

## PRESCRIBING INFORMATION

# Gemcitabine “Ebewe” Powder for solution for Infusion 200 mg vial and 1000 mg vial

## COMPOSITION

### Powder for solution for infusion:

Vials contain gemcitabine hydrochloride equivalent to 200 mg gemcitabine and 1000 mg.

Each 200 mg vial contains 3.9 mg (< 1 mmol) sodium.

Each 1000 mg vial contains 19.6 mg (< 1 mmol) sodium.

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

## CLINICAL PARTICULARS

### Therapeutic Indications

Palliative treatment of patients with locally advanced or metastatic non-small cell lung cancer and locally advanced or metastatic adenocarcinoma of the pancreas and for patients with 5-FU refractory pancreatic cancer.

Gemcitabine is indicated for the treatment of patients with bladder cancer at the invasive stage.

**Breast cancer:** 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.

**Ovarian cancer:** Gemcitabine in combination with carboplatin is indicated for the treatment of patients with recurrent epithelial ovarian carcinoma that has relapsed at least six months after platinum based therapy.

### Posology and Method of Administration

**Gemcitabine should only be prescribed by a physician qualified in the use of anticancer chemotherapy.**

#### Bladder cancer

**Combination use:** The recommended dose for gemcitabine is 1000 mg/m<sup>2</sup>, given by 30-minute intravenous infusion. The dose should be given on days 1, 8 and 15 of each 28-day cycle in combination with cisplatin. Cisplatin is given at a recommended dose of 70 mg/m<sup>2</sup> 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/m<sup>2</sup>, 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 intravenous infusions 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/m<sup>2</sup>, 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 of gemcitabine is 1250 mg/m<sup>2</sup>, given as a 30-minute intravenous infusion on days 1 and 8 of the 21 day treatment cycle. Dosage reduction with each cycle or within a cycle may be applied based upon the grade of toxicity experienced by the patient. Cisplatin has been used at doses between 75-100 mg/m<sup>2</sup> once every 3 weeks.

#### Breast cancer

**Combination use:** Gemcitabine in combination with paclitaxel is recommended using paclitaxel (175 mg/m<sup>2</sup>) administered on day 1 over approximately 3 hours as an intravenous infusion, followed by gemcitabine (1250 mg/m<sup>2</sup>) 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 applied based upon the grade of toxicity experienced by the patient. Patients should have an absolute granulocyte count of at least 1,500 (x10<sup>9</sup>/l) prior to initiation of gemcitabine with paclitaxel combination.

#### Ovarian cancer

**Combination use:** Gemcitabine in combination with carboplatin is recommended using gemcitabine 1000 mg/m<sup>2</sup> administered on days 1 and 8 of each 21-day cycle as a 30-minute intravenous infusion. After gemcitabine, carboplatin should 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-hematological toxicity**

Periodic physical examination and checks of renal and hepatic function should be made to detect non-hematological 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 and 4) non-hematological toxicity, except nausea/vomiting, therapy with gemcitabine should be withheld or decreased depending on the judgment 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 Physicians Information.

#### Dose modification due to hematological toxicity

**Upon initiation of the 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 (x10<sup>9</sup>/l) and thrombocyte count of 100,000 (x10<sup>9</sup>/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 as monotherapy or in combination with cisplatin**

Absolute granulocyte count (x10 <sup>9</sup> /l)	Platelet count (x10 <sup>9</sup> /l)	% 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 *

\* Omitted treatment will not be re-instated within a cycle before the absolute granulocyte count reaches at least 500 (x10<sup>9</sup>/l) and the platelet count reaches 50,000 (x10<sup>9</sup>/l).

**Dose modification of gemcitabine within a cycle for breast cancer given in combination with paclitaxel**

Absolute granulocyte count (x10 <sup>9</sup> /l)	Platelet count (x10 <sup>9</sup> /l)	% of standard dose of gemcitabine
≥ 1,200 and	> 75,000	100
1000 - < 1,200 or	50,000-75,000	75
700 - < 1,000 and	≥ 50,000	50
< 700 or	< 50,000	Omit dose *

\* Omitted treatment 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 1500 (x10<sup>9</sup>/l) and the platelet count reaches 100,000 (x10<sup>9</sup>/l).

**Dose modification of gemcitabine within a cycle for ovarian cancer, given in combination with carboplatin**

Absolute granulocyte count (x10 <sup>9</sup> /l)	Platelet count (x10 <sup>9</sup> /l)	% of standard dose of gemcitabine
> 1,500 and	≥ 100,000	100
1000-1,500 or	75,000-100,000	50
< 1000 or	< 75,000	Omit dose *

\* Omitted treatment 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 1500 (x10<sup>9</sup>/l) and the platelet count reaches 100,000 (x10<sup>9</sup>/l).

**Dose modification due to hematological 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 hematological toxicities:

1. Absolute granulocyte count < 500 x 10<sup>9</sup>/l for more than 5 days
2. Absolute granulocyte count < 100 x 10<sup>9</sup>/l for more than 3 days
3. Febrile neutropenia
4. Platelets < 25,000 x10<sup>9</sup>/l
5. Delay of next treatment cycle by more than 1 week due to toxicity

### Method of administration

**Gemcitabine “Ebewe”** is tolerated well during infusion and may be administered in outpatient settings. 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 “Instructions for Use/Handling”.

### 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 “Special Warnings and Precautions for Use” & “Pharmacokinetic Properties”).

**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 “Pharmacokinetic Properties”).

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

### Contraindications

Hypersensitivity to the active substance or to any of the excipients.

Breast-feeding (see section “Pregnancy and Lactation”).

### Special Warnings and Precautions for Use

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

**Hematological toxicity:** Gemcitabine can suppress bone marrow function as manifested by leucopenia, thrombocytopenia and anemia.

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 dysfunction is detected (see section “Posology and Method of Administration”). 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 insufficiency:** 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 insufficiency.

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

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

**Concomitant radiotherapy:** Concomitant radiotherapy (given together or ≤ 7 days apart): Toxicity has been reported (see section “Interactions with other Medicaments and other forms of Interaction”) for details and recommendations for use).

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**Live vaccinations:** Yellow fever vaccine and other live attenuated vaccines are not recommended in patients treated with gemcitabine (see section “Interactions with other Medicaments and other forms of Interaction”).

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

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

**Renal:** Clinical findings consistent with the hemolytic uremic syndrome (HUS) were rarely reported in patients receiving gemcitabine (see section “Undesirable Effects”). Gemcitabine should be discontinued at the first signs of any evidence of microangiopathic hemolytic anemia, such as rapidly falling hemoglobin 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 “Preclinical Safety Data”). Therefore, men being treated with gemcitabine are advised not to father a child during and up to 6 months after treatment and see further advice regarding cryoconservation of sperm prior to treatment because of the possibility of infertility due to therapy with gemcitabine (see section “Pregnancy and Lactation”).

### Sodium:

**Powder for solution for infusion:** Vials contain gemcitabine hydrochloride equivalent to 200 mg gemcitabine and 1000 mg.

Each 200 mg vial contains 3.9 mg (< 1mmol) sodium.

Each 1000 mg vial contains 19.6 mg (< 1mmol) sodium.

**These should be taken into consideration in patients on a controlled sodium diet.**

**Interactions with other Medicaments and other forms of Interaction**

No specific interaction studies have been performed (see section “Pharmacokinetic Properties”).

**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 radiosensitizing activity. In a single trial, where gemcitabine at a dose of 1,000 mg/m<sup>2</sup> 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 esophagitis and pneumonitis was observed, particularly in patients receiving large volumes of radiotherapy (median treatment volumes 4,795 cm<sup>3</sup>). 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 66Gy were applied concomitantly with an administration of gemcitabine (600 mg/m<sup>2</sup>, four times) and cisplatin (80 mg/m<sup>2</sup> twice) during 6 weeks. The optimum regimen for safe administration of gemcitabine with therapeutic doses of radiation has not yet been determined in all tumor 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” phenomena. 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. esophagitis, colitis and pneumonitis) in association with both concurrent and non-concurrent use of gemcitabine.

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

### 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 “Preclinical Safety Data”). Based on results from animal studies and the mechanism of action of gemcitabine, this substance should not be used during pregnancy unless clearly necessary. Women should be advised not to become pregnant during treatment with gemcitabine and to warn their attending physician immediately, should this occur after all.

**Breast-feeding:** It is not known whether gemcitabine is excreted in human milk and adverse effects to the nursing child can not be excluded. Breast-feeding must be discontinued during gemcitabine therapy.

**Fertility:** In fertility studies gemcitabine caused hypospermatogenesis in male mice (see section “Preclinical Safety Data”). Therefore, males being treated with gemcitabine are advised to avoid conception during and up to 6 months after cessation of treatment and seek further advice regarding cryoconservation of sperm prior to treatment because of the possibility of infertility due to therapy with gemcitabine.

**Effects on Ability to Drive and Use Machines**

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

### Undesirable Effects

The most commonly reported adverse drug reactions associated with Gemcitabine “Ebewe” include: nausea with or without vomiting, raised liver transaminases (AST/ALT) and alkaline phosphatase, reported in approximately 60% of patients; proteinuria and hematuria reported in approximately 50% of patients; dyspnea 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 “Special Warnings and Precautions for Use”). Dose-limiting adverse reactions are reductions in thrombocyte, leucocyte and granulocyte counts (see section “Posology and Method of Administration”).

### Clinical trial data:

Frequencies are defined as: Very common (≥ 1/10), Common (≥ 1/100 to < 1/10), Uncommon (≥ 1/1000 to < 1/100), Rare (≥ 1/10000 to < 1/1000), Very Rare (< 1/10000).

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 severity.

System organ class	Frequency grouping
Blood and lymphatic system disorder	<i>Very common</i> <ul style="list-style-type: none"><li>• Leucopenia (Neutropenia Grade 3 = 19.3%; Grade 4 = 6%)</li></ul> Bone marrow suppression is usually mild to moderate and mostly affects the granulocyte count (see section “Posology and Method of Administration”). <ul style="list-style-type: none"><li>• Thrombocytopenia</li><li>• Anemia</li></ul> <i>Common</i> <ul style="list-style-type: none"><li>• Febrile neutropenia</li></ul> <i>Very rare</i> <ul style="list-style-type: none"><li>• Thrombocytosis</li></ul>
Immune system disorders	<i>Very rare</i> <ul style="list-style-type: none"><li>• Anaphylactoid reaction</li></ul>
Metabolism and nutrition disorders	<i>Common</i> <ul style="list-style-type: none"><li>• Anorexia</li></ul>
Nervous system disorders	<i>Common</i> <ul style="list-style-type: none"><li>• Headache</li><li>• Insomnia</li><li>• Somnolence</li></ul>
Cardiac disorders	<i>Rare</i> <ul style="list-style-type: none"><li>• Myocardial infarct</li></ul>
Vascular disorders	<i>Rare</i> <ul style="list-style-type: none"><li>• Hypotension</li></ul>
Respiratory, thoracic and mediastinal disorders	<i>Very common</i> <ul style="list-style-type: none"><li>• Dyspnea – usually mild, resolves rapidly without treatment</li></ul> <i>Common</i> <ul style="list-style-type: none"><li>• Cough</li><li>• Rhinitis</li></ul> <i>Uncommon</i> <ul style="list-style-type: none"><li>• Interstitial pneumonitis (see section “Special Warnings and Precautions for Use”)</li><li>• Bronchospasm – usually mild and transient but may require parenteral treatment</li></ul>
Gastrointestinal disorders	<i>Very common</i> <ul style="list-style-type: none"><li>• Vomiting</li><li>• Nausea</li></ul> <i>Common</i> <ul style="list-style-type: none"><li>• Diarrhea</li><li>• Stomatitis and ulceration of oral mucosa</li><li>• Constipation</li></ul>
Hepatobiliary disorders	<i>Very common</i> <ul style="list-style-type: none"><li>• Elevation of liver transaminases (AST and ALT) and alkaline phosphatase</li></ul> <i>Common</i> <ul style="list-style-type: none"><li>• Increased bilirubin</li></ul> <i>Rare</i> <ul style="list-style-type: none"><li>• Increased gamma-glutamyl transferase (GGT)</li></ul>
Skin and subcutaneous tissue disorders	<i>Very common</i> <ul style="list-style-type: none"><li>• Allergic skin rash frequently associated with pruritus</li></ul> <i>Common</i> <ul style="list-style-type: none"><li>• Alopecia</li><li>• Itching</li><li>• Sweating</li></ul> <i>Rare</i> <ul style="list-style-type: none"><li>• Ulceration</li><li>• Vesicle and sore formation</li><li>• Scaling</li></ul> <i>Very rare</i> <ul style="list-style-type: none"><li>• Severe skin reactions, including desquamation and bullous skin eruptions</li></ul>
Musculoskeletal and connective tissue disorder	<i>Common</i> <ul style="list-style-type: none"><li>• Back Pain</li><li>• Myalgia</li></ul>
Renal and urinary disorders	<i>Very common</i> <ul style="list-style-type: none"><li>• Hematuria</li><li>• Mild proteinuria</li></ul>
General disorders and administration site conditions	<i>Very common</i> <ul style="list-style-type: none"><li>• 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.</li><li>• Edema/peripheral edema-including facial edema.</li></ul> Edema is usually reversible after stopping treatment. <i>Common</i> <ul style="list-style-type: none"><li>• Fever</li><li>• Asthenia</li><li>• Chills</li></ul> <i>Rare</i> <ul style="list-style-type: none"><li>• Injection site reactions mainly mild in nature</li></ul>
Injury, poisoning and procedural complications	Radiation toxicity (see section “Interactions with other Medicaments and other forms of Interaction”).

## Postmarketing experience (spontaneous reports) frequency not known (can not 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 edema

Adult respiratory distress syndrome (see section "Special Warnings and Precautions for Use").

### Gastrointestinal disorders

Ischemic 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 "Special Warnings and Precautions for Use")

Hemolytic uremic syndrome (see section "Special Warnings and Precautions for Use")

### Injury, poisoning and procedural complications

Radiation recall

### Combination use in breast cancer

The frequency of Grade 3 and 4 hematological 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 hemorrhagic 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 vs. gemcitabine & paclitaxel

	Number (% of patients)			
	Paclitaxel arm (N=259)		Gemcitabine and paclitaxel arm (N=262)	
	Grade 3	Grade 4	Grade 3	Grade 4
<b>Hematological</b>				
Anemia	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)*
<b>Non-hematological</b>				
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 vs. gemcitabine & cisplatin

	Number (% of patients)			
	MVAC (methotrexate, vinblastine, adriamycin and cisplatin arm) (N=196)		Gemcitabine and cisplatin arm (N=200)	
	Grade 3	Grade 4	Grade 3	Grade 4
<b>Hematological</b>				
Anemia	30 (16)	4 (2)	47 (24)	7 (4)
Thrombocytopenia	15 (8)	25 (13)	57 (29)	57 (29)
<b>Non-hematological</b>				
Nausea and vomiting	37 (19)	3 (2)	44 (22)	0
Diarrhea	15 (8)	1 (1)	6 (3)	0
Infection	19 (10)	10 (5)	4 (2)	1 (1)
Stomatitis	34 (18)	8 (4)	2 (1)	0

### Combination use in ovarian cancer

#### Grade 3 and 4 adverse events carboplatin vs. gemcitabine & carboplatin

	Number (% of patients)			
	Carboplatin arm (N=174)		Gemcitabine and carboplatin arm (N=175)	
	Grade 3	Grade 4	Grade 3	Grade 4
<b>Hematological</b>				
Anemia	10 (5.7)	4 (2.3)	39 (22.3)	5 (5.1)
Neutropenia	19 (10.9)	2 (1.1)	73 (41.7)	90 (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)
<b>Non-hematological</b>				
Hemorrhage	0	0	3 (1.8)	0
Febrile neutropenia	0	0	2 (1.1)	0
Infection without neutropenia	0	0	0	0

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

### Overdose

There is no known antidote for overdose of gemcitabine. Doses as high as 5700 mg/m<sup>2</sup> have been administered by intravenous infusion over 30 minutes every 2 weeks with clinically acceptable toxicity. In the event of suspected overdose, the patient blood counts should be monitored and the patient should receive supportive therapy, as necessary.

## PHARMACOLOGICAL PROPERTIES

### 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 tumor 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 G<sub>1</sub>/S phase boundary. *In vitro*, the cytotoxic effect of gemcitabine is dependent on both concentration and time.

### Antitumoral activity in preclinical models

In animal tumor models, antitumoral activity of gemcitabine is schedule-dependant. When gemcitabine is administered daily, high mortality among the animals but minimal antitumoral activity is observed. If, however, gemcitabine is given every third or fourth day, it can be administered in non-lethal doses with substantial antitumoral activity against a broad spectrum of mouse tumors.

### Mechanism of action

Cellular metabolism and mechanism of action: Gemcitabine (dFdC), which is a pyrimidine antimetabolite, is metabolized 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. 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 randomized 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 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% response, 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 randomized, phase III study of 135 patients with stage IIIB or IV NSCLC, a combination of gemcitabine and cisplatin showed a statistically higher response rate than a combination of cisplatin and etoposide (40.6% and 21.2%, respectively, p=0.025). A statistically significant prolongation of 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 randomized 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, 47.2% in the GCb arm versus 30.9% in the Cb (p=0.0016), and median survival, 18 months GCb versus 17.3 Cb (p=0.73) favored the GCb arm.

**Breast cancer:** In a randomized 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. After 3077 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).

### Pharmacokinetic Properties

The pharmacokinetics of gemcitabine has 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, approx. 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<sup>2</sup> 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 1000 mg/m<sup>2</sup>/30 minutes are greater than 5 µg/ml for approximately 30 minutes after the end of the infusion and greater than 0.4 µg/ml for an additional hour.

### Distribution

The volume of distribution of the central compartment was 12.4 l/m<sup>2</sup> for women and 17.5 l/m<sup>2</sup> for men (inter-individual variability was 91.9%). The volume of distribution of the peripheral compartment was 47.4 l/m<sup>2</sup>.

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 metabolized by cytidine deaminase in the liver, kidney, blood and other tissues. Intracellular metabolism of gemcitabine produces the gemcitabine mono, di and triphosphates (dFdCMP, dFdCDP and dFdCTP) of which dFdCDP and dFdCTP are considered active. These intracellular metabolites have not been detected in plasma or urine. The primary metabolite, 2'-deoxy-2', 2'-difluorouridine (dFdU), is not active and is found in plasma and urine.

### Excretion

Systemic clearance ranged from 29.2 l/hr/m<sup>2</sup> to 92.2 l/hr/m<sup>2</sup> 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 1000 mg/m<sup>2</sup> 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 2–7 l/hr/m<sup>2</sup>.

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 feces.

### dFdCTP kinetics

This metabolite can be found in peripheral blood mononuclear cells and the information below refers to these cells. Intracellular concentrations increase in proportion to gemcitabine doses of 35-350 mg/m<sup>2</sup>/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 saturated 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/m<sup>2</sup>): 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/m<sup>2</sup> (range 11–22 l/m<sup>2</sup>).

Mean steady-state volume distribution (V<sub>ss</sub>): 150 l/m<sup>2</sup> (range 96–228 l/m<sup>2</sup>).

Tissue distribution: Extensive.

Mean apparent clearance: 2.5 l/hr/m<sup>2</sup> (range 1–4 l/hr/m<sup>2</sup>).

Urinary excretion: All.

### Gemcitabine and paclitaxel combination therapy

Gemcitabine 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.

### 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-dependant hematopoietic suppression which was reversible.

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

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

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

## PHARMACEUTICAL PARTICULARS

### List of Excipients

#### Powder for solution for infusion

Mannitol (E421), Sodium acetate (E262), Sodium hydroxide (E524) for pH adjustment, Water for injection.

### Incompatibilities

Should not be mixed with other medicinal products except those mentioned in section "Instructions for use/ Handling".

### Shelf Life

Powder for solution for infusion - 30 months.

**Shelf life after dilution:** Chemical and physical in-use stability has been demonstrated for 24 h at 25°C.

From a microbiological point of view, the solution should be administered immediately after dilution. 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 h at room temperature. Unless reconstitution and further dilution has taken place in controlled and validated aseptic conditions.

### Special Precautions for Storage

#### Powder for solution for infusion

Do not refrigerate or freeze. For storage conditions of the diluted medicinal product see section "Shelf Life".

### Nature and contents of container

#### Powder for solution for infusion

Clear colorless type I glass vials 10 ml and 50 ml.

### Instructions for Use/Handling.

#### Powder for solution for infusion

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.

- Parenteral drugs should be inspected visually for particulate matter and discoloration, prior to administration, whenever solution and container permit.
- Use aseptic technique during the reconstitution and any further dilution of gemcitabine for IV infusion.
- 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 1000 mg vial. The total volume after reconstitution is 5.26 ml (200 mg vial) or 26.3 ml (1000 mg vial) respectively. This results in a concentration of gemcitabine 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, colorless to light straw-colored solution.

### 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.

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

### Presentations

**Powder for solution for infusion:** Vials contain gemcitabine hydrochloride equivalent to

Gemcitabine "Ebewe" 200 mg - 1vial

Gemcitabine "Ebewe" 1000 mg - 1 vial

## MANUFACTURER

EBEWE Pharma Ges.m.b.H., A-4866 Unterach, Austria

## LICENSE HOLDER

Pharmalogic LTD, P.O.B. 3838, Petah-Tikva 49130

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