SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Gemcitabine 200 mg Powder for Solution for Infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

One vial contains gemcitabine hydrochloride equivalent to 200 mg gemcitabine.
After reconstitution, the solution contains 38 mg/ml of gemcitabine.

Excipients
Each 200 mg vial contains 3.5 mg (<1 mmol) sodium.
For a full list of excipients see section 6.1.

3 PHARMACEUTICAL FORM

Powder for solution for infusion.
White to off-white plug or powder.

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 unresectable, locally recurrent or metastatic breast cancer who have relapsed following adjuvant/neoadjuvant chemotherapy. The Prior chemotherapy must have included an anthracycline unless clinically contraindicated.
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4.2 Posology and method of administration

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

Recommended posology

Bladder cancer
Combination use
The recommended dose for gemcitabine is 1000 mg/m^2, as a 30-minute infusion. The dose must be administered on Days 1, 8 and 15 for a 28-day cycle in combination with cisplatin. Cisplatin is given at the recommended dose of 70 mg/m^2 on Day 1 following gemcitabine or D2 of each 28-day cycle. This 4four-week cycle is then repeated. Dosage reduction with each cycle or within a cycle may be considered based upon the grade of toxicity experienced by the patient.

Pancreatic cancer
The recommended dose is 1000 mg/m^2, admistered as a 30-minute intravenous infusion. The administration should be repeated once weekly for 7 consecutive weeks followed by one week of rest. From the next cycle, the administration must be repeated once weekly for 3 consecutive weeks every 4 weeks. Dosage reduction with each cycle or within a cycle may be considered based upon the grade of toxicity experienced by the patient.

Non small Cell lung cancer
Monotherapy
The recommended dose is 1000 mg/m^2, administered as a 30-minute intravenous infusion. The administration should be repeated once weekly for 3 weeks, followed by a one-week rest period. This 4four-week cycle is then repeated. Dosage reduction with each cycle or within a cycle may be considered based upon the grade of toxicity experienced by the patient.

Combination use
The recommended dose of gemcitabine is 1250 mg/m^2 body surface area given as a 30-minute intravenous infusion on Days 1 and 8 of the treatment cycle (21 day cycles). Dosage reduction with each cycle or within a cycle may

be considered 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
To use gemcitabine in combination with paclitaxel is recommended to administer paclitaxel (175 mg/m^2) on Day 1 over approximately 3-hours as an intravenous infusion, followed by gemcitabine (1250 mg/m^2) as a 30-minute intravenous infusion on Days 1 and 8 of each 21-day cycle. Dosage reduction with each cycle or within a cycle may be considered 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 in combination with paclitaxel .

Ovarian cancer
Combination use
The recommended dose of gemcitabine in combination with carboplatin is 1000 mg/m^2 as a 30-minute intravenous infusion. On days 1 and 8 of each 21-day cycle. Carboplatin is to be administered after gemcitabine, day 1 at a dosage that allows a target AUC of 4.0 mg/mL·min to be reached. Dosage reduction with each cycle or within a cycle may be considered based upon the grade of toxicity experienced by the patient.

Toxicity monitoring and dose modification due to toxicity

Dose modification due to non haematological toxicity
Periodic physical examination and checks of renal and hepatic function mustbe made to detect non- haematological toxicity. Dosage reduction with each cycle or within a cycle may be considered based upon the grade of toxicity experienced by the patient. In general, in the event of severe (Grade 3 or 4) non-haematological toxicity, excluding nausea/vomiting, treatment with gemcitabine must be reduced or suspended in line with the judgement of the physician. Treatment may be postponed, in-line with the judgement of the physician, until the toxicity has resolved.

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 undergo hematological monitoring before each dose; Complete Blood count with Differential and platelet.. Prior to the initiation of a cycle, patients must have an absolute granulocyte count of at least 1500 (x 10^6/L) and a platelet count of 100,000 (x 10^6/L).

Within a cycle
Dose modifications of gemcitabine within a cycle must be adjusted as shown in the tables below:

Dose modification of gemcitabine administed as a monotherapy or in

combination with cisplatin within a cycle in bladder cancer, NSCLC and pancreatic cancer,			
Absolute granulocyte count (x 10^6/L)		**Platelet count (x 10^6/L)**	**Percentage of the average dose of Gemcitabine (%)**
> 1000 and		> 100,000	100
500-1000	or	50,000-100,000	75
<500	or	< 50,000	No dose *

* Omitted treatment is not to be re-instated within a cycle before the absolute granulocyte count reaches at least 500 (x10^6/L) and the platelet count reaches 50,000 (x10^6/L).

Dose modification of gemcitabine in combination with paclitaxel within a cycle in breast cancer		
Absolute granulocyte count (x 10^6/L)	**Platelet count (x 10^6/L)**	**Percentage of the average dose of Gemcitabine (%)**
≥ 1200 and	>75,000	100
1000- <1200 or	50,000-75,000	75
700- <1000 and	≥ 50,000	50
<700 or	<50,000	Omit dose*

*Omitted treatment is not to be re-instated within a cycle. Treatment will start on day 1 of the next cycle once the absolute granulocyte count has reached at least 1,500 (x10^6/L) and the platelet count reaches 100,000 (x10^6/L).

Dose modification of gemcitabine in combination with carboplatin within a cycle in breast cancer			
Absolute granulocyte count (x 10^6/L)		**Platelet count (x 10^6/L)**	**Percentage of the average 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*

*Omitted treatment isnot to be re-instated within a cycle. Treatment will begin on day 1 of the next cycle once the absolute granulocyte count reaches at least 1,500 (x10^6/L) and the platelet count has reached 100,000 (x10^6/L).

Dose modifications, in the following cycles, due to haematological toxicity cycles, for all indications

The dose of gemcitabine must be reduced to 75% of the initial dose of the first cycle, in the event that the following haematological toxicities are observed:

- 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 over one week due to toxicity

Method of administration
Gemcitabine is well tolerated during infusion and can be administered as outpatient care. In the event of extravasation the infusion must generally be stopped immediately and re-administered in different vein. The patient must be closely monitored after the administration.

For reconstitution instructions, see section 6.6.

Special populations

Patients with renal impairment or hepatic impairment
Gemcitabine must be administered with caution in patients with hepatic or renal impairment as there is insufficient information from clinical studies to allow for clear recommendations regarding the doses to be administered in these patient populations (see sections 4.4 and 5.2).

Elderly patients (> 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).

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

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients.
Breast-feeding (see section 4.6).

4.4 Special warnings and precautions for use

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

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.

Haematological toxicity

Gemcitabine can suppress bone marrow function, manifesting as leucopaenia, thrombocytopaenia and anaemia.

Patients receiving gemcitabine should be monitored prior to each dose, including for platelet, leukocyte and granulocyte counts. Treatment interruption or modification mustbe considered each time drug-induced bone marrow toxicity is detected (see section 4.2). However, myelosuppression is short lived and usually does not require a dose reduction and only rarely requires 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 impairment and renal impairment

Gemcitabine mustbe used with caution in patients with or renal impairmentas there is insufficient information from clinical studies to allow for clear recommendation regarding the doses to be administered in these patient populations (see section 4.2).

The administration of gemcitabine in patients who also have liver metastases or a history of hepatitis, alcoholism or cirrhosis may results in exacerbation of 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 $\leq$7 days) toxicity has been reported (see section 4.5 for details and recommendations for use).

Live vaccinations

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

Cardiovascular

Due to the risk of cardiac and/or vascular disorders ongemcitabine, special attention must be paid topatients with a history of cardiovascular events.

Capillary leak syndrome

Cases of capillary leak syndrome have been reported in patients receiving gemcitabine alone or in combination with other anti-cancer agents(see section 4.8). In general, treatments for this condition exist if it is diagnosed early and treated appropriately, but fatal cases have been reported. Thiscondition

involves causes systemic capillary hyperpermeability, with leakage of fluid and proteins from the intravascular space into the interstitium. The clinical characterstics 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 occurs 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 experiencedPRES, 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 mustbe 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 beenreported 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 falling sudden drops in haemoglobin with concurrent thrombocytopenia, and elevated serum bilirubin, creatinine, urea, or LDH levels. Renal impairment may not be reversible on treatment discontinuation and dialysis may be required.

Fertility
In fertility studies gemcitabine caused hypospermatogenesis in male mice (see section 5.3). Men treated with gemcitabine are therefore advised not to father a child during and in the 3months following treatment and to seek additional information on cryopreservationof sperm before beginning treatment due tothe possibility of infertility related to gemcitabine (see section 4.6).

Sodium

Gemcitabine 200 mg powder for solution for infusion contains 3.5 mg (<1 mmol) of sodium per vial. This should be taken into consideration by patients on a controlled sodium diet.

Gemcitabine 1 g powder for solution for infusion contains 17.5 mg (< 1 mmol) sodium per vial. This should be taken into consideration by patients on a controlled sodium diet.

4.5 Interaction with other medicinal products and other forms of interaction

No specific interaction studies have been conducted (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 one clinical trial on patients with non-small cell lung cancer, where gemcitabine was administered at a dose of 1,000 mg/m^2 concomitantly with thoracic radiotherapy for a duration of up to 6 consecutive weeks, significant toxicity in the form of severe, potentially life threatening mucositis, including oesophagitis, and pneumonitis were observed, particularly in patients who received large volumes of radiotherapy [median treatment volume 4,795 cm^3]. Subsequent studies have suggested that gemcitabine may feasibly be administered with radiotherapy at lower doses with predictable toxicity, as was the case in one phase II study in non-small cell lung cancer, in which doses of thoracic radiotherapy of 66 Gy were administered concomitantly with gemcitabine (600 mg/m^2, four times) and cisplatin (80 mg/m^2 twice) for 6 weeks. The optimum regimen for safe administration of
gemcitabine with therapeutic doses of radiotherapyhas not yet been determined in all tumour types.

Non-concomitant (administered with an interval of >7 days -- Analysis of the data does not indicate that toxicity increases 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 target tissues (for example 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 a risk of potentially fatal systemic, , disease, particularly in immunosuppressed patients.

4.6 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 insufficient data on the use of gemcitabine in pregnant women. Animal studies in animals have demonstrated reproductive toxicity (see section 5.3). Based on the results ofanimal studies and on the mechanism of action of gemcitabine, this product must should not be used during pregnancy except where necessary. Patients must be informed of the risk related not to treatment with gemcitabine and toduring pregnancy, and must immediately , inform their doctor in the event of pregnancy.

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

Fertility
In fertility studies gemcitabine caused hypospermatogenesis in male mice (see section 5.3). Therefore, men treated with gemcitabine are therefire advised not to father a child during and in the 3 months following treatment and to additional information on cryopresevation of sperm before beginning to treatment due to the possibility of infertility related to gemcitabine.

4.7 Effects on ability to drive and use machines

The effects on ability to drive and use machines have not been studied. However, it has been reported that gemcitabine can cause mild to moderate drowsiness, particularly in combination with alcohol consumption. Patients must be advised against driving or using machinery until it is observed that they are no longer drowsy.

4.8 Undesirable effects

The most commonly reported adverse reactions associated with Gemcitabine include: nausea with or without vomiting, elevated liver transaminases (AST/ALT) and alkaline phosphatase levels, reported in approximately 60% of patients; proteinuria and haematuria reported in approximately 50% of patients; dyspnoea reported in 10 to 40% of patients (higher incidence rate in patients with lung cancer); allergic drug eruptions, occurring in approximately 25% of patients and are associated with pruritusin 10% of patients.

The frequency and severity of adverse reactions depends onthe dose, the infusion rate and the intervals between doses (see section 4.4). Dose-limiting adverse reactions are : reduced platelets, leukocyte and granulocyte counts (see section 4.2).

Data from clinical studiesFrequencies are defined as follows: Very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1000 to <1/100), rare (≥1/10,000 to <1/1000), very Rare (<1/10,000) and frequency not known (cannot be estimated based on available data).

The table below displaying the adverse reactions and their frequency is based on data from clinical studies. Within each frequency grouping, adverse reactionsare presented in order of decreasing seriousness.

System Organ Class	Frequency grouping
Infections and infestations	Common • Infections. Unknown frequency • Sepsis.
Blood and lymphatic system disorders	Very common • Leucopaenia (Neutropaenia Grade 3 = 19.3 %; Grade 4 = 6 %). Myelosuppression is generally mild to moderate and primarilyaffects 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
Infections and infestations	Common • Infections Not known • Sepsis
Metabolism and nutrition disorders	Common • Anorexia
Nervous system disorders	Common • Headache • Insomnia • Somnolence Uncommon • Stroke Very rare • Posterior reversible encephalopathy syndrome (see section 4.4)
Cardiac disorders	Rare • Myocardial infarct Uncommon • Arrhythmia, primarily supraventricular arrhythmia • Heart Failure
Vascular disorders	Rare • Hypotension • Clinical signs of peripheral vasculitis and gangrene Very rare • Capillary leak syndrome (see section 4.4)

System Organ Class	Frequency grouping
Respiratory, thoracic and mediastinal disorders	Very common • Dyspnoea –usually mild and passes rapidly without treatment Common • Cough • Rhinitis Uncommon • Interstitial pneumonitis (see section 4.4) • Bronchospasm –usually mild and transient but may require parenteral treatment Rare • Pulmonary Oedema. • Adult respiratory distress syndrome (see section 4.4).
Gastrointestinal disorders	Very common • Vomiting • Nausea Common • Diarrhoea • Stomatitis and ulceration of the mouth • Constipation Very rare • Ischaemic colitis
Hepatobiliary disorders	Very common • Elevation of liver transaminases (AST and ALT) and alkaline phosphatase levels Common • Elevated bilirubin Uncommon • Serious hepatotoxicity, including hepatic failure and death. Rare • Elevated gamma-glutamyl transferase (GGT) levels
Skin and subcutaneous tissue disorders	Very common • Allergic skin rash frequently associated with pruritus • Alopecia Common • Pruritus • Sweating

	Rare • Ulceration • Blister and sore formation • ScalingDesquamation • Severe skin reactions, including desquamation and bullous eruptions Very rare • Toxic epidermal necrolysis • Stevens-Johnson syndrome Not known • Pseudocellulitis. • Acute generalized exanthematous pustulosis.

System Organ Class	Frequency grouping
Musculoskeletal and connective tissue disorders	Common • Back pain • Myalgia
Renal and urinary disorders	Very Common • Haematuria • Mild proteinuria Uncommon • Renal impairment (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 oedemaincluding 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	• 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
Arrythmias, 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 toxicity, including neutropenia, increases when gemcitabine is administeredin combination with paclitaxel. However, the increased frequency of these adverse reactions is not associated with an increased rate of infectiousor haemorrhagic events. Fatigue and febrile neutropaenia occur more frequently when gemcitabine is adminstered in combination with paclitaxel. Fatigue, not associated with anaemia, generally resolves after the first cycle.

Grade 3 and 4 Adverse Reactions

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 persisting for over 7 days was reported in 12.6% of patients in the gemcitabine-paclitaxel combination arm and 5.0% of patients enrolled in the arm receiving paclitaxel

Combination use in bladder cancer

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

Combination use in ovarian cancer

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

Sensory neuropathy was most commonly reported in the carboplatin combination arm than with Carboplatin monotherapy

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 Yellow Card Scheme
Website: 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 5700 mg/m^2 have been administered as30-minute IV infusion every two weeks with acceptable clinical toxicity. If overdose is suspected, the patient must undergo monitoring including appropriate blood counts and receive supportive therapy, if necessary.

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-tumor activity in preclinical models
In animal tumour models, the anti-tumour activity of gemcitabine is schedule-dependent. When gemcitabine is administered daily, high mortality but minimal anti-tumour activity is observed. among animals. However if, gemcitabine is given every third or fourth day, it can be administered in non-lethal doses with substantial anti-tumouractivity in a large number 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 active difluorodeoxycytidine diphosphate (dFdCDP) and difluorodeoxycytidine triphosphate (dFdCTP) . The cytotoxic effect of gemcitabine is due to inhibition of DNA synthesis by the dual mechanism of action of dFdCDP and dFdCTP. First, dFdCDP inhibits ribonucleotide reductase, which is solely responsible for catalysing the reactions that produce deoxynucleoside triphosphates (dCTP) for DNA synthesis. Inhibition of this enzyme by dFdCDP results in reduced concentration of deoxynucleosides in

general and, dCTP in particular,. Second, dFdCTP competes with dCTP for incorporation into DNA (self-potentiation).

In the same way , a small quantity of gemcitabine can also be incorporated into RNA.As such , 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 forming DNA strands. After gemcitabine is incorporated into DNA, one additional nucleotide is added to the growing DNA strands. After this addition there is primarily a complete inhibition of further DNA synthesis (masked chain termination). After incorporation into DNA, gemcitabine appears to induce the programmed cell death process known as apoptosis.

Clinical particulars

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 increase in the time to progression from 0.9 to 2.3 months (log-rank p<0.0002) and a statistically significant increase in median survival from 4.4 to 5.7 months (log-rank p<0.0024) were observed in patients treated with gemcitabine compared with 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 non-small cell lung cancer (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 increase in the time to progression, from 3.7 to 5.6 months (log-rank p<0.0012) and a statistically significant increase in median survival from 7.6 to 9.1 months (log-rank p<0.004) were observed in patients treated with gemcitabine/cisplatin compared with 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 increase in the time to progression, from 4.3 to 6.9 months (p=0.014) was observed in

patients treated with gemcitabine/cisplatin compared with patients treated with etoposide/cisplatin.
In both studies similar tolerance was observed in the both 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 increase in the time to disease progression of disease, from 5.8 to 8.6 months (log-rank p= 0.0038) was observed in patients treated with GCb compared with patients treated with Cb. Differences in terms of response rate which was 47.2% in the GCb arm versus 30.9% in the Cb arm (p=0.0016) and in median survival, which was 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 after adjuvant/neoadjuvant chemotherapy, gemcitabine in combination with paclitaxel showed a statistically significant increase in time to disease progression from 3.98 to 6.14 months (log-rank p=0.0002) in patients treated with gemcitabine/paclitaxel compared with 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 with 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 aged 29 to 79 years. Of these patients, approximately 45% had non-small cell lung cancer and 35% were diagnosed with pancreatic cancer. The following pharmacokinetic parameters were obtained for doses ranging from 500 to 2,592 mg/m^2 that were infused from 0.4 to 1.2 hours.

Peak plasma concentrations (obtained in 5 minutes of the end of the infusion) were 3.2 to
45.5 μg/ml. Plasma concentrations of gemcitabine following a dose of 1,000 mg/m^2/30-minutes were higher than 5 μg/ml for almost 30-minutes after the end of the infusion, and above 0.4 μg/ml for an the following 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 (the 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 did not vary depending on sex. Plasma protein binding was was considered to be negligible.
The half-life was.
Between 42 and 94 minutes depending on age and sex . For the recommended dosing regimen, elimination elimination of gemcitabine should be virtually

complete in 5 to 11 hours following the start of 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.

Elemination

Systemic clearance is between 29.2 l/hr/m^2 and 92.2 /hr/m^2 depending on gender and age (inter-individual variability was 52.2%). In women, clearance is approximately 25% lower than the values in men. Although rapid, it seems that, in men and women, clearance decreaseswith age. For the recommended dose of 1000 mg/m^2 administered inas a 30-minute infusion, lower clearance values for women and men should not require a gemcitabine dose reduction.
Urinary excretion: Shows that less than 10% of the drug is excreted in its unchanged form..
Renal clearance is 2 to 7 L/h/m^2.

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

dFdCTP kinetics

This metabolite can be found in circulating polymorphonuclear and the following information refers to these cells. Intracellular concentrations increase in in line with the dose of gemcitabine doses between 35 and-350 mg/m^2/30-min, which give steady state concentrations of 0.4-5 μg/ml. For plasma concentrations of gemcitabine beyond 5 μg/ml, dFdCTP levels do not increase, suggesting that formation is saturable in these cells.
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/m²/30- min give steady state concentrations of 0.4- to 5 μg/ml. For plasma concentrations of gemcitabine beyond 5 μg/mlμg/mL, dFdCTP levels do not increase, suggesting that formation is saturable in these cells.

The Peak plasma concentrations (3-15 minutes after the end of an infusion of, 1000 mg/m^2) over 30 minutes) is 28to 52 μg/ml. The lowest plasma concentration after weekly administered are : 0.07 to1.12 μg/ml, with no apparent accumulation. The triphasic plasma concentration versus time curve, shows an average terminal half-life of - 65 hours (range 33 to 84 hours).
Formation of dFdU from the parent compound is 91%-98%.

The mean volume of distribution of the central compartment is 18 L/m^2 (range 11to22 l/m^2).
The mean steady state volume of distribution (Vss)is 150 L/m^2 (range 96 to228 L/m^2).
Tissue distribution: is significant
Mean apparent clearance is 2.5 L/hr/m^2 (range 1-4 L/hr/m^2). Excretion is entirely via the urine

Gemcitabine and paclitaxel combination therapy
Combination therapy did not alter the pharmacokinetics of either gemcitabine or paclitaxel.
Gemcitabine and carboplatin combination therapy

When administered in combination with carboplatin the pharmacokinetics of gemcitabine was not altered

Renal impairment
Mild to moderate renal impairment (creatinine clearance between 30 and 80 ml/min) has noproven , significant effect on the pharmacokinetic properties of gemcitabine.

5.3 Preclinical safety data

In repeat-dose studies for up to 6 months performed in mice and dogs, the main observation was programmed and dose-dependent suppression of haematopoiesis, the effects of which were reversible.

Gemcitabine has demonstrateds mutagenic effects in an *in vitro* mutation test and an *in vivo* bone marrow micronucleus test. Long term animal studies assessing the carcinogenic potential have not been conducted.

In fertility studies, gemcitabine caused reversible hypospermatogenesis in male mice. No effects on female fertility were detected.

Assessment of experimental animal studies has shown reproductive toxicity for example congenital abnormalities and other effects on embryonic development pregnancy progression and peri- and postnatal development.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Gemcitabine 200 mg powder for solution for infusion contains:
Mannitol (E421)
Sodium acetate (E262)
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

As packaged for sale:
3 years

After reconstitution: Chemical and physical in-use stability has been demonstrated for 21 days at 25°C. 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.

6.4 Special precautions for storage

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

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

6.5 Nature and contents of container

(For 200 mg vials):
The product is contained in 10 ml Type I clear tubular glass vial and are closed with 20 mm grey bromobutyl rubber stopper and sealed with 20 mm aluminium flip off royal blue seal.

1 vial per pack.

Not all pack sizes may be marketed.

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 5 ml of sterile sodium chloride 9 mg/ml (0.9 %) solution for injection, without preservative, to the 200 mg vial or 25 ml sterile sodium chloride 9 mg/ml (0.9 %) solution for injection, without preservative, to the 1 g vial. The total volume after reconstitution is 5.26 ml (200 mg vial) or 26.3 ml (1 g vial) respectively. This yields a gemcitabine concentration of 38 mg/ml, which includes accounting for the displacement volume of the lyophilised powder. Shake to dissolve. Further dilution with sterile sodium chloride 9 mg/ml (0.9 %) solution for injection, without preservative can be done. Reconstituted solution is a 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.

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

7 MARKETING AUTHORISATION HOLDER

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