no adequate data from the use of gemcitabine in pregnant patients. Studies in animals have shown reproductive toxicity (see section 5.3). Based on results from animal studies and the mechanism of action of gemcitabine, this substance should not be used during pregnancy, unless clearly necessary. Women should be advised not to become pregnant during treatment with gemcitabine and to warn their attending physician immediately, should this occur.

Lactation:
It is not known whether gemcitabine is excreted in human milk and adverse events on the suckling child cannot be excluded. Breast-feeding must be discontinued during gemcitabine therapy.

Fertility:
In fertility studies, gemcitabine caused hypospermatogenesis in male mice (see section 5.3). Therefore, men being treated with gemcitabine are advised not to father a child during and up to 6 months after treatment and to seek further advice regarding cryoconservation of sperm prior to treatment because of the possibility of infertility due to therapy with gemcitabine.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

The most commonly reported adverse reactions associated with gemcitabine treatment include: nausea, with or without vomiting, and raised liver transaminases ((AST/ ALT) and alkaline phosphatase, reported in approximately 60% of patients; proteinuria and haematuria reported in approximately 50% of patients; dyspnoea reported in 10-40% of patients (highest incidence in lung cancer patients); allergic skin rashes occurring 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). Dose-limiting adverse reactions are reductions in thrombocyte, leucocyte, and granulocyte counts (see section 4.2).

Clinical trial data
Frequencies are defined as: Very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000).

System Organ Class	Frequency Grouping
Blood and lymphatic system disorders	*Very common:* • Leucopenia (Neutropaenia grade 3 =19.3% ; grade 4 =6%)

	• Thrombocytopaenia • Anaemia Bone marrow suppression is usually mild to moderate and mostly affects the granulocyte count (see section 4.2) *Common:* • Febrile neutropenia *Very rare:* • Thrombocytosis
Immune system disorders	*Very Rare:* • Anaphylactoid reaction
Metabolism and nutrition disorders	*Common:* • Anorexia
Nervous system disorders	*Common:* • Headache • Insomnia • Somnolence ***Uncommon*** Cerebrovascular accident
Cardiac disorders	*Uncommon:* • Arrhythmias, predominantly supraventricular in nature • Heart failure *Rare:* • Myocardial infarct
Vascular disorders	*Rare:* • Clinical signs of peripheral vasculitis and gangrene • Hypotension
Respiratory, thoracic and mediastinal disorders	*Very common:* • Dyspnoea -usually mild and passes rapidly without treatment *Common:* • Cough • Rhinitis *Uncommon:* • Interstitial pneumonitis (see section 4.4) • Bronchospasm – usually mild and transient but may require parenteral treatment *Rare:* • Pulmonary oedema • Adult respiratory distress syndrome (see section 4.4)
Gastrointestinal disorders	*Very common:* • Vomiting • Nausea

	Common: • Diarrhoea • Stomatitis & ulceration of the mouth • Constipation *Very rare:* • Ischaemic colitis
Hepatobiliary disorders	*Very common:* • Elevation of liver transaminases (ASTand ALT) and alkaline phosphatase *Common:* • Increased bilirubin *Uncommon:* • Serious hepatotoxicity, including liver failure and death *Rare:* • Increased gamma glutamyl transferase (GGT)
Skin and subcutaneous tissue disorders	*Very common:* • Allergic skin rash frequently associated with pruritus • Alopecia *Common:* • Itching • Sweating *Rare:* • Severe skin reactions, including desquamation and bullous skin eruptions • Ulceration • Vesicle and sore formation • Scaling *Very rare:* • Toxic epidermal necrolysis • Stevens-Johnson Syndrome
Musculoskeletal and connective tissue disorders	***Common:*** • **Back pain** • **Myalgia**
Renal and urinary disorders	*Very common:* • Haematuria • Mild proteinurea *Uncommon:* • Renal failure (see section 4.4) • Haemolytic uraemic syndrome (see section 4.4)
General disorders and administration site conditions	*Very common:* • Influenza-like symptoms -the most common symptoms are fever, headache, chills, myalgia, asthenia, and anorexia. Cough, rhinitis, malaise, perspiration and sleeping difficulties have also been reported. • Oedema/peripheral oedema – including facial oedema. Oedema is usually reversible after stopping treatment *Common:*

	• Fever • Asthenia • Chills *Rare:* • Injection site reactions -mainly mild in nature
Injury, poisoning, and procedural complications	*Rare:* • Radiation toxicity (see section 4.5) • Radiation recall

Combination use in breast cancer

The frequency of grade 3 and 4 haematological toxicities, particularly neutropaenia, increases when gemcitabine is used in combination with paclitaxel. However, the increase in these adverse reactions is not associated with an increased incidence of infections or haemorrhagic events. Fatigue and febrile neutropaenia occur more frequently when gemcitabine is used in combination with paclitaxel. Fatigue, which is not associated with anaemia, usually resolves after the first cycle.

Grade 3 and 4 Adverse Events. Paclitaxel versus gemcitabine plus paclitaxel:

	Number (%) of Patients			
	Paclitaxel Arm (n= 259)		Gemcitabine plus Paclitaxel Arm (n= 262)	
	Grade 3	Grade 4	Grade 3	Grade 4
Laboratory				
Anaemia	5(1.9)	1 (0.4)	15 (5.7)	3 (1.1)
Thrombocytopaenia	0	0	14 (5.3)	1 (0.4)
Neutropaenia	11 (4.2)	17 (6.6)*	82 (31.3)	45 (17.2)*
Non-laboratory				
Febrile neutropenia	3 (1.2)	0	12 (4.6)	1 (0.4)
Fatigue	3 (1.2)	1 (0.4)	15 (5.7)	2 (0.8)
Diarrhoea	5 (1.9)	0	8(3.1)	0
Motor neuropathy	2 (0.8)	0	6 (2.3)	1 (0.4)
Sensory neuropathy	9 (3.5)	0	14 (5.3)	1 (0.4)

* Grade 4 neutropenia lasting for more than 7 days occurred in 12.6% of patients in the combination arm and 5.0% of patients in the paclitaxel arm.

Combination use in bladder cancer

Grade 3 and 4 Adverse Events. MVAC versus gemcitabine plus cisplatin:

	Number (%) of Patients			
	MVAC (methotrexate, vinblastine, doxorubicin and cisplatin) Arm (n= 196)		Gemcitabine plus cisplatin Arm (n= 200)	
	Grade 3	Grade 4	Grade 3	Grade 4
Laboratory				
Anaemia	30 (16)	4 (2)	47 (24)	7 (4)
Thrombocytopaenia	15 (8)	25 (13)	57 (29)	57 (29)
Non-laboratory				
Nausea and vomiting	37 (19)	3 (2)	44 (22)	0 (0)
Diarrhoea	15 (8)	1 (1)	6 (3)	0 (0)
Infection	19 (10)	10 (5)	4 (2)	1 (1)
Stomatitis	34 (18)	8 (4)	2 (1)	0 (0)

Combination use in ovarian cancer

Grade 3 and 4 Adverse Events. Carboplatin versus gemcitabine plus carboplatin:

	Number (%) of Patients			
	Carboplatin Arm (n= 174)		Gemcitabine plus carboplatin Arm (n= 175)	
	Grade 3	Grade 4	Grade 3	Grade 4
Laboratory				
Anaemia	10 (5.7)	4 (2.3)	39 (22.3)	9 (5.1)
Neutropaenia	19 (10.9)	2 (1.1)	73 (41.7)	50 (28.6)
Thrombocytopaenia	18 (10.3)	2 (1.1)	53 (30.3)	8 (4.6)
Leucopaenia	11 (6.3)	1 (0.6)	84 (48.0)	9 (5.1)
Non-laboratory				
Haemorrhage	0 (0.0)	0 (0.0)	3 (1.8)	(0.0)
Febrile neutropaenia	0 (0.0)	0 (0.0)	2 (1.1)	(0.0)
Infection without neutropaenia	0 (0)	0 (0.0)	(0.0)	1 (0.6)

Sensory neuropathy was also more frequent in the combination arm than with single agent carboplatin.

4.9 Overdose

There is no known antidote for overdose of gemcitabine. Single doses of up to 5.7 g/m^2 have been administered as intravenous infusions 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

Pharmacotherapeutic group: pyrimidine analogues
ATC code: L01BC05

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

Antitumour Activity in Preclinical Models:
In animal tumour models, the antitumour activity of gemcitabine is schedule dependent. When gemcitabine is administered daily, high animal mortality but minimal antitumoural activity is seen. If, however, gemcitabine is given every third or fourth day, it can be administered in non-lethal doses with substantial antitumoural activity against a broad spectrum of mouse tumours.

Cellular Metabolism and Mechanisms of Action:
Gemcitabine (dFdC), which is a pyrimidine antimetabolite, is metabolised intracellularly by nucleoside kinase to the active diphosphate (dFdCDP) and triphosphate (dFdCTP) nucleosides. The cytotoxic action of gemcitabine is 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 (dCTP) 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 (self-potentiation).

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

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

Non small cell lung cancer: In a randomised phase III study of 522 patients with inoperable, locally advanced or metastatic NSCLC, gemcitabine in combination with cisplatin showed a statistically significant higher response rate than cisplatin alone (31.0% and 12.0%, respectively, p<0.0001). A statistically significant prolongation of the time to progression, from 3.7 to 5.6 months (log-rank p<0.0012) and a statistically significant prolongation of median survival from 7.6 months to 9.1 months (log-rank p<0.004) was observed in patients treated with gemcitabine/cisplatin compared to patients treated with cisplatin.

In another randomised phase III study of 135 patients with stage IIIB or IV NSCLC, a combination of gemcitabine and cisplatin showed a statistically significant higher response rate than a combination of cisplatin and etoposide (40.6% and 21.2%, respectively, p=0.025). A statistically significant prolongation of the time to progression, from 4.3 to 6.9 months (p=0.014) was observed in patients treated with gemcitabine/cisplatin compared to patients treated with etoposide/cisplatin.

In both studies it was found that tolerability was similar in the two treatment arms.

Ovarian carcinoma: In a randomised phase III study, 356 patients with advanced epithelial ovarian carcinoma who had relapsed at least 6 months after completing platinum based therapy were randomised to therapy with gemcitabine and carboplatin (GCb), or carboplatin (Cb). A statistically significant prolongation of the time to progression of disease, from 5.8 to 8.6 months (log-rank p= 0.0038) was observed in the patients treated with GCb compared to patients treated with Cb. Differences in response rate of 47.2% in the GCb arm versus 30.9% in the Cb arm (p=0.0016) and median survival 18 months (GCb) versus 17.3 (Cb) (p=0.73) favoured the GCb arm.

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

5.2 Pharmacokinetic properties

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

Peak plasma concentrations (obtained within 5 minutes of the end of the infusion) were 3.2 to 45.5 µg/ml. Plasma concentrations of the parent compound following a dose of 1,000 mg/m^2/30-minutes 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.

Distribution
The volume of distribution of the central compartment was 12.4 l/m^2 for women and 17.5 l/m^2 for men (inter-individual variability was 91.9%). The volume of distribution of the peripheral compartment was 47.4 l/m^2. The volume of the peripheral compartment was not sensitive to gender.

The plasma protein binding was considered to be negligible.

Half-life: This ranged from 42 to 94 minutes depending on age and gender. For the recommended dosing schedule, gemcitabine elimination should be virtually complete within 5 to 11 hours of the start of the infusion. Gemcitabine does not accumulate when administered once weekly.

Metabolism:
Gemcitabine is rapidly 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.

Excretion:
Systemic clearance ranged from 29.2 l/hr/m^2 to 92.2 l/hr/m^2 depending on gender and age (inter-individual variability was 52.2%). Clearance for women is approximately 25% lower than the values for men. Although rapid, clearance for both men and women appears to decrease with age. For the recommended gemcitabine dose of 1,000 mg/m^2 given as a 30 minute infusion, lower clearance values for women and men should not necessitate a decrease in the gemcitabine dose.

Urinary excretion: Less than 10% is excreted as unchanged drug.

Renal clearance was 2 to 7 l/hr/m^2.

During the week following administration, 92 to 98% of the dose of gemcitabine administered is recovered, 99% in the urine, mainly in the form of dFdU and 1% of the dose is excreted in faeces.

dFdCTP Kinetics:
This metabolite can be found in peripheral blood mononuclear cells and the information below refers to these cells.

Intracellular concentrations increase in proportion to gemcitabine doses of 35-350 mg/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.

Half-life of terminal elimination: 0.7-12 hours.

dFdU Kinetics:
Peak plasma concentrations (3-15 minutes after end of 30 minute infusion, 1,000 mg/m^2):
28-52µg/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 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 (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.

Gemcitabine and Paclitaxel Combination Therapy:
Combination therapy did not alter the pharmacokinetics of either gemcitabine or paclitaxel.

Gemcitabine and Carboplatin Combination Therapy:
When given in combination with carboplatin the pharmacokinetics of gemcitabine were not altered.

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

5.3 Preclinical safety data

In repeated dose studies of up to 6 months duration in mice and dogs, the principal finding was schedule and dose-dependent haematopoetic suppression, which was reversible. Gemcitabine showed mutagenic potential in an *in-vitro* mutation test and in an *in-vivo* bone marrow micronucleus test. Long-term animal studies have not been conducted to evaluate the carcinogenic potential of gemcitabine.

In fertility studies, gemcitabine caused reversible hypospermatogenesis in male mice. No effect on the fertility of females has been detected.

Evaluation of experimental animal studies has shown reproductive toxicity e.g. birth defects and other effects on the development of the embryo or foetus, the course of gestation or peri- and postnatal development.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Mannitol, E421
Sodium acetate trihydrate
Hydrochloric acid (for pH-adjustment)
Sodium hydroxide (for pH-adjustment)

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal product except those mentioned in section 6.6.

6.3 Shelf life

As packaged for sale:
2 years

After reconstitution:
Chemical and physical in-use stability has been demonstrated for 35 days at 25°C.
From a microbiological point of view, the product should be used immediately.
Solutions should not be refrigerated, as crystallisation may occur.

6.4 Special precautions for storage

As packaged for sale:
This medicinal product does not require any special storage conditions.

In-use:
For storage condition of the reconstituted medicinal product, see section 6.3.

6.5 Nature and contents of container

2 g vial: Type I clear glass vial with bromobutyl stopper. Vials may be sheathed in protective ONCO-TAIN sleeves.
Pack sizes: carton containing a single vial or packs of 5 single vial cartons. Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Reconstitution:
For single use only

This medicinal product has only been shown to be compatible with sodium chloride 9 mg/ml (0.9%) solution for injection. Accordingly, only this diluent should be used for reconstitution. Compatibility with other active substances has not been studied. Therefore, it is not recommended to mix this medicinal product with other active substances when reconstituted.

Reconstitution at concentrations greater than 38 mg/ml may result in incomplete dissolution, and should be avoided.

To reconstitute, slowly add the appropriate volume of sodium chloride 9 mg/ml (0.9%) solution for injection (as stated in the table below) and shake to dissolve.

Presentation	Volume of sodium chloride 9 mg/ml (0.9%) solution for injection to be added	Displacement volume	Final concentration
200 mg	5 ml	0.26 ml	38 mg/ml
1 g	25 ml	1.3 ml	38 mg/ml
2 g	50 ml	2.6 ml	38 mg/ml

The appropriate amount of medicinal product may be further diluted with sodium chloride 9 mg/ml (0.9%) solution for injection.

Parenteral medicinal products should be inspected visually for particulate matter and discolouration, prior to administration, whenever solution and container permit.

Any unused solution should be discarded as described below.

Guidelines for the Safe Handling of Cytotoxic Medicinal Products:
Local guidelines on safe preparation and handling of cytotoxic medicinal products must be adhered to. Cytotoxic preparations should not be handled by pregnant staff. The preparation of injectable solutions of cytotoxic agents must be carried out by trained specialist personnel with knowledge of the medicines used. This should be performed in a designated area. The work surface should be covered with disposable plastic-backed absorbent paper.

Suitable eye protection, disposable gloves, face mask and disposable apron should be worn. Precautions should be taken to avoid the medicinal product accidentally coming into contact with the eyes. If accidental contamination occurs, the eye should be washed with water thoroughly and immediately.

Syringes and infusion sets should be assembled carefully to avoid leakage (use of Luer lock fittings is recommended). Large bore needles are recommended to minimise pressure and the possible formation of aerosols. The latter may also be reduced by the use of a venting needle.

Actual spillage or leakage should be mopped up wearing protective gloves. Excreta and vomit must be handled with care.

Disposal:
Adequate care and precaution should be taken in the disposal of items used to reconstitute this medicinal product. Any unused dry product or contaminated materials should be placed in a high-risk waste bag. Sharp objects (needles, syringes, vials, etc) should be placed in a suitable rigid container. Personnel concerned with the collection and disposal of this waste should be aware of the hazard involved. Waste material should be destroyed by incineration. Any unused product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Hospira UK Limited
Queensway
Royal Leamington Spa
Warwickshire CV31 3RW
United Kingdom

8 MARKETING AUTHORISATION NUMBER

PA 437/58/3

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of First Authorisation: 9th November 2007

10 DATE OF REVISION OF THE TEXT

April 2014