SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Gemcitabine medac 38 mg/ml powder for solution for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One vial contains gemcitabine hydrochloride equivalent to 200 mg gemcitabine.
One vial contains gemcitabine hydrochloride equivalent to 1,000 mg gemcitabine.
One vial contains gemcitabine hydrochloride equivalent to 1,500 mg gemcitabine.

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

Excipients with known effect
Each 200 mg vial contains 3.5 mg (< 1 mmol) sodium.
Each 1,000 mg vial contains 17.5 mg (< 1 mmol) sodium.
Each 1,500 mg vial contains 26.3 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 powder.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

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

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

Gemcitabine is indicated for the treatment of patients with locally advanced or metastatic epithelial ovarian carcinoma, in combination with carboplatin, in patients with relapsed disease following a recurrence-free interval of at least 6 months after platinum-based, first-line therapy.

Gemcitabine, in combination with paclitaxel, is indicated for the treatment of patients with unresectable, locally recurrent or metastatic breast cancer who have relapsed following adjuvant/neoadjuvant chemotherapy. Prior chemotherapy should have included an anthracycline unless clinically contraindicated.

4.2 Posology and method of administration

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

Posology

Bladder cancer
Combination use
The recommended dose for gemcitabine is 1,000 mg/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. Dose 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. Dose 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 should be repeated once weekly for 3 weeks, followed by a 1-week rest period. This 4-week cycle is then repeated. Dose 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 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). Dose 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 10^6/l) prior to initiation of gemcitabine + paclitaxel combination.

Ovarian cancer
Combination use
Gemcitabine, in combination with carboplatin, is recommended using gemcitabine 1,000 mg/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. Dose 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. Dose reduction with each cycle or within a cycle may be applied based upon the grade of toxicity experienced by the patient. In general, for severe (Grade 3 or 4) non-haematological toxicity, except nausea/vomiting, therapy with gemcitabine should be withheld or decreased depending on the judgement of the treating physician. Doses should be withheld until toxicity has resolved in the opinion of the physician.

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

Dose modification due to haematological toxicity
Initiation of a cycle
For all indications, the patient must be monitored before each dose for platelet and granulocyte counts. Patients should have an absolute granulocyte count of at least 1,500 (x 10^6/l) and platelet count of 100,000 (x 10^6/l) prior to the initiation of a cycle.

Within a cycle
Dose modifications of gemcitabine within a cycle should be performed according to the following tables:

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

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

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

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

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

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

Dose modifications due to haematological toxicity in subsequent cycles, for all indications
The gemcitabine dose should be reduced to 75% of the original cycle initiation dose, in the case of the following haematological toxicities:

- Absolute granulocyte count < 500 x 10^6/l for more than 5 days
- Absolute granulocyte count < 100 x 10^6/l for more than 3 days
- Febrile neutropenia
- Platelets < 25,000 x 10^6/l
- Cycle delay of more than 1 week due to toxicity

Method of administration

Gemcitabine is tolerated well during infusion and may be administered ambulant. If extravasation occurs, generally the infusion must be stopped immediately and started again in another blood vessel. The patient should be monitored carefully after the administration.

For instructions on reconstitution of the medicinal product before administration, see section 6.6.

Special populations

Renal or hepatic impairment
Gemcitabine should be used with caution in patients with hepatic or renal impairment as there is insufficient information from clinical studies to allow for clear dose recommendations for these patient populations (see sections 4.4 and 5.2).

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

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Breast-feeding (see section 4.6).

4.4 Special warnings and precautions for use

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

Haematological toxicity
Gemcitabine can suppress bone marrow function as manifested by leucopenia, thrombocytopenia and anaemia.
Patients receiving gemcitabine should be monitored prior to each dose for platelet, leucocyte and granulocyte counts. Suspension or modification of therapy should be considered when drug-induced bone marrow depression is detected (see section 4.2). However, myelosuppression is short lived and usually does not result in dose reduction and rarely in discontinuation.
Peripheral blood counts may continue to deteriorate after gemcitabine administration has been stopped. In patients with impaired bone marrow function, the treatment should be started with caution. As with other cytotoxic treatments, the risk of cumulative bone-marrow suppression must be considered when gemcitabine treatment is given together with other chemotherapy

Hepatic or renal impairment
Gemcitabine should be used with caution in patients with hepatic or renal impairment as there is insufficient information from clinical studies to allow clear dose recommendations for these patient populations (see section 4.2).

Administration of gemcitabine in patients with concurrent liver metastases or a pre-existing medical history of hepatitis, alcoholism or liver cirrhosis may lead to exacerbation of the underlying hepatic impairment.

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

Concomitant radiotherapy
Concomitant radiotherapy (given together or ≤7 days apart): toxicity has been reported (see section 4.5 for details and recommendations for use).

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

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

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

Capillary leak syndrome
Capillary leak syndrome has been reported in patients receiving gemcitabine as single agent or in combination with other chemotherapeutic agents (see section 4.8). The condition is usually treatable if

recognised early and managed appropriately, but fatal cases have been reported. The condition involves systemic capillary hyperpermeability during which fluid and proteins from the intravascular space leak into the interstitium. The clinical features include generalised oedema, weight gain, hypoalbuminaemia, severe hypotension, acute renal impairment and pulmonary oedema. Gemcitabine should be discontinued and supportive measures implemented if capillary leak syndrome develops during therapy. Capillary leak syndrome can occur in later cycles and has been associated in the literature with adult respiratory distress syndrome.

Pulmonary
Pulmonary effects, sometimes severe (such as pulmonary oedema, interstitial pneumonitis or adult respiratory distress syndrome [ARDS]) have been reported in association with gemcitabine therapy. If such effects develop, consideration should be made to discontinuing gemcitabine therapy. Early use of supportive care measures may help ameliorate the condition.

Renal
Haemolytic uraemic syndrome
Clinical findings consistent with the haemolytic uraemic syndrome (HUS) were rarely reported (post-marketing data) in patients receiving gemcitabine (see section 4.8). HUS is a potentially life-threatening disorder. Gemcitabine should be discontinued at the first signs of any evidence of microangiopathic haemolytic anaemia, such as rapidly falling haemoglobin with concomitant thrombocytopenia, elevation of serum bilirubin, serum creatinine, blood urea nitrogen, or LDH. Renal failure may not be reversible with discontinuation of therapy and dialysis may be required.

Fertility
In fertility studies gemcitabine caused hypospermatogenesis in male mice (see section 5.3). Therefore, men being treated with gemcitabine are advised not to father a child during and up to 6 months after treatment and to seek further advice regarding cryoconservation of sperm prior to treatment because of the possibility of infertility due to therapy with gemcitabine (see section 4.6).

Sodium
200 mg and 1,000 mg vial
This medicinal product contains less than 1 mmol sodium (23 mg) per vial, that is to say essentially 'sodium-free'.

1,500 mg vial
This medicinal product contains 26.3 mg sodium per vial, equivalent to 1.3 % of the WHO recommended maximum daily intake of 2 g sodium for an adult.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed.

Radiotherapy
Concurrent (given together or ≤ 7 days apart) - Toxicity associated with this multimodality therapy is dependent on many different factors, including dose of gemcitabine, frequency of gemcitabine administration, dose of radiation, radiotherapy planning technique, the target tissue, and target volume. Pre-clinical and clinical studies have shown that gemcitabine has radiosensitising activity. In a single trial, where gemcitabine at a dose of 1,000 mg/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-concurrent (given >7 days apart) - Analysis of the data does not indicate any enhanced toxicity when gemcitabine is administered more than 7 days before or after radiation, other than radiation recall. Data suggest that gemcitabine can be started after the acute effects of radiation have resolved or at least one week after radiation.

Radiation injury has been reported on targeted tissues (e.g. oesophagitis, colitis and pneumonitis) in association with both concurrent and non-concurrent use of gemcitabine.

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

4.6 Fertility, pregnancy and lactation

Pregnancy
There are no adequate data from the use of gemcitabine in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3). Based on results from animal studies and the mechanism of action of gemcitabine, this medicinal product 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 unknown whether gemcitabine is excreted in human milk, and adverse effects on the breast-fed infant cannot be excluded. Gemcitabine medac is contraindicated during breast-feeding (see section 4.3).

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 somnolence, especially in combination with alcohol consumption. Patients should be cautioned against driving or operating machinery until it is established that they do not become somnolent.

4.8 Undesirable effects

The most commonly reported adverse drug reactions associated with gemcitabine treatment include: nausea with or without vomiting, raised liver transaminases (AST/ALT) and alkaline phosphatase, reported in approximately 60% of patients; proteinuria and haematuria reported in approximately 50% of patients; dyspnoea reported in 10 - 40% of patients (highest incidence in lung cancer patients); allergic skin rashes occur in approximately 25% of patients and are associated with itching in 10% of patients.

The frequency and severity of the adverse reactions are affected by the dose, infusion rate and intervals between doses (see section 4.4). Dose-limiting adverse reactions are reductions in thrombocyte, leucocyte and granulocyte counts (see section 4.2).

Clinical trial data
Frequencies are defined as: Very common (≥1/10), Common (≥1/100 to <1/10), Uncommon (≥1/1,000 to <1/100), Rare (≥1/10,000 to <1/1,000), Very rare (<1/10,000), Not known (cannot be estimated from the available data).

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

System Organ Class	**Frequency grouping**
Infections and infestations	Common Infections Not known Sepsis
Blood and lymphatic system disorders	Very common 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). Thrombocytopenia, anaemia Common Febrile neutropenia Very rare Thrombocytosis, thrombotic microangiopathy
Immune system disorders	Very rare Anaphylactoid reaction
Metabolism and nutrition disorders	Common Anorexia
Nervous system disorders	Common Headache, insomnia, somnolence Uncommon Cerebrovascular accident Very rare Posterior reversible encephalopathy syndrome (see section 4.4.)
Cardiac disorders	Uncommon Arrhythmias, predominantly supraventricular in nature, heart failure Rare Myocardial infarct
Vascular disorders	Rare Clinical signs of peripheral vasculitis and gangrene, hypotension

System Organ Class	Frequency grouping
	Very rare Capillary leak syndrome (see section 4.4.)
Respiratory, thoracic and mediastinal disorders	Very common Dyspnoea – usually mild and passes rapidly without treatment Common Cough, rhinitis Uncommon Interstitial pneumonitis (see section 4.4), bronchospasm – usually mild and transient but may require parenteral treatment Rare Pulmonary oedema, adult respiratory distress syndrome (see section 4.4)
Gastrointestinal disorders	Very common Vomiting, nausea Common Diarrhoea, stomatitis and ulceration of the mouth, constipation Very rare Ischaemic colitis
Hepatobiliary disorders	Very common Elevation of liver transaminases (AST and ALT) and alkaline phosphatase Common Increased bilirubin Uncommon Serious hepatotoxicity, including liver failure and death Rare Increased gamma-glutamyl transferase (GGT)

System Organ Class	Frequency grouping
Skin and subcutaneous tissue disorders	Very common Allergic skin rash frequently associated with pruritus, alopecia Common Itching, sweating Rare Severe skin reactions, including desquamation and bullous skin eruptions, ulceration, vesicle and sore formation, scaling Very rare Toxic epidermal necrolysis, Stevens-Johnson syndrome Not known Pseudocellulitis
Musculoskeletal and connective tissue disorders	Common Back pain, myalgia
Renal and urinary disorders	Very common Haematuria, mild proteinuria Uncommon Renal failure (see section 4.4), haemolytic uraemic syndrome (see section 4.4)
General disorders and administration site conditions	Very common Influenza-like symptoms – the most common symptoms are fever, headache, chills, myalgia, asthenia and anorexia. Cough, rhinitis, malaise, perspiration and sleeping difficulties have also been reported. Oedema/peripheral oedema –including facial oedema. Oedema is usually reversible after stopping treatment Common Fever, asthenia, chills Rare Injection site reactions, mainly mild in nature
Injury, poisoning, and procedural complications	Rare Radiation toxicity (see section 4.5), radiation recall

Combination use in breast cancer

The frequency of Grade 3 and 4 haematological toxicities, particularly 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)	1(0.6)

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

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

There is no known antidote for overdose of gemcitabine. Doses as high as 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 G_1/S phase boundary. *In vitro*, the cytotoxic effect of gemcitabine is dependent on both concentration and time.

Antitumoural activity in preclinical models
In animal tumour models, antitumoural activity of gemcitabine is schedule-dependent. When gemcitabine is administered daily, high mortality among the animals, but minimal antitumoural activity, is observed. If, however, gemcitabine is given every third or fourth day, it can be

administered in non-lethal doses with substantial antitumoural activity against a broad spectrum of mouse tumours.

Mechanism of action

Cellular metabolism and mechanism of action: Gemcitabine (dFdC), which is a pyrimidine antimetabolite, is metabolised intracellularly by nucleoside kinase to the active diphosphate (dFdCDP) and triphosphate (dFdCTP) nucleosides. The cytotoxic effect of gemcitabine is due to inhibition of DNA synthesis by two mechanisms of action by dFdCDP and dFdCTP. First, dFdCDP inhibits ribonucleotide reductase, which is uniquely responsible for catalysing the reactions that produce deoxynucleoside triphosphates (dCTP) for DNA synthesis. Inhibition of this enzyme by dFdCDP reduces the concentration of deoxynucleosides in general and, in particular, dCTP. Second, dFdCTP competes with dCTP for incorporation into DNA (self-potentiation).

Likewise, a small amount of gemcitabine may also be incorporated into RNA. Thus, the reduced intracellular concentration of dCTP potentiates the incorporation of dFdCTP into DNA. DNA polymerase epsilon lacks the ability to eliminate gemcitabine and to repair the growing DNA strands. After gemcitabine is incorporated into DNA, one additional nucleotide is added to the growing DNA strands. After this addition there is essentially a complete inhibition in further DNA synthesis (masked chain termination). After incorporation into DNA, gemcitabine appears to induce the programmed cell death process known as apoptosis.

Clinical 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 substance.

Renal clearance was 2 to 7 l/hr/m².

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

dFdCTP kinetics
This metabolite can be found in peripheral blood mononuclear cells and the information below refers to these cells. Intracellular concentrations increase in proportion to gemcitabine doses of 35 - 350 mg/m²/30 minutes, which give steady-state concentrations of 0.4 - 5 µg/ml. At gemcitabine plasma concentrations above 5 µg/ml, dFdCTP levels do not increase, suggesting that the formation is saturable in these cells.
Half-life of terminal elimination: 0.7 - 12 hours.

dFdU kinetics
Peak plasma concentrations (3 – 15 minutes after end of 30-minute infusion, 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 (Vss): 150 l/m² (range 96 - 228 l/m²).
Tissue distribution: Extensive.
Mean apparent clearance: 2.5 l/hr/m² (range 1 - 4 l/hr/m²).
Urinary excretion: All.

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

Gemcitabine and carboplatin combination therapy
When given in combination with carboplatin the pharmacokinetics of gemcitabine were not altered.

Renal impairment
Mild to moderate renal insufficiency (GFR from 30 ml/min to 80 ml/min) has no consistent, significant effect on gemcitabine pharmacokinetics.

5.3 Preclinical safety data

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

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

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

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Mannitol (E421)
Sodium acetate trihydrate (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

5 years.

After reconstitution
Chemical and physical in-use stability has been demonstrated for 35 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 25 °C, unless reconstitution/dilution has taken place in controlled and validated aseptic conditions.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

Reconstituted solution
Do not refrigerate (crystallisation may occur).
For storage conditions after reconstitution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

Type I clear glass vials of 10 ml, 50 ml or 100 ml, closed with chlorobutyl rubber stoppers.

Pack sizes: carton containing a single vial containing 200 mg, 1,000 mg or 1,500 mg gemcitabine.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Reconstitution
For single use only.
This medicinal product has only been shown to be compatible with sodium chloride 9 mg/ml (0.9 %) solution for injection. Accordingly, only this diluent should be used for reconstitution. Compatibility with other active substances has not been studied. Therefore, it is not recommended to mix this medicinal product with other active substances when reconstituted.
Reconstitution at concentrations greater than 38 mg/ml may result in incomplete dissolution, and should be avoided.
To reconstitute, slowly add the appropriate volume of sodium chloride 9 mg/ml (0.9 %) solution for injection (as stated in the table below) and shake to dissolve.

Presentation	Presentation volume of sodium chloride 9 mg/ml (0.9 %) solution for injection to be added	Reconstituted volume	Final concentration
200 mg	5 ml	5.26 ml	38 mg/ml
1,000 mg	25 ml	26.3 ml	38 mg/ml
1,500 mg	37.5 ml	39.5 ml	38 mg/ml

The appropriate amount of this medicinal product may be further diluted with sodium chloride 9 mg/ml (0.9 %) solution for injection.
Parenteral medicinal products should be inspected visually for particulate matter and discolouration, prior to administration, whenever solution and container permit.
Any unused solution should be discarded as described below.

Guidelines for the safe handling of cytotoxic medicinal products
Local guidelines on safe preparation and handling of cytotoxic medicinal products must be adhered to. Cytotoxic preparations should not be handled by pregnant staff. The preparation of injectable solutions of cytotoxic agents must be carried out by trained specialist personnel with knowledge of the medicines used. This should be performed in a designated area. The work surface should be covered with disposable plastic-backed absorbent paper.
Suitable eye protection, disposable gloves, face mask and disposable apron should be worn.
Precautions should be taken to avoid the medicinal product accidentally coming into contact with the eyes. If accidental contamination occurs, the eyes should be washed with water thoroughly and immediately.
Syringes and infusion sets should be assembled carefully to avoid leakage (use of Luer lock fittings is recommended). Large bore needles are recommended to minimise pressure and the possible formation of aerosols. The latter may also be reduced by the use of a venting needle.
Actual spillage or leakage should be mopped up wearing protective gloves. Excreta and vomit must be handled with care.

Disposal
Adequate care and precaution should be taken in the disposal of items used to reconstitute this medicinal product. Any unused dry product or contaminated materials should be placed in a high-risk waste bag. Sharp objects (needles, syringes, vials, etc.) should be placed in a suitable rigid container. Personnel concerned with the collection and disposal of this waste should be aware of the hazard involved. Waste material should be destroyed by incineration.

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

7. MARKETING AUTHORISATION HOLDER

medac
Gesellschaft für klinische
Spezialpräparate mbH
Theaterstr. 6
22880 Wedel
Germany
Tel.: +49 4103 8006-0
Fax: +49 4103 8006-100

8. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

[To be completed nationally]

10. DATE OF REVISION OF THE TEXT

<{MM/YYYY}>