SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Gemcitabine 38 mg/mL Concentrate for Solution for Infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One mL of Gemcitabine Concentrate for Solution for Infusion contains gemcitabine hydrochloride, equivalent to 38 mg gemcitabine.

The quantitative composition of each presentation is provided in the table below:

Presentation	Strength	Quantity of gemcitabine (as hydrochloride)	Volume of Solution
200 mg/5.3 mL	38 mg/mL	200 mg	5.3 mL
1 g/26.3 mL	38 mg/mL	1 g	26.3 mL
2 g/52.6 mL	38 mg/mL	2 g	52.6 mL

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Concentrate for solution for infusion.

A clear, colourless or light straw-coloured solution, practically free from visible particles.

pH: 2.0-3.0

Osmolarity: 266 mOsmol/L

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Gemcitabine is indicated for the treatment of locally advanced or metastatic bladder cancer in
combination with cisplatin.

Gemcitabine is indicated for treatment of patients with locally advanced or metastatic adenocarcinoma of the pancreas.

Gemcitabine, in combination with cisplatin, is indicated as first line treatment of patients with locally advanced or metastatic non-small cell lung cancer (NSCLC). Gemcitabine monotherapy can be considered in elderly patients or those with performance status 2.

Gemcitabine is indicated for the treatment of patients with 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.

Gemcitabine, in combination with paclitaxel, is indicated 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.

4.2 Posology and method of administration

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

Posology

Bladder cancer
Combination use
The recommended dose for gemcitabine is 1 000 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 grade of toxicity experienced by the patient.

Pancreatic cancer
The recommended dose of gemcitabine is 1 000 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 grade of toxicity experienced by the patient.

Non small Cell lung cancer
Monotherapy
The recommended dose of gemcitabine is 1 000 mg/m^2, given by 30-minute intravenous infusion. This should be repeated once weekly for 3 weeks, followed by a 1-week rest period. This 4-week cycle is then repeated. Dosage reduction with each cycle or within a cycle may be applied based upon the grade of toxicity experienced by the patient.

Combination use
The recommended dose for gemcitabine is 1 250 mg/m^2 body surface area given as a 30-minute intravenous infusion on Days 1 and 8 of the treatment cycle (21 days). Dosage reduction with each cycle or within a cycle may be applied based upon the grade of toxicity experienced by the patient. Cisplatin has been used at doses between 75-100 mg/m^2 once every 3 weeks.

Breast cancer
Combination use
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 (1 250 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 grade of toxicity experienced by the patient. Patients should have an absolute granulocyte count of at least 1 500 (x 10^6/L) prior to initiation of gemcitabine + paclitaxel combination.

Ovarian cancer
Combination use
Gemcitabine in combination with carboplatin is recommended using gemcitabine 1 000 mg/m^2 administered on Days 1 and 8 of each 21-day cycle as a 30-minute intravenous infusion. After gemcitabine, carboplatin will be given on Day 1 consistent with a target Area under curve (AUC) of 4.0 mg/mL·x min. Dosage reduction with each cycle or within a cycle may be applied based upon the grade of toxicity experienced by the patient.

Monitoring for toxicity and dose modification due to toxicity

Dose modification 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 grade 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 resolved in the opinion of the physician.

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

Dose modification due to haematological toxicity
Initiation of a cycle
For all indications, the patient must be monitored before each dose for platelet and granulocyte counts. Patients should have an absolute granulocyte count of at least 1 500 (x 10^6/L) and platelet count of 100 000 (x 10^6/L) prior to the initiation 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, NSCLC and pancreatic cancer, given in monotherapy or in combination with cisplatin			
Absolute granulocyte count (x 10^6/L)		**Platelet count (x 10^6/L)**	**Percentage of standard dose of gemcitabine (%)**
> 1 000	and	> 100 000	100
500-1 000	or	50 000-100 000	75
< 500	or	< 50,000	Omit dose*

**Treatment omitted will not be re-instated within a cycle before the absolute granulocyte count reaches at least 500 (x 10^6/L) and the platelet count reaches 50 000 (x 10^6/L).*

Dose modification of gemcitabine within a cycle for breast cancer, given in combination with paclitaxel			
Absolute granulocyte count (x 10^6/L)		**Platelet count (x 10^6/L)**	**Percentage of standard dose of gemcitabine (%)**
≥ 1 200	and	> 75 000	100
1 000- < 1 200	or	50 000-75 000	75
700- < 1 000	and	≥ 50 000	50
< 700	or	< 50 000	Omit dose*

**Treatment omitted will not be re-instated within a cycle. Treatment will start on day 1 of the next cycle once the absolute granulocyte count reaches at least 1 500 (x 10^6/L) and the platelet count reaches 100 000 (x 10^6/L).*

Dose modification of gemcitabine within a cycle for ovarian cancer, given in combination with carboplatin			
Absolute granulocyte count (x 10^6/L)		**Platelet count (x 10^6/L)**	**Percentage of standard dose of gemcitabine (%)**
> 1 500	and	≥ 100 000	100
1 000-1 500	or	75 000-100 000	50
< 1 000	or	< 75 000	Omit dose*

**Treatment omitted will not be re-instated within a cycle. Treatment will start on day 1 of the next cycle once the absolute granulocyte count reaches at least 1 500 (x 10^6/L) and the platelet count reaches 100 000 (x 10^6/L).*

Dose modifications 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 < 500 x 10^6/L for more than 5 days
- Absolute granulocyte count < 100 x 10^6/L for more than 3 days

- Febrile neutropaenia
- Platelets < 25 000 x 10^6/L
- Cycle delay of more than 1 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 further dilution of the solution, see section 6.6

Special populations

Patients with renal or hepatic 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 patients (> 65 years of age)
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 of age)
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 the active substance or to any of the excipients listed in section 6.1.
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 suppression 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.

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.

Hepatic and renal impairment
Gemcitabine should be used with caution in patients with hepatic impairment 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).

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 impairment.

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

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).

Nervous system

Posterior reversible encephalopathy syndrome
Reports of 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. Acute hypertension and seizures were reported in most gemcitabine patients experiencing PRES, but other symptoms such as headache, lethargy, confusion and blindness could also be present. Diagnosis is optimally confirmed by magnetic resonance imaging (MRI). PRES was typically reversible with appropriate supportive measures. Gemcitabine should be permanently discontinued and supportive measures implemented, including blood pressure control and anti-seizure therapy, if PRES develops during therapy.

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.

Capillary leak syndrome
Capillary leak syndrome has been reported in patients receiving gemcitabine as single agent or in combination with other chemotherapeutic agents (see section 4.8). The condition is usually treatable if recognised early and managed appropriately, but fatal cases have been reported. The condition involves systemic capillary hyperpermeability during which fluid and proteins from the intravascular space leak into the interstitium. The clinical features include generalised oedema, weight gain, hypoalbuminaemia, severe hypotension, acute renal impairment and pulmonary oedema. Gemcitabine should be discontinued, and supportive measures implemented if capillary leak syndrome develops during therapy. Capillary leak syndrome can occur in later cycles and has been associated in the literature with adult respiratory distress syndrome.

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 made to discontinuing gemcitabine therapy. Early use of supportive care measure may help ameliorate the condition.

Renal

Haemolytic uraemic syndrome
Clinical findings consistent with the haemolytic uraemic syndrome (HUS) were rarely reported (post-marketing data) in patients receiving gemcitabine (see section 4.8). HUS is a potentially life-threatening disorder. Gemcitabine should be discontinued at the first signs of any evidence of microangiopathic haemolytic anaemia, such as rapidly falling haemoglobin with concomitant thrombocytopaenia, 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 conceive a child during and in the 3 months following 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).

Excipient information

Gemcitabine 200 mg Concentrate for Solution for Infusion
This medicinal product contains less than 1 mmol sodium (23 mg) per vial, that is to say essentially ‘sodium-free’.

Gemcitabine 1 g Concentrate for Solution for Infusion
This medicinal product contains less than 1 mmol sodium (23 mg) per vial, that is to say essentially ‘sodium-free’.

Gemcitabine 2 g Concentrate for Solution for Infusion
This medicinal product contains less than 1 mmol sodium (23 mg) per vial, that is to say essentially 'sodium-free'.

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) - Analysis of the data 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

Women of childbearing potential/male and female contraception
Due to the genotoxic potential of gemcitabine (see section 5.3), women of childbearing potential must use effective methods of contraception during their treatment with gemcitabine and for 6 months after treatment discontinuation. Men

must be advised to use effective methods of contraception and not conceive a child during treatment with gemcitabine and in the 3 months following its discontinuation.

Pregnancy
There are no adequate data from the use of gemcitabine in pregnant women. 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 after all.

Breast-feeding
It is not known whether gemcitabine is excreted in human milk and adverse effects 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 conceive a child during and in the 3 months following 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 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); allergic skin rashes occur in approximately 25% of patients and were 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), Not known (cannot be estimated from the available data).

The following table of undesirable effects and frequencies is based on data from clinical trials. Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

SYSTEM ORGAN CLASS	FREQUENCY GROUPING
Infections and infestations	***Common*** • Infections ***Not known*** • Sepsis
Blood and lymphatic system disorders	***Very common*** • Leucopaenia (Neutropaenia Grade 3 = 19.3%; Grade 4 = 6%). Bone-marrow suppression is usually mild to moderate and mostly affects the granulocyte count (see section 4.2 and 4.4) • Thrombocytopaenia • Anaemia ***Common*** • Febrile neutropaenia ***Very rare*** • Thrombocytosis • Thrombotic microangiopathy
Immune system disorders	***Very Rare*** • Anaphylactoid reaction
Metabolism and nutrition disorders	***Common*** • Anorexia
Nervous system disorders	***Common*** • Headache • Insomnia • Somnolence ***Uncommon***

SYSTEM ORGAN CLASS	FREQUENCY GROUPING
	• Cerebrovascular accident ***Very rare*** • Posterior reversible encephalopathy syndrome (see section 4.4.)
Cardiac disorders	***Uncommon*** • Arrhythmias, predominantly supraventricular in nature • Heart failure ***Rare*** • Myocardial infarct
Vascular disorders	***Rare*** • Clinical signs of peripheral vasculitis and gangrene • Hypotension ***Very rare*** • Capillary leak syndrome (see section 4.4)
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) ***Not known*** • Pulmonary eosinophilia

SYSTEM ORGAN CLASS	FREQUENCY GROUPING
Gastrointestinal disorders	***Very common*** • Vomiting • Nausea ***Common*** • Diarrhoea • Stomatitis and ulceration of the mouth • Constipation ***Very rare*** • Ischaemic colitis
Hepatobiliary disorders	***Very common*** • Elevation of liver transaminases (AST and 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

SYSTEM ORGAN CLASS	FREQUENCY GROUPING
	• Stevens-Johnson Syndrome ***Not known*** • Pseudocellulitis • Acute generalised exanthematous pustulosis
Musculoskeletal and connective tissue disorders	***Common*** • Back pain • Myalgia
Renal and urinary disorders	***Very Common*** • Haematuria • Mild proteinuria ***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 neutropaenia	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 neutropaenia lasting for more than 7 days occurred in 12.6% of patients in the combination arm and in 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* 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)

**Methotrexate, Vinblastine, Doxorubicin and Cisplatin*

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.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation 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 via the Yellow Card Scheme at: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

There is no known antidote for overdose of gemcitabine. Doses as high as 5 700 mg/m^2 have been administered by intravenous 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 receive supportive therapy, as necessary.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antineoplastic agents/pyrimidine analogues.
ATC code: L01BC05

Cytotoxic activity in cell cultures
Gemcitabine shows significant cytotoxic effects against a variety of cultured murine and human tumour cells. Its action is phase-specific such that gemcitabine primarily kills cells that are undergoing DNA synthesis (S-phase) and, under certain circumstances, blocks the progression of cells at the junction of the G1/S phase boundary. *In vitro*, the cytotoxic effect of gemcitabine is dependent on both concentration and time.

Antitumoral activity in preclinical models
In animal tumour models, antitumoural activity of gemcitabine is schedule-dependent. When
gemcitabine is administered daily, high mortality among the animals but minimal antitumoural activity is observed. If, however, gemcitabine is given every third or fourth day, it can be administered in nonlethal doses with substantial antitumoural activity against a broad spectrum of mouse tumours.

Mechanism of action
Cellular metabolism and mechanism 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 effect of gemcitabine is due to inhibition of DNA synthesis by two mechanisms of action by dFdCDP and dFdCTP. First, dFdCDP inhibits ribonucleotide reductase, which is uniquely responsible for catalysing the reactions that produce deoxynucleoside triphosphates (dCTP) for DNA synthesis. Inhibition of this enzyme by dFdCDP reduces the concentration of deoxynucleosides in general and, in particular, 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 reduced intracellular concentration of dCTP potentiates the incorporation of dFdCTP into DNA. DNA polymerase epsilon lacks the ability to eliminate gemcitabine and to 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 appears to induce the programmed cell 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.

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

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.

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.

Elimination
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-minutes, 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.

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): 28-52 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 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.

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 repeat-dose studies of up to 6 months in duration in mice and dogs, the principal finding was schedule and dose-dependent haematopoietic suppression which was reversible.

Gemcitabine is mutagenic in an *in vitro* mutation test and an *in vivo* bone marrow micronucleus test. Long-term animal studies evaluating the carcinogenic potential have not been performed.

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

Water for Injections
Hydrochloric acid (E507) (for pH adjustment)
Sodium hydroxide (E524) (for pH adjustment)

6.2 Incompatibilities

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

6.3 Shelf life

Unopened vial
18 months

In-Use: Further dilution
After dilution, chemical and physical in-use stability has been demonstrated for:

Diluent	**Target Concentration**	**Storage Conditions**	**Time period**
0.9% sodium chloride solution for infusion	0.1 mg/mL and 26 mg/mL	2-8 °C in the absence of light in non-PVC (polyolefin) infusion bags	84 days
0.9% sodium chloride solution for infusion	0.1 mg/mL and 26 mg/mL	2-8 °C in the absence of light in PVC infusion bags	24 hours

0.9% sodium chloride solution for infusion	0.1 mg/mL and 26 mg/mL	25 °C under normal lighting conditions in PVC infusion bags	24 hours
5% glucose solution for infusion	0.1 mg/mL and 26 mg/mL	25 °C under normal lighting conditions in PVC infusion bags	24 hours

From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2 to 8 °C, unless dilution has taken place in controlled and validated aseptic conditions.

6.4 Special precautions for storage

Store in a refrigerator (2 °C to 8 °C).

For storage conditions after dilution of the medicinal product, see section 6.3

6.5 Nature and contents of container

200 mg/5.3 mL presentation
A 10 mL, Type I clear glass vial, stoppered with a chlorobutyl closure and sealed with an aluminium seal and flip-off top.
Each vial of the 200 mg presentation contains 5.3 mL concentrate. Each pack contains 1 vial.

1 g/26.3 mL presentation
A 30 mL, Type I clear glass vial, stoppered with a chlorobutyl closure and sealed with an aluminium seal and flip-off top.
Each vial of the 1 g presentation contains 26.3 mL concentrate. Each pack contains 1 vial.

2 g/52.6 mL presentation
A 100 mL, Type I clear glass vial, stoppered with a chlorobutyl closure and sealed with an aluminium seal and flip-off top.
Each vial of the 2 g presentation contains 52.6 mL concentrate. Each pack contains 1 vial.

6.6 Special precautions for disposal and other handling

Handling

The normal safety precautions for cytostatic agents must be observed when preparing and disposing of the infusion solution. Handling of the concentrate should be done in a safety box and protective coats and gloves should be used. If no safety box is available, the equipment should be supplemented with a mask and protective glasses. If the preparation comes into contact with the eyes, this may cause serious irritation. The eyes should be rinsed immediately and thoroughly with water. If there is lasting irritation, a doctor should be consulted. If the solution is spilled on the skin, rinse thoroughly with water.

Instructions for dilution
An approved diluent for gemcitabine solution is sodium chloride 9 mg/mL (0.9%) solution for injection (without preservative).

1. Use the aseptic technique during any dilution of gemcitabine for intravenous infusion administration.

2. Parenteral medicinal products should be inspected visually for particulate matter and discolouration prior to administration. If particulate matter is observed, do not administer.

3. Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

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