

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Gemcitabine 100 mg/ml Concentrate for Solution for Infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml contains Gemcitabine hydrochloride equivalent to 100 mg gemcitabine.

Each vial of 2 ml concentrate for solution for infusion contains Gemcitabine hydrochloride equivalent to 200 mg gemcitabine.

Each vial of 10 ml concentrate for solution for infusion contains Gemcitabine hydrochloride equivalent to 1000 mg gemcitabine

Each vial of 15 ml concentrate for solution for infusion contains Gemcitabine hydrochloride equivalent to 1500 mg gemcitabine

Each vial of 20 ml concentrate for solution for infusion contains Gemcitabine hydrochloride equivalent to 2000 mg gemcitabine

Excipients with known effect:

9.192 mg/ml (0.4 mmol/ml) sodium.

440 mg/ml (44 % w/v) ethanol anhydrous

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Concentrate for solution for infusion

Clear, colourless to slightly yellow solution. pH in the range of approximately 6.0 to 7.5 and osmolarity in the range of approximately 270 to 330 mOsmol/Litre after dilution with 0.9 % sodium chloride solution at 0.1 mg/ml concentration.

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 anticancer chemotherapy.

Recommended posology:

Bladder cancer

Combination use

The recommended dose for gemcitabine is 1000 mg/m², 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/m² 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 1000 mg/m², 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 1000 mg/m², 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 1250 mg/m² body surface area given as a 30-minute intravenous infusion on Day 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/m² once every 3 weeks.

Breast cancer

Combination use

Gemcitabine, in combination with paclitaxel, is recommended using paclitaxel (175 mg/m²) administered on Day 1 over approximately 3-hours as an intravenous infusion, followed by gemcitabine (1250 mg/m²) 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 10⁶/l) prior to initiation of gemcitabine + paclitaxel combination.

Ovarian cancer

Combination use

Gemcitabine, in combination with carboplatin, is recommended using gemcitabine 1000 mg/m² 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•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.

Gemcitabine 100 mg/ml concentrate for solution for infusion contains 440 mg ethanol anhydrous per ml concentrate. This should be taken into consideration in high-risk groups such as patients with liver disease or epilepsy (see also section 4.4).

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 10⁶/l) and platelet count of 100,000 (x 10⁶/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 (x10⁶/l) and the platelet count reaches 50,000 (x10⁶/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 (x10⁶/l) and the platelet count reaches 100,000 (x10⁶/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 (x10⁶/l) and the platelet count reaches 100,000 (x10⁶/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 10⁶/l for more than 5 days
- Absolute granulocyte count < 100 x 10⁶/l for more than 3 days
- Febrile neutropenia
- Platelets < 25,000 x 10⁶/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 dilution, see section 6.6.

Special populations*Patients with renal or hepatic impairment*

Gemcitabine should be used with caution in patients with hepatic or renal insufficiency 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).

Older people (> 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 older people (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.

Concentration must be diluted (100 mg/ml) or life-threatening overdose may occur.

Gemcitabine concentrate for solution for infusion must be diluted. The total quantity of the Gemcitabine concentrate for solution for infusion required for an individual patient should be diluted with sterile sodium chloride 9 mg/ml (0.9%) solution to a final concentration of 0.1 to 9 mg/ml. (see section 6.6 for dilution instructions).

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

Gemcitabine concentrate for solution for infusion requires appropriate dilution before use. The concentration of gemcitabine in Gemcitabine concentrate for solution for infusion differs from other gemcitabine products (see section 6.6 for further instructions on dilution).

Concentration must be diluted (100 mg/ml) or life-threatening overdose may occur.

Gemcitabine concentrate for solution for infusion must be diluted. The total quantity of the Gemcitabine concentrate for solution for infusion required for an individual patient should be diluted with sterile sodium chloride 9 mg/ml (0.9%) solution to a final concentration of 0.1 to 9 mg/ml. (see section 6.6 for dilution instructions)

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 leucopenia, thrombocytopenia 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 and renal impairment Administration of gemcitabine in patients with concurrent liver metastases or a preexisting 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.

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).

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.

Capillary leak syndrome (CLS)

Capillary leak syndrome has been reported in patients receiving gemcitabine as single agent or in combination with 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.

Posterior reversible encephalopathy syndrome (PRES)

Posterior reversible encephalopathy syndrome (PRES) has also been identified in patients receiving gemcitabine as single agent or combination with chemotherapeutic agents. PRES is a rare clinical-radiologic syndrome with reversible cortical dysfunction and subcortical oedema which includes a number of clinical features such as consciousness impairment, seizure activity, headache, visual abnormalities, focal neurological signs and acute hypertension. This event is potentially reversible if recognized promptly and treated with supportive measures, blood pressure control, anticonvulsant therapy, and/or correction of the underlying cause (e.g., withdrawal of offending agent) to avoid any central nervous system (CNS) injury or death. The clinical abnormalities and associated magnetic resonance imaging (MRI) findings usually resolve within days to weeks if managed appropriately. PRES can occur in later cycles of treatment. Conditions including infection/ sepsis/ septic shock, preeclampsia/eclampsia and autoimmune diseases chronic renal failure and chronic hypertension have been associated with PRES. Patients who receive other chemotherapeutic agents that are associated PRES could be at risk of developing PRES.

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 thrombocytopenia, elevation of serum bilirubin, serum creatinine, blood urea nitrogen, or LDH. Renal failure may not be reversible with discontinuation of therapy and dialysis may be required.

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 100 mg/ml Concentrate for solution for Infusion contains 206 mg (9.0 mmol) of sodium per maximum daily dose (2250 mg). This should be taken into consideration by patients on a controlled sodium diet.

Ethanol

Gemcitabine 100 mg/ml concentrate for solution for infusion contains 440 mg ethanol anhydrous per ml concentrate. This may be harmful in patients suffering from alcoholism and should also be taken into consideration in high-risk groups such as patients with liver disease or epilepsy. Consideration should be given to possible effects on the central nervous system and other effects.

4.5 Interaction with other medicinal products and other forms of interactions

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 $1,000 \text{ mg/m}^2$ 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 $4,795 \text{ cm}^3$]. 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 hydrochloride.

Others

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

The amount of alcohol in this medicinal product may alter the effects of other medicines.

4.6 Fertility, pregnancy and lactation

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 hydrochloride, 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 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

The amount of alcohol in this medicinal product may impair the ability to drive or 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% of patients; dyspnoea reported in 10-40% of patients (highest incidence in lung cancer patients); allergic skin rashes 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). 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 ($\geq 1/10$), Common ($\geq 1/100$ to $< 1/10$), Uncommon ($\geq 1/1,000$ to $< 1/100$), Rare ($\geq 1/10,000$ to $< 1/1,000$), Very Rare ($< 1/10,000$).

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
<i>Blood and lymphatic system disorders</i>	<p><i>Very Common</i></p> <ul style="list-style-type: none"> - Leucopenia (Neutropenia Grade 3 = 19.3 %; Grade 4 = 6 %). <p>Bone-marrow suppression is usually mild to moderate and mostly affects the granulocyte count (see section 4.2 and 4.4).</p> <ul style="list-style-type: none"> - Thrombocytopenia - Anaemia <p><i>Common</i></p> <ul style="list-style-type: none"> - Febrile neutropenia <p><i>Very Rare</i></p> <ul style="list-style-type: none"> - Thrombocytosis - Thrombotic microangiopathy
<i>Immune system disorders</i>	<p><i>Very Rare</i></p> <ul style="list-style-type: none"> - Anaphylactoid reaction
<i>Infections and infestations</i>	<p><i>Common</i></p> <ul style="list-style-type: none"> - Infections <p><i>Not known</i></p> <ul style="list-style-type: none"> - Sepsis
<i>Metabolism and nutrition disorders</i>	<p><i>Common</i></p> <ul style="list-style-type: none"> - Anorexia
<i>Nervous system disorders</i>	<p><i>Common</i></p> <ul style="list-style-type: none"> - Headache - Insomnia - Somnolence <p><i>Uncommon</i></p> <ul style="list-style-type: none"> -Cerebrovascular accident <p><i>Very rare</i></p> <ul style="list-style-type: none"> -Posterior reversible encephalopathy syndrome (see section 4.4)
<i>Cardiac disorders</i>	<p><i>Uncommon</i></p> <ul style="list-style-type: none"> -Arrhythmias, predominantly supraventricular in nature -Heart failure

System Organ Class	Frequency grouping
	<p><i>Rare</i></p> <ul style="list-style-type: none"> -Myocardial infarct
<i>Vascular disorders</i>	<p><i>Rare</i></p> <ul style="list-style-type: none"> -Clinical signs of peripheral vasculitis and gangrene -Hypotension <p><i>Very rare</i></p> <ul style="list-style-type: none"> -Capillary leak syndrome (see section 4.4)
<i>Respiratory, thoracic and mediastinal disorders</i>	<p><i>Very Common</i></p> <ul style="list-style-type: none"> -Dyspnoea – usually mild and passes rapidly without treatment <p><i>Common</i></p> <ul style="list-style-type: none"> -Cough -Rhinitis <p><i>Uncommon</i></p> <ul style="list-style-type: none"> -Interstitial pneumonitis (see section 4.4) -Bronchospasm – usually mild and transient but may require parenteral treatment. <p><i>Rare</i></p> <ul style="list-style-type: none"> -Pulmonary oedema -Adult respiratory distress syndrome (see section 4.4.)
<i>Gastro-intestinal disorders</i>	<p><i>Very Common</i></p> <ul style="list-style-type: none"> -Vomiting -Nausea <p><i>Common</i></p> <ul style="list-style-type: none"> -Diarrhoea -Stomatitis and ulceration of the Mouth -Constipation <p><i>Very rare</i></p> <ul style="list-style-type: none"> - Ischaemic colitis
<i>Hepato-biliary disorders</i>	<p><i>Very Common</i></p> <ul style="list-style-type: none"> -Elevation of liver transaminases (AST and ALT) and alkaline phosphatase <p><i>Common</i></p> <ul style="list-style-type: none"> -Increased bilirubin <p><i>Uncommon</i></p> <ul style="list-style-type: none"> -Serious hepatotoxicity, including liver failure and death <p><i>Rare</i></p> <ul style="list-style-type: none"> -Increased gamma-glutamyl transferase (GGT)
<i>Skin and subcutaneous tissue disorders</i>	<p><i>Very Common</i></p> <ul style="list-style-type: none"> -Allergic skin rash frequently associated with pruritus -Alopecia <p><i>Common</i></p> <ul style="list-style-type: none"> -Itching -Sweating <p><i>Rare</i></p> <ul style="list-style-type: none"> -Severe skin reactions, including desquamation and bullous skin eruptions

System Organ Class	Frequency grouping
	<ul style="list-style-type: none"> -Ulceration -Vesicle and sore formation -Scaling <p><i>Very Rare</i></p> <ul style="list-style-type: none"> -Toxic epidermal necrolysis -Stevens-Johnson Syndrome <p><i>Not known</i></p> <ul style="list-style-type: none"> -Pseudocellulitis
Musculoskeletal and connective tissue disorders	<p><i>Common</i></p> <ul style="list-style-type: none"> -Back pain -Myalgia
Renal and urinary disorders	<p><i>Very Common</i></p> <ul style="list-style-type: none"> -Haematuria -Mild proteinuria <p><i>Uncommon</i></p> <ul style="list-style-type: none"> -Renal failure (see section 4.4) -Haemolytic uraemic syndrome (see section 4.4)
General disorders and administration site conditions	<p><i>Very Common</i></p> <p>-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.</p> <p>-Oedema/peripheral oedema - including facial oedema. Oedema is usually reversible after stopping treatment.</p> <p><i>Common</i></p> <ul style="list-style-type: none"> -Fever -Asthenia -Chills <p><i>Rare</i></p> <ul style="list-style-type: none"> -Injection site reactions – mainly mild in nature.
Injury, poisoning, and procedural complications	<p><i>Rare</i></p> <ul style="list-style-type: none"> -Radiation toxicity (see section 4.5). -Radiation recall

Combination use in breast cancer

The frequency of Grade 3 and 4 haematological toxicities, particularly neutropenia, 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 neutropenia 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)
Thrombocytopenia	0	0	14 (5.3)	1 (0.4)
Neutropenia	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)
Thrombocytopenia	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)
Neutropenia	19 (10.9)	2 (1.1)	73 (41.7)	50 (28.6)
Thrombocytopenia	18 (10.3)	2 (1.1)	53 (30.3)	8 (4.6)
Leucopenia	11 (6.3)	1 (0.6)	84 (48.0)	9 (5.1)
Non-laboratory				
Haemorrhage	0 (0)	0 (0)	3 (1.8)	0 (0)
Febrile neutropenia	0 (0)	0 (0)	2 (1.1)	0 (0)
Infection without neutropenia	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 national reporting system:

HPRA Pharmacovigilance

Website: www.hpra.ie

4.9 Overdose

There is no known antidote for overdose of gemcitabine hydrochloride. Doses as high as 5700 mg/m² 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.

Anti-tumoural activity in preclinical models

In animal tumour models, anti-tumoural activity of gemcitabine is schedule-dependent.

When gemcitabine is administered daily, high mortality among the animals but minimal anti-tumoural activity is observed. 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.

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-potential).

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 (logrank $p=0.0002$) 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

Absorption

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/m² 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/m²/30-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/m² for women and 17.5 l/m² for men (inter-individual variability was 91.9%).

The volume of distribution of the peripheral compartment was 47.4 l/m². 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/m² to 92.2 l/hr/m² 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/m² 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/m².

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/m²/30-minutes, 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, 1000 mg/m²): 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/m² (range 11-22 l/m²).

Mean steady-state volume of distribution (V_{ss}): 150 l/m² (range 96-228 l/m²).

Tissue distribution: Extensive.

Mean apparent clearance: 2.5 l/hr/m² (range 1-4 l/hr/m²).

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 perinatal and postnatal development.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Macrogol 300
Propylene Glycol
Ethanol anhydrous
Sodium Hydroxide (for pH adjustment)
Hydrochloric acid, concentrated (for pH adjustment)

6.2 Incompatibilities

DEHP (di-(2-ethylhexyl) phthalate) content may leach from PVC containers upon storage of diluted solution of gemcitabine concentrate for solution for infusion in the plasticised polyvinyl chloride (PVC) containers. Consequently, the preparation, storage and administration of diluted solution should be carried out using non-PVC-containing equipment.

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

6.3 Shelf life

Unopened vials:

2 years.

After opening before dilution:

Each vial is for single use and should be used immediately after opening. If not used immediately, in-use storage times and conditions are the responsibility of the user.

After dilution:

Chemical and physical in-use stability after dilution in 0.9 % sodium chloride solution has been demonstrated for 60 days at 25°C and 2 °C to 8 °C.

From a microbiological point of view, the solution for infusion 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° C to 8°C unless dilution has taken place in controlled and validated aseptic condition.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

For storage conditions of the medicinal product after first opening or dilution, see section 6.3.

6.5 Nature and contents of container

The concentrate is a clear, colourless to slightly yellow solution. It is filled in 2 ml type I clear glass vials sealed with 13 mm rubber stoppers and 13 mm aluminium flip-off seals.

The concentrate is a clear, colourless to slightly yellow solution. It is filled in 10 ml type I clear glass vials sealed with 20 mm rubber stoppers and 20 mm aluminium flip-off seals.

The concentrate is a clear, colourless to slightly yellow solution. It is filled in 15 ml type I clear glass vials sealed with 20 mm rubber stoppers and 20 mm aluminium flip-off seals.

The concentrate is a clear, colourless to slightly yellow solution. It is filled in 20 ml type I clear glass vials sealed with 20 mm rubber stoppers and 20 mm aluminium flip-off seals.

Pack sizes:

1 x 2 ml vial

1 x 10 ml vial

1 x 15 ml vial

1 x 20 ml vial

Not all pack sizes may be marketed.

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 solution for infusion 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

The only approved diluent for dilution of gemcitabine sterile concentrate is sodium chloride 9 mg/ml (0.9%) solution for injection (without preservative).

- Use aseptic techniques preparation for gemcitabine for intravenous infusion administration.
- Gemcitabine concentrate for solution for infusion is a clear, colourless to slightly yellow solution with a concentration of 100 mg/ml gemcitabine. The total quantity of the Gemcitabine concentrate for solution for infusion required for an individual patient should be diluted with sterile sodium chloride 9 mg/ml (0.9%) solution. The concentration of the final diluted solution prepared using the maximum dose of gemcitabine (~ 2.25g) should be approximately 0.1 to 9mg/ml. The concentration of 4.5mg/ml (achieved with 500 ml of diluent) to 9mg/ml (achieved with 250 ml of diluent) corresponds to the osmolarity of approximately 1000 mOsmol/Kg to 1700 mOsmol/Kg. Diluted solution is a clear colourless to slightly yellow solution.
- The preparation, storage and administration of diluted solution should be carried out using non-PVC-containing equipment

Preparation of the infusion solution

Gemcitabine concentrate for solution for infusion contains 100 mg gemcitabine per ml concentrate solution. The concentrate solution should be diluted prior to administration.

If the vials are stored under refrigeration, allow the required number of boxes of Gemcitabine concentrate for solution for infusion to stand below 25°C for 5 minutes before use. More than one vial of Gemcitabine concentrate for solution for infusion may be necessary to obtain the required dose for the patient.

Aseptically withdraw the required amount of Gemcitabine concentrate for solution for infusion using a calibrated syringe.

The required volume of Gemcitabine concentrate for solution for infusion must be injected into infusion bag containing sodium chloride 9 mg/ml (0.9%) solution for infusion.

Mix the infusion bag manually using a rocking motion. Further dilution with the same diluent can be done to a final concentration of 0.1 to 9 mg/ml.

As with all parenteral medicinal products, Gemcitabine infusion solution should be inspected visually for particulate matter and discolouration prior to administration. If particulate matter is observed, do not administer. (see section 6.3 for shelf life after first opening or dilution)

Gemcitabine infusion solution is for single use only. Any unused product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Accord Healthcare Ireland Ltd.
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Euro Business Park
Little Island
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8 MARKETING AUTHORISATION NUMBER

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