

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Gemcitabine 1000 mg powder for solution for infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

One vial contains gemcitabine hydrochloride equivalent to 1000 mg gemcitabine.

After reconstitution, the solution contains 38 mg/ml of gemcitabine.

Excipient with known effects

Each vial contains 22.985 mg (<1 mmol) sodium.

For the full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Powder for solution for infusion.

White to off white freeze dried cake.

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 the 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 a performance of 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/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 1,000 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 1,000 mg/m², given by 30-minute intravenous infusion. This administration 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/m² 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/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 (1,250 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 1,000 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 to be reached. 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 the 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 10⁶ /l)	Platelet count (x 10⁶ /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 reinstated 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 10⁶ /l)	Platelet count (x 10⁶ /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 reinstated 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 ovarian cancer, given in combination with carboplatin		
Absolute granulocyte count (x 10⁶ /l)	Platelet count (x 10⁶ /l)	Percentage of standard dose of gemcitabine (%)
>1,500 and	≥100,000	100
1,000 - < 1,500 or	75,000-100,000	50
<1000 or	<75,000	Omit dose*

*Treatment omitted 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 1,500 (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

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).

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.

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.

4.3 Contraindications

Hypersensitivity to gemcitabine 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

Severe cutaneous adverse reactions (SCARs) including Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), and acute generalized 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.

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 leukopenia, thrombocytopenia and anaemia.

Patients receiving gemcitabine should be monitored prior to each dose for platelet, leukocyte and granulocyte counts. Suspension or modification of therapy should be considered when 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.

Blood counts may continue to decrease after cessation of treatment with gemcitabine. The treatment must be initiated with caution in patients with impaired bone marrow function. As with other cytolytic treatments, the risk of cumulative bone-marrow suppression taken into consideration in cases of combined or sequential chemotherapy.

Hepatic and renal impairment

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

The 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.

Renal and hepatic function must be checked periodically (including virology testing).

Concomitant radiotherapy

Concomitant radiotherapy (given simultaneously or with an interval of ≤ 7 days): 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

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. This condition involves systemic capillary hyperpermeability during which fluid and proteins from the intravascular space leak into the interstitium. The clinical characteristics include generalised oedema, weight gain, hypoalbuminaemia, severe hypotension, acute renal failure and pulmonary oedema.

Gemcitabine must be stopped and symptomatic treatments must be initiated if capillary leak syndrome develops during treatment. Capillary leak syndrome may occur during

subsequent cycles and has been associated with adult respiratory distress syndrome in the literature.

Posterior reversible encephalopathy syndrome

Cases of posterior reversible encephalopathy syndrome (PRES) with potentially severe consequences have been reported in patients receiving gemcitabine alone or in combination with other chemotherapeutic anti-cancer agents. Severe hypertension and seizures have been reported in the majority of patients receiving gemcitabine who experienced PRES, but other symptoms such as headaches, lethargy, confusion and blindness may also be present. The diagnosis is ideally confirmed through magnetic resonance imaging (MRI). PRES was generally reversible with appropriate symptomatic treatment. If PRES develops during treatment, gemcitabine must be permanently discontinued and symptomatic treatments must be initiated such as blood pressure control and anti-seizure medication.

Pulmonary

Pulmonary effects, which are sometimes severe (such as pulmonary oedema, interstitial lung disease and adult respiratory distress syndrome (ARDS)) have been reported in association with gemcitabine treatment. If such effects occur, discontinuation of treatment with gemcitabine should be considered. Early initiation of supportive measures may help to improve the patient's condition.

Renal

Haemolytic uraemic syndrome

Clinical signs consistent with haemolytic uraemic syndrome (HUS) have been reported in rare cases (post-marketing data) in patients receiving gemcitabine (see section 4.8). HUS is a potentially life-threatening condition. Gemcitabine must be stopped at the first signs of microangiopathic haemolytic anaemia, such as rapidly falling haemoglobin with concurrent thrombocytopenia, and elevated serum bilirubin, serum creatinine, blood urea nitrogen, or LDH levels. Renal failure may not be reversible with discontinuation of therapy and dialysis may be required.

Sodium

Gemcitabine 1000 mg contains 22.985 mg (<1 mmol) sodium per vial, i. e., 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

Concomitant use (given simultaneously or with an interval of 7)- The toxicity related to this multimodality therapy is on numerous different factors, including the dose of gemcitabine, its frequency of administration, the dose of radiation, the radiotherapy planning technique, the target tissue, and the target volume. Pre-clinical and clinical studies have demonstrated that gemcitabine has radiosensitising activity. In a single trial, where gemcitabine at a dose of 1,000 mg/m² 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 cm³]. 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/m², four times) and cisplatin (80 mg/m², 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-concomitant (administered with an interval of >7 days) - Analysis of the data does not indicate any enhanced toxicity when gemcitabine is administered more than 7 days before or after radiotherapy, other than radiation recall. The data suggest that gemcitabine can be initiated after the acute effects of radiation therapy have resolved or at least one week after radiation.

Radiation injury has been reported in the targeted tissues (e.g., oesophagitis, colitis, and pneumonitis) whether or not gemcitabine was administered concomitantly with the radiotherapy.

Others

The yellow fever vaccine and 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 age / contraception in men and women

Due to the genotoxic potential of gemcitabine (see section 5.3), women of childbearing age must use effective methods of contraception during treatment with gemcitabine and for 6 months after treatment discontinuation. Men must be advised to use effective methods of contraception and not to father a child during treatment with gemcitabine and in the 3 months following its discontinuation.

Pregnancy

There is insufficient 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 passes into the breast milk, and adverse effects on the foetus have not been ruled out. Breast-feeding must be stopped during treatment with gemcitabine.

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 drowsiness, particularly in combination with alcohol consumption. Patients must be advised against driving or operating machinery until it is observed that they are no longer drowsy.

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 to 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

Frequency Organ System	Very Common	Common	Uncommon	Rare	Very rare	Not known
Infections and infestations		Infections				Sepsis
Blood and Lymphatic System Disorders	leucopenia (Neutropenia 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). thrombocytopenia, anaemia	febrile neutropenia.			thrombocytosis, Thrombotic microangiopathy	
Immune System Disorders					anaphylactoid reaction	
Metabolism and nutrition disorders		anorexia				
Nervous system disorders		somnolence, headache, insomnia	stroke		posterior reversible encephalopathy syndrome (see section 4.4)	
Cardiac disorders			arrhythmias, predominantly supraventricular in nature,	myocardial infarct		

			heart failure			
Vascular disorders				hypotension, clinical signs of peripheral vasculitis and gangrene.	capillary leak syndrome (see section 4.4)	
Respiratory, thoracic, and mediastinal disorders	dyspnoea usually mild and passes rapidly without treatment.	cough, rhinitis	interstitial pneumonitis (see section 4.4), bronchospasm usually mild and transient but may require parenteral treatment.	pulmonary oedema, adult respiratory distress syndrome (see section 4.4)		
Gastro-intestinal disorders	nausea, vomiting.	stomatitis and ulceration of mouth, diarrhoea, constipation.			ischaemic colitis	
Hepatobiliary disorders	elevation of liver transaminases (AST and ALT) and alkaline phosphate.	increased bilirubin.	serious hepatotoxicity, including liver failure and death	increased gamma-glutamyl transferase (GGT).		
Skin and subcutaneous tissue disorders	allergic skin rash frequently associated with pruritus, alopecia	itching, sweating		vesicle and sore formation, ulceration, scaling, severe skin reactions, including desquama	Toxic epidermal necrolysis, Stevens-Johnson Syndrome	Pseudoeczema, acute generalised exanthematous pustulosis

				tion and bullous skin eruptions		
Musculoskeletal and connective tissue disorders		back pain, myalgia				
Renal and urinary disorders	haematuria, mild proteinuria		renal failure (see section 4.4), haemolytic uraemic syndrome (see section 4.4)			
General disorders and administration site conditions	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.	fever, asthenia, chills		Injection site reactions - mainly mild in nature.		
Injury poisoning and procedural complications				radiation toxicity (see section 4.5), radiation recall		

Postmarketing experience (spontaneous reports) frequency not known (can't be estimated from the available data)

Nervous system disorders

Cerebrovascular accident

Cardiac disorders

Arrhythmias, predominantly supraventricular in nature

Heart failure

Vascular disorders

Clinical signs of peripheral vasculitis and gangrene

Respiratory, thoracic and mediastinal disorders

Pulmonary oedema

Adult respiratory distress syndrome (see section 4.4)

Gastrointestinal disorders

Ischaemic colitis

Hepatobiliary disorders

Serious hepatotoxicity, including liver failure and death

Skin and subcutaneous tissue disorders

Severe skin reactions, including desquamation and bullous skin eruptions,

Lyell's Syndrome, Steven-Johnson Syndrome

Renal and urinary disorders

Renal failure (see section 4.4)

Haemolytic uraemic syndrome (see section 4.4)

Injury, poisoning and procedural complications

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 (0.0)	3 (1.8)	(0.0)
Febrile neutropenia	0 (0.0)	0 (0.0)	2 (1.1)	(0.0)
Infection without neutropenia	0 (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, 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 of up to 5,700 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: 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 anti-tumoural 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 efficacy and safety

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/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.

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/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 5µg/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

This metabolite can be found in circulating polymorphnuclear cells, and the following information refers to these cells. Intracellular concentrations increase in line with the dose of gemcitabine: doses between 35- and 350 mg/m²/30- min give steady state concentrations of 0.4- to 5 µg/ml. For plasma concentrations of gemcitabine beyond 5 µg/ml, dFdCTP levels do not increase, suggesting that formation is saturable in these cells.

Peak plasma concentrations (3-15 minutes after end of 30-minute infusion, 1,000 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 -288 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

Mannitol,
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 products except those mentioned in section 6.6.

6.3 Shelf life

Unopened vials: 2 years

Reconstituted solution

Chemical and physical in-use stability has been demonstrated for 24 hours at 30⁰C

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 room temperature, unless reconstitution (and further dilution, if applicable) has taken place in controlled and validated aseptic conditions.

Solutions of reconstituted gemcitabine should not be refrigerated, as crystallisation may occur.

This medicine is for single use only

6.4 Special precautions for storage

Vial before opening

Store in the original package.

For storage conditions of the reconstituted medicinal product see section 6.3.

6.5 Nature and contents of container

50 ml type I moulded glass vial with bromobutyl rubber stopper and with 20 mm neck and flip off tear off aluminium seal.

Carton containing a single vial containing 1000 mg gemcitabine.

6.6 Special precautions for disposal

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 reconstitution (and further dilution, if performed)

The only approved diluent for reconstitution of gemcitabine sterile powder is sodium chloride 9 mg/ml (0.9%) solution for injection (without preservative). Due to solubility considerations, the maximum concentration for gemcitabine upon reconstitution is 40 mg/ml. Reconstitution at concentrations greater than 40 mg/ml may result in incomplete dissolution and should be avoided.

1. Use aseptic technique during the reconstitution and any further dilution of gemcitabine for intravenous infusion administration.
2. To reconstitute, add 25 ml sterile sodium chloride 9 mg/ml (0.9%) solution for injection, without preservative, to the 1000 mg vial. The total volume after reconstitution is 26.3 ml (1000 mg vial). This yields a gemcitabine concentration of 38mg/ml, which includes accounting for the displacement volume of the lyophilised powder. Shake to dissolve. Further dilution with sterile sodium chloride 90 mg/ml (0.9%) solution for injection, without preservative, can be done. Reconstituted solution is clear, colourless to light straw-coloured solution.
3. Parenteral medicinal products should be inspected visually for particulate matter and discolouration prior to administration. If particulate matter is observed, do not administer.

Disposal

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

7 MARKETING AUTHORISATION HOLDER

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