Safeguarding public health

MHRA

Public Assessment Report

Decentralised Procedure

Gemcitabine 200 mg, 1 g and 2 g Powder for Solution for Infusion

UK/H/939/001-003/DC

Mayne Pharma Plc

Medicines and Healthcare products Regulatory Agency

Lay summary

The Medicines and Healthcare products Regulatory Agency (MHRA) granted Mayne Pharma Plc Marketing Authorisations (licences) for the medicinal products Gemcitabine 200 mg,1 g and 2 g Powder for Solution for Infusion (Product Licence numbers: 04515/0211-3). These medicines are available on prescription only.

Gemcitabine can be used to treat pancreatic, bladder, breast or non-small cell lung cancer. Gemcitabine works by interfering with the growth of cancer cells, causing them to die.

The data submitted in support of the application for Gemcitabine 200 mg, 1 g and 2 g Powder for Solution for Infusion raised no clinically significant safety concerns and it was therefore judged that the benefits of using this product outweigh the risks; hence a Marketing Authorisation has been granted.

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Module 1

Information about decentralised procedure

Name of the product in the Reference Member State	Gemcitabine 200mg,1g and 2g Powder for Solution for Infusion
Type of application (Eudratrack details)	Level 1 Abridged Level 2 Initial Level 3 10.3 Level 4 Chemical substance Level 5 Prescription only
Name of the active substance	Gemcitabine hydrochloride
Pharmacotherapeutic classification (ATC code)	Antineoplastic and immunomodulating agents-antineoplastic agents- pyrimidine analogues (L01BC05)
Pharmaceutical form and strength(s)	Powder for solution for infusion, 200 mg,1 g and 2 g
Reference numbers for the Mutual Recognition Procedure	UK/H/0939/001-3/DC
Reference Member State	UK
Member States concerned	AT, BE, CY, CZ, DE, DK, EE, EL, ES, FI, FR, HU, IE, IS, IT, LT, LU, LV, NL, NO, PL, PT, SE, SK
Date of start of the procedure	25 September 2006
End date of decentralised procedure	31 July 2007
Marketing Authorisation Number(s)	PL 04515/0211-3
Name and address of the authorisation holder	Mayne Pharma plc Queensway, Leamington Spa, Warwickshire, UK, CV31 3RW

Module 2

SUMMARY OF PRODUCT CHARACTERISTICS

200 mg strength:

1 NAME OF THE MEDICINAL PRODUCT

Gemcitabine 200 mg Powder for Solution for Infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains 200 mg gemcitabine (as hydrochloride)

Contains approximately 0.15 mmol (3.5 mg) sodium per 200 mg vial

One ml of the reconstituted solution for infusion (see section 6.6) contains 38 mg gemcitabine (as hydrochloride).

For full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Powder for solution for infusion (powder for infusion)

White to off-white powder.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Bladder Cancer:
Locally advanced or metastatic bladder cancer in combination with cisplatin.

Breast Cancer:
Locally advanced or metastatic breast cancer in combination with paclitaxel in patients experiencing a relapse after adjuvant/neoadjuvant chemotherapy. The preceding chemotherapy should have included an anthracycline unless clinically contraindicated.

Non-Small Cell Lung Cancer:
Locally advanced or metastatic non-small cell lung cancer in combination with other cytostatic medicinal products. Palliative treatment of adult patients with locally advanced or metastatic non-small cell lung cancer.

Pancreatic Cancer:
Locally advanced or metastatic adenocarcinoma of the pancreas in patients who are in good general condition with adequate bone marrow reserves.

4.2 Posology and method of administration

For intravenous infusion, following reconstitution.

Upon reconstitution a colourless or slightly yellow solution is produced.
Bladder cancer (combination therapy):
Adults: The recommended dose for gemcitabine is 1000 mg/m^2, given as a 30 minute infusion. The dose should be given on day 1, 8, and 15 of each 28 day cycle in combination with cisplatin. Cisplatin is given at a dose of 70 mg/m^2 on day 1 following gemcitabine or day 2 of each 28 day cycle. This four week cycle is then repeated. Dosage reduction with each cycle or within a cycle may be applied based upon the amount of toxicity experienced by the patient.

Breast cancer (combination therapy):
Adults: It is recommended that gemcitabine is used together with paclitaxel according to the following procedure:

Paclitaxel (175 mg/m^2) is intravenously infused over 3 hours on day 1 followed by gemcitabine (1250 mg/m^2) intravenously infused for 30 minutes on days 1 and 8 of each 21 day treatment cycle. Dosage reduction with each cycle or within a cycle may be applied based upon the amount of toxicity experienced by the patient. The absolute granulocyte count should be at least 1.5 x 10^9/l before treatment with gemcitabine + paclitaxel combination.

Non-small cell lung cancer (combination therapy):
Adults: Gemcitabine, in combination with cisplatin, has been investigated using two dosing regimens. One regimen used a three week schedule and the other used a four week schedule.

The three week schedule used gemcitabine 1250 mg/m^2, given by 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 amount of toxicity experienced by the patient.

The four week schedule used gemcitabine 1000 mg/m^2, given by 30 minute intravenous infusion, on days 1, 8, and 15 of each 28 day cycle. Dosage reduction with each cycle or within a cycle may be applied based upon the amount of toxicity experienced by the patient.

Cisplatin has been used at doses between 75-100 mg/m^2 once every 3 or 4 weeks.

Non-small cell lung cancer (single agent use):
Adults: The recommended dose of gemcitabine is 1000 mg/m^2, given by 30 minute intravenous infusion. This should be repeated once weekly for three weeks, followed by a one week rest period. This four-week cycle is then repeated. Dosage reduction is applied based upon the amount of toxicity experienced by the patient.

Cancer of the pancreas:

Adults: The recommended dose of gemcitabine is 1000 mg/m^2, given by 30 minute intravenous infusion. This should be repeated once weekly for up to 7 weeks, followed by a one week rest period. Subsequent cycles should consist of gemcitabine infusions once weekly for 3 consecutive weeks, followed by a one week rest period. Dosage reduction with each cycle or within a cycle may be applied based upon the amount of toxicity experienced by the patient.

Dosage adjustment in the presence of haematological toxicity:
Patients must be monitored before each dose for platelet, leucocyte, and granulocyte counts. The dose of gemcitabine must be either reduced or withheld in the presence of haematological toxicity according to the dose modifications below.

Non-small cell lung cancer, bladder cancer and pancreatic cancer:
Table 1 provides recommendations on the dose modification of gemcitabine when used as a single agent or in combination with cisplatin. Dosage adjustments based upon the following scale should occur at day 8 and/or day 15 within the 21 or 28 day cycle for non-small cell
lung cancer and bladder cancer, and for any dose within the 7 or 3 week cycle for pancreatic cancer.

Table 1

Absolute Granulocyte Count (x 10^9/l)		Platelet Count (x 10^9/l)	% of Total Dose
>1	and	>100	100
0.5-1	or	50-100	75
<0.5	or	<50	Withhold*

*Treatment may be reinstated on day 1 of the next cycle.

For cisplatin dosage adjustment in combination therapy, see the manufacturers' prescribing information.

Breast cancer:
Table 2 provides recommendations on dose modification of gemcitabine when used in combination with paclitaxel. Dosage adjustments based upon the following scale should occur at day 8 within the 21 day cycle for breast cancer.

Table 2

Absolute Neutrophil Count (x 10^9/l)		Platelet Count (x 10^9/l)	% of Total Dose
≥1.2	and	>75	100
1-<1.2	or	50-75	75
0.7-<1	and	≥50	50
<0.7	or	<50	Withhold*

*Treatment may be reinstated on day 1 of the next cycle.

Dose adjustment of gemcitabine (in combination with paclitaxel) for subsequent cycles is based upon haematological toxicity. Patients who experienced sustained Grade 4 febrile neutropenia, required gemcitabine omission on days 8, or had a prolonged delay of the start of cycle (≥2 weeks) should receive 75% of the starting dose of the previous cycle. For day 8 dosing, gemcitabine will be administered at the same dose as day 1.

For paclitaxel dosage adjustment in combination therapy, see the manufacturers' prescribing information.

Elderly patients:
Gemcitabine has been well tolerated in patients over the age of 65. Although gemcitabine clearance and half-life is affected by age, there are no specific recommendations on dose adjustment for the elderly.

Children:
Gemcitabine has not been studied in children. Use in children is not recommended.

Hepatic and renal impairment:
No studies have been done in patients with significant hepatic or renal impairment, see section 4.4.

4.3 Contraindications

Hypersensitivity to gemcitabine or to any of the excipients

Breast-feeding during treatment with gemcitabine

In combination with yellow fever vaccine (see section 4.5)

4.4 Special warnings and precautions for use

Warnings:
Prolongation of the infusion time and reduction of the recommended interval between doses increase toxicity.

In rare cases kidney failure, including haemolytic uremic syndrome, have been reported. Treatment should be discontinued if signs of micro-angiopathic haemolytic anaemia, such as rapidly falling haemoglobin levels with concurrent thrombocytopenia, increase of serum bilirubin, serum creatinine, blood urea nitrogen or lactate dehydrogenase. The kidney failure can be irreversible, even if the treatment of gemcitabine have been discontinued, and may necessitate dialysis.

Pulmonary effects, sometimes severe (such as pulmonary oedema, interstitial pneumonitis, or adult respiratory distress syndrome), have been reported rarely in association with gemcitabine therapy, see section 4.8. The aetiology of these effects is unknown. If severe pulmonary effects develop, gemcitabine must be discontinued. Early use of supportive care measures may help ameliorate the condition. The risk of adverse pulmonary reaction appears to be higher in patients with lung cancer and lung metastases

than with other tumour types, which should be taken into consideration when treating such patients.

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

Interaction between gemcitabine and radiotherapy, see section 4.5.

If extravasation occurs, the infusion must be stopped immediately and started again in another blood vessel. The patient should be monitored carefully after the administration.

Precautions:
Treatment with gemcitabine should be started by, or in consultation with, a physician with considerable experience in the use of cytotoxic medicinal products.

Patients receiving therapy with gemcitabine must be monitored closely. Laboratory facilities should be available to monitor patient status. Treatment for a patient compromised by toxicity may be required.

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.

Before each dose, thrombocyte, leucocyte and granulocyte counts must be checked, see section 4.2. Peripheral blood levels may continue to deteriorate after gemcitabine treatment has been stopped.
Gemcitabine must be used with caution in patients with renal impairment and hepatic impairment as there is insufficient information from clinical studies to allow clear dose recommendations for this group of patients.

Periodic checks of liver and kidney functions, including transaminases and serum creatinine, should also be performed in patients receiving gemcitabine.

Women of child-bearing potential should take steps to avoid pregnancy, see section 4.6.

Men being treated with gemcitabine are advised to use effective contraception, see section 4.6.

4.5 Interaction with other medicinal products and other forms of interaction

Radiotherapy:
Concurrent (given together or ≤ 7 days apart): Based on the result of preclinical studies and clinical trials, gemcitabine has radiosensitising activity. In a single trial, where gemcitabine at a dose of 1000 mg/m^2 was administered concurrently for up to 6 consecutive weeks with therapeutic thoracic radiation to patients with non-small cell lung cancer, significant toxicity in the form of severe and potentially life-threatening mucositis, especially oesophagitis and pneumonitis, was observed, particularly in patients receiving

large volumes of radiotherapy (median treatment volumes 4795 cm^3). Studies done subsequently have suggested that it is feasible to administer gemcitabine at lower doses with concurrent radiotherapy with predictable toxicity, such as a Phase II study in non-small cell lung cancer. Thoracic radiation doses of 66 Gy were administered with gemcitabine (600 mg/m^2, four times) and cisplatin (80 mg/m^2, twice) during 6 weeks. The optimum regimen for safe administration of gemcitabine with therapeutic doses of radiation has not yet been determined.

Sequential (given >7 days apart): Available information does not indicate any enhanced toxicity with administration of gemcitabine in patients who receive prior 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. Available information does not indicate any enhanced toxicity from radiation therapy following gemcitabine exposure.

Oral anticoagulants (e.g. Warfarin):
Increase frequency of INR (International Normalised Ratio) monitoring due to the potential for increased anticoagulant effects.

Yellow fever vaccine:
Contraindicated due to the potential risk of fatal systemic vaccinal disease.

Live attenuated vaccines (except yellow fever):
Concomitant use not recommended due to the risk of systemic, possible fatal, disease, particularly in immunosuppressed patients. Use of an inactivated vaccine is recommended where on exists (e.g. poliomyelitis).

Phenytoin:
Concomitant use is not recommended. Risk of exacerbation of convulsions due to decreased phenytoin gastrointestinal absorption. Risk of toxicity enhancement, or reduced efficacy of gemcitabine due to increased hepatic metabolism by phenytoin.

Ciclosporin, tacrolimus:
Excessive immunosuppression with risk of lymphoproliferation.

4.6 Pregnancy and lactation

Pregnancy:
There are no data on the use of gemcitabine in pregnant patients. Studies in animals have shown reproductive toxicity (see section 5.3). Based on results from animal studies and the mechanism of action of gemcitabine, this substance should not be used during pregnancy, especially during the first trimester, unless clearly necessary. The advantages of treatment should be weighed against the possible risk for the fetus in every individual case.

Women of childbearing potential and men should use effective contraception during and up to 3 months after treatment. Men should be advised to seek further advice regarding cryoconservation of sperm prior to treatment because of the possibility of infertility.

Lactation:
It is unknown if gemcitabine in excreted in human milk. Lactation is contraindicated due to the potential harmful effects to the newborn.

Fertility:
There are no human data on the effect of gemcitabine on fertility. In animals adverse effects of gemcitabine have been observed (see section 5.3).

4.7 Effects on ability to drive and use machines

Gemcitabine can cause mild to moderate tiredness. This is particularly the case in combination with alcohol. The ability to drive vehicles or operate machinery may be affected. Patients experiencing tiredness should not drive or operate machinery.

4.8 Undesirable effects

The most commonly reported adverse reactions associated with gemcitabine treatment include: nausea, with or without vomiting, and raised liver transaminases (aspartate aminotransferase/alanine aminotransferase) 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 occurring in approximately 25% of patients, and 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 platelet, leucocyte, and granulocyte counts (see section 4.2).

The following table of undesirable effects and frequencies is based on clinical trial and post-marketing spontaneous reports.

Frequencies: 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)

Blood and lymphatic system disorders	*Very common:* Leucopenia, thrombocytopenia, neutropenia (frequency of grade 3 is 19.3% and of grade 4 is 6%), anaemia Bone marrow suppression is usually mild to moderate and mostly affects the granulocyte count (see sections 4.2 and 4.4) *Common:* Febrile neutropenia *Very rare:* Thrombocythaemia
Immune system disorders	*Very Rare:* Anaphylactoid reaction
Metabolism and nutrition disorders	*Common:* Anorexia
Nervous system disorders	*Common:* Headache, somnolence, insomnia

Cardiac disorders	*Rare:* Myocardial infarct, cardiac insufficiency, arrhythmia (predominantly supraventricular in nature)
Vascular disorders	*Rare:* Hypotension *Very rare:* Clinical signs of peripheral vasculitis, gangrene
Respiratory, thoracic and mediastinal disorders	*Very common:* Dyspnoea (usually mild and passes rapidly without treatment) *Common:* Cough, rhinitis *Uncommon:* Pulmonary oedema, bronchospasm, interstitial pneumonitis together with pulmonary infiltrates (see section 4.4) *Rare:* Adult respiratory distress syndrome (see section 4.4)
Gastrointestinal disorders	*Very common:* Nausea, vomiting *Common:* Diarrhoea, constipation, stomatitis, ulceration of the mouth
Hepatobiliary disorders	*Very common:* Elevation of liver transaminases (aspartate aminotransferase and alanine aminotransferase) and alkaline phosphatase *Common:* Increased bilirubin *Rare:* Increased gamma glutamyl transferase *Very rare:* Serious hepatotoxicity, including liver failure and death (see sections 4.3 and 4.4)
Skin and subcutaneous tissue disorders	*Very common:* Allergic skin rash frequently associated with pruritus (the rash is usually mild, not dose-limiting and responsive to local therapy), alopecia (usually mild with minimal hair loss) *Common:* Sweating, itching *Rare:* Scaling, vesicle formation, ulceration *Very rare:* Severe skin reactions including ecdysis and bullous skin eruptions
Musculoskeletal and connective tissue disorders	*Common:* Myalgia, back pain
Renal and urinary	*Very common:* Mild proteinurea, haematuria (rarely

disorders	clinically significant, and not usually associated with any change in serum creatinine or blood urea nitrogen) *Rare:* Haemolytic uraemic syndrome, renal failure – may lead to death or require dialysis (see section 4.4)
General disorders and administration site conditions	*Very common:* Oedema/peripheral oedema (the reaction is not associated with signs of cardiac, hepatic or renal insufficiency and is usually reversible after stopping treatment), influenza-like symptoms (the most common symptoms are fever, headache, back pain, shivering, muscle pain, asthenia, malaise and anorexia. Cough, rhinitis, sweating and sleeping difficulties have also been reported) *Common:* Fever, asthenia, facial oedema Rare: Injection site reactions (mainly mild in nature)
Injury, poisoning and procedural complications	*Very common:* Radiation toxicity (see section 4.5)

Gemcitabine plus paclitaxel:

	Number (%) of Patients			
	Paclitaxel Arm (n= 259)		**Gemcitabine plus Paclitaxel Arm (n= 262)**	
	Grade 3	**Grade 4**	**Grade 3**	**Grade 4**
Blood and Lymphatic				
Haemoglobin	5 (1.9)	1 (0.4)	15 (5.7)	3 (1.1)
Platelets	0	0	14 (5.3)	1 (0.4)
Neutrophils/ granulocytes	11 (4.2)	17 (6.6)*	82 (31.3)	45 (17.2)*
Febrile neutropenia	3 (1.2)	0	12 (4.6)	1 (0.4)
General Disorders and Administration Site Conditions				
Fatigue	3 (1.2)	1 (0.4)	15 (5.7)	2 (0.8)

Gastro-intestinal Disorders				
Diarrhoea	5 (1.9)	0	8(3.1)	0
* 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.				

The increase in these adverse reactions is not associated with an increased incidence of infections of 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.

Gemcitabine plus cisplatin:
An increase of the following grade 3 and 4 effects (gemcitabine + cisplatin versus MVAC (methotrexate, vinblastine, doxorubicin and cisplatin)) have been observed.

Haematological toxicity:
haemoglobin (G3: 24% and 16% respectively; G4: 4% and 2% respectively);
thrombocytes (G3: 29% and 8% respectively; G4: 29% and 13% respectively).

Non-haematological toxicity:
Nausea and vomiting (G3: 22% and 19% respectively; G4: 0% and 2% respectively);
diarrhoea (G3: 3% and 8% respectively; G4: 0% and 1% respectively);
infection (G3: 2% and 10% respectively; G4: 1% and 5% respectively);
stomatitis (G3: 1% and 18% respectively; G4: 0% and 4% respectively).

Gemcitabine plus carboplatin:
An increase of the following grade3 and 4 effects (gemcitabine + carboplatin versus carboplatin alone) have been observed.

Haematological toxicity:
haemoglobin (G3: 22.3% and 5.7% respectively; G4: 5.1% and 2.3% respectively);
neutrophils (G3: 41.7% and 10.9% respectively; G4: 28.6% and 1.1% respectively);
thrombocytes (G3: 30.3% and 10.3% respectively; G4: 4.6% and 1.1% respectively).
Non-haematological toxicity:
bleeding (G3: 1.8% and 0% respectively; G4: 0% and 0% respectively);
neutropenia with fever (G3: 1.1% and 0% respectively; G4: 0% and 0% respectively);
infection without neutropenia (G3: 0.6% and 0% respectively; G4: 0% and 0% respectively)

4.9 Overdose

There is no antidote to gemcitabine. Single doses of up to 5.7 g/m^2 have been administered as intravenous infusions over 30 minutes every other week with clinically acceptable toxicity. The main toxicities observed were myelosuppression, paraesthesias and severe skin rash. If there is a suspicion of overdose then the patient's blood counts should be monitored and treatment given as required.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: pyrimidine analogue
ATC code: L01BC05

Cytotoxic Activity in Cell Culture Models:
Gemcitabine exhibits significant cytotoxicity activity against a variety of cultured murine and human tumour cells. It exhibits cell phase specificity, primarily killing cells undergoing DNA synthesis (S-phase) and under certain conditions blocking the progression of cells through the G1/S-phase boundary. *In vitro* the cytotoxic action of gemcitabine is both concentration and time dependent.

Antitumour Activity in Preclinical Models:
In animal tumour models, the antitumour activity of gemcitabine is schedule dependent. Generally it was found that treatment at a 3 or 4 day interval was more effective and /or less toxic than daily administration of gemcitabine.

Cellular Metabolism and Mechanisms of Action:
Gemcitabine (dFdC) is metabolised intracellularly by nucleoside kinases to the active diphosphate (dFdCDP) and triphosphate (dFdCTP) nucleosides. The cytotoxic action of gemcitabine appears to be due to inhibition of DNA synthesis by two actions of dFdCDP and dFdCTP. First, dFdCDP inhibits ribonucleotide reductase, which is uniquely responsible for catalysing the reactions that generate the deoxynucleoside triphosphates (dCTP) for DNA synthesis. Inhibition of this enzyme by dFdCDP causes a reduction in the concentrations of deoxynucleosides in general, and especially in that of 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 reduction in the intracellular concentration of dCTP potentiates the incorporation of dFdCTP into DNA. DNA polymerase epsilon is essentially unable to remove gemcitabine and 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 then appears to induce the programmed cellular death process known as apoptosis.

Gemcitabine and Paclitaxel Combination:
The combination of gemcitabine and paclitaxel was shown to be synergistic in a Calu-6 human lung xenograft model, which compared single-agent gemcitabine or paclitaxel versus the combination. In this model, minimal activity was seen with the paclitaxel monotherapy, while synergy was demonstrated with the combination of gemcitabine and paclitaxel. There is pharmacodynamic evidence, when paclitaxel is administered prior to gemcitabine in patients with NSCLC, that paclitaxel increases accumulation of the active metabolite, gemcitabine triphosphate (dFdCTP). The increased concentration of dFdCTP allows the metabolite to be effectively incorporated into RNA, resulting in an increased apoptotic index. This study also identified an increase in ribonucleotide levels with the combination of gemcitabine and paclitaxel, in which the author suggests that paclitaxel may enhance the antitumour activity of gemcitabine.

5.2 Pharmacokinetic properties

Gemcitabine Pharmacokinetics:

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/m^2 that were infused from 0.4 to 1.2 hours.

Peak plasma concentrations (obtained within 5 minutes of the end of the infusion):
3.2 to 45.5 µg/ml.

Volume of distribution of the central compartment:
12.4 l/m^2 for women and 17.5 l/m^2 for men (inter-individual variability was 91.9%).

Volume of distribution of the peripheral compartment:
47.4 l/m^2. The volume of the peripheral compartment was not sensitive to gender.

Plasma protein binding:
Negligible.
Systemic clearance:
Ranged from 29.2 l/hr/m^2 to 92.2 l/hr/m^2 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/m^2 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 unchanged.

Renal clearance:
2 to 7 l/hr/m^2.

Half-life:
Ranged from 42 to 94 minutes depending on age and gender. For the recommended dosing schedule, gemcitabine elimination should be virtually complete within 5 to 11 hours of the start of the infusion. Gemcitabine does not accumulate when administered once weekly.

Metabolism:

Gemcitabine is rapidly metabolised by cytidine deaminase in the liver, kidney, blood, and other tissues.

Intracellular metabolism of gemcitabine produces the gemcitabine mono, di, and triphosphates (dFdCMP, dFdCDP, and dFdCTP), of which dFdCDP and dFdCTP are considered active. These intracellular metabolites have not been detected in plasma or urine.

The primary metabolite, 2'-deoxy-2',2'-difluorouridine (dFdU), is not active and is found in plasma and urine.

dFdCTP Kinetics:

This metabolite can be found in peripheral blood mononuclear cells and the information below refers to these cells.

Half-life of terminal elimination:
0.7-12 hours.

Intracellular concentrations increase in proportion to gemcitabine doses of 35-350 mg/m^2/30 min, 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. Parent plasma concentrations following a dose of 1,000 mg/m^2/30 min 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.

dFdU Kinetics*:*

Peak plasma concentrations (3-15 minutes after end of 30 minute infusion, 1,000 mg/m^2):
28-52µg/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 hours).
Formation of dFdU from parent compound:
91%-98%.

Mean volume of distribution of central compartment:
18 l/m^2 (range 11-22 l/m^2).

Mean steady-state volume of distribution (Vss):
150 l/m^2 (range 96-228 l/m^2).

Tissue distribution:
Extensive.

Mean apparent clearance:
2.5 $l/hr/m^2$ (range 1-4 $l/hr/m^2$).

Urinary excretion:
All.

Overall Elimination:

Amount recovered in one week:
92%-98%, of which 99% is dFdU, 1% of the dose is excreted in faeces.

Gemcitabine and Carboplatin Combination Therapy:
When given in combination with carboplatin the pharmacokinetics of gemcitabine were not altered.

Gemcitabine and Paclitaxel Combination Therapy:
Combination therapy did not alter the pharmacokinetics of either gemcitabine or paclitaxel.

5.3 Preclinical safety data

In repeated dose studies of up to 6 months duration in mice and dogs, the principle finding was haematopoetic suppression. This effect is related to the cytotoxic properties of the active substance and was reversible when treatment was withdrawn. The effect was dose and dosage interval dependent. Gemcitabine showed mutagenic potential in in-vitro and in in-vivo tests. Long-term animal studies have not been conducted to evaluate the carcinogenic potential of gemcitabine.

In reproductive studies several species tertogenic and fetotoxic effects (cleft palate, fused pulmonary artery, absence of gallbladder, decreased foetal viability) have been observed at doses below the human therapeutic dose. Infertility studies, gemcitabine caused reversible, dose and dosage interval dependent hypospermatogenesis in male mice. No effect on the fertility of female mice has been detected.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Mannitol, E421
Sodium acetate trihydrate
Hydrochloric acid (for pH-adjustment)
Sodium hydroxide (for pH-adjustment)

6.2 Incompatibilities

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

6.3 Shelf life

As packaged for sale:
2 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. Solutions 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

200 mg vial: Type I clear glass vial with bromobutyl stopper. Vials may be sheathed in protective ONCO-TAIN sleeves. Pack sizes: carton containing a single vial or packs of 5 single vial cartons. Not all pack sizes may be marketed.

6.6 Special precautions for disposal

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	Volume of sodium chloride 9 mg/ml (0.9%) solution for injection to be added	Displacement volume	Final concentration
200 mg	5 ml	0.26 ml	38 mg/ml
1 g	25 ml	1.3 ml	38 mg/ml
2 g	50 ml	2.6 ml	38 mg/ml

The appropriate amount of 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 eye 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 product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Mayne Pharma Plc
Queensway
Royal Leamington Spa
Warwickshire
CV31 3RW
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

PL 04515/0211

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

31/07/2007

10 DATE OF REVISION OF THE TEXT

31/07/2007

1 g Strength:

1 NAME OF THE MEDICINAL PRODUCT

Gemcitabine 1 g Powder for Solution for Infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains 1 g gemcitabine (as hydrochorlide)

Contains approximately 0.75 mmol (17.5 mg) sodium per 1 g vial

One ml of the reconstituted solution for infusion (see section 6.6) contains 38 mg gemcitabine (as hydrochloride).

For full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Powder for solution for infusion (powder for infusion)

White to off-white powder.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Bladder Cancer:
Locally advanced or metastatic bladder cancer in combination with cisplatin.

Breast Cancer:
Locally advanced or metastatic breast cancer in combination with paclitaxel in patients experiencing a relapse after adjuvant/neoadjuvant chemotherapy. The preceding chemotherapy should have included an anthracycline unless clinically contraindicated.

Non-Small Cell Lung Cancer:
Locally advanced or metastatic non-small cell lung cancer in combination with other cytostatic medicinal products. Palliative treatment of adult patients with locally advanced or metastatic non-small cell lung cancer.

Pancreatic Cancer:
Locally advanced or metastatic adenocarcinoma of the pancreas in patients who are in good general condition with adequate bone marrow reserves.

4.2 Posology and method of administration

For intravenous infusion, following reconstitution.
Upon reconstitution a colourless or slightly yellow solution is produced.

Bladder cancer (combination therapy):
Adults: The recommended dose for gemcitabine is 1000 mg/m^2, given as a 30 minute infusion. The dose should be given on day 1, 8, and 15 of each 28 day cycle in combination with cisplatin. Cisplatin is given at a dose of 70 mg/m^2 on day 1 following gemcitabine or day 2 of each 28 day cycle. This four week cycle is then repeated. Dosage reduction with each cycle or within a cycle may be applied based upon the amount of toxicity experienced by the patient.

Breast cancer (combination therapy):
Adults: It is recommended that gemcitabine is used together with paclitaxel according to the following procedure:

Paclitaxel (175 mg/m^2) is intravenously infused over 3 hours on day 1 followed by gemcitabine (1250 mg/m^2) intravenously infused for 30 minutes on days 1 and 8 of each 21 day treatment cycle. Dosage reduction with each cycle or within a cycle may be applied based upon the amount of toxicity experienced by the patient. The absolute granulocyte count should be at least 1.5 x 10^9/l before treatment with gemcitabine + paclitaxel combination.

Non-small cell lung cancer (combination therapy):
Adults: Gemcitabine, in combination with cisplatin, has been investigated using two dosing regimens. One regimen used a three week schedule and the other used a four week schedule.

The three week schedule used gemcitabine 1250 mg/m^2, given by 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 amount of toxicity experienced by the patient.

The four week schedule used gemcitabine 1000 mg/m^2, given by 30 minute intravenous infusion, on days 1, 8, and 15 of each 28 day cycle. Dosage reduction with each cycle or within a cycle may be applied based upon the amount of toxicity experienced by the patient.

Cisplatin has been used at doses between 75-100 mg/m^2 once every 3 or 4 weeks.

Non-small cell lung cancer (single agent use):
Adults: The recommended dose of gemcitabine is 1000 mg/m^2, given by 30 minute intravenous infusion. This should be repeated once weekly for three weeks, followed by a one week rest period. This four-week cycle is then repeated. Dosage reduction is applied based upon the amount of toxicity experienced by the patient.

Cancer of the pancreas:
Adults: The recommended dose of gemcitabine is 1000 mg/m^2, given by 30 minute intravenous infusion. This should be repeated once weekly for up to 7 weeks, followed by a one week rest period. Subsequent cycles should consist of gemcitabine infusions once weekly for 3 consecutive weeks, followed by a one week rest period. Dosage

reduction with each cycle or within a cycle may be applied based upon the amount of toxicity experienced by the patient.

Dosage adjustment in the presence of haematological toxicity:
Patients must be monitored before each dose for platelet, leucocyte, and granulocyte counts. The dose of gemcitabine must be either reduced or withheld in the presence of haematological toxicity according to the dose modifications below.
Non-small cell lung cancer, bladder cancer and pancreatic cancer:
Table 1 provides recommendations on the dose modification of gemcitabine when used as a single agent or in combination with cisplatin. Dosage adjustments based upon the following scale should occur at day 8 and/or day 15 within the 21 or 28 day cycle for non-small cell lung cancer and bladder cancer, and for any dose within the 7 or 3 week cycle for pancreatic cancer.

Table 1

Absolute Granulocyte Count (x 10^9/l)		Platelet Count (x 10^9/l)	% of Total Dose
>1	and	>100	100
0.5-1	or	50-100	75
<0.5	or	<50	Withhold*

*Treatment may be reinstated on day 1 of the next cycle.

For cisplatin dosage adjustment in combination therapy, see the manufacturers' prescribing information.

Breast cancer:
Table 2 provides recommendations on dose modification of gemcitabine when used in combination with paclitaxel. Dosage adjustments based upon the following scale should occur at day 8 within the 21 day cycle for breast cancer.

Table 2

Absolute Neutrophil Count (x 10^9/l)		Platelet Count (x 10^9/l)	% of Total Dose
≥1.2	and	>75	100
1-<1.2	or	50-75	75
0.7-<1	and	≥50	50
<0.7	or	<50	Withhold*

*Treatment may be reinstated on day 1 of the next cycle.

Dose adjustment of gemcitabine (in combination with paclitaxel) for subsequent cycles is based upon haematological toxicity. Patients who experienced sustained Grade 4 febrile neutropenia, required gemcitabine omission on days 8, or had a prolonged delay of the start of cycle (≥2 weeks) should receive 75% of the starting dose of the previous cycle. For day 8 dosing, gemcitabine will be administered at the same dose as day 1.

For paclitaxel dosage adjustment in combination therapy, see the manufacturers' prescribing information.

Elderly patients:
Gemcitabine has been well tolerated in patients over the age of 65. Although gemcitabine clearance and half-life is affected by age, there are no specific recommendations on dose adjustment for the elderly.

Children:
Gemcitabine has not been studied in children. Use in children is not recommended.

Hepatic and renal impairment:
No studies have been done in patients with significant hepatic or renal impairment, see section 4.4.

4.3 Contraindications

Hypersensitivity to gemcitabine or to any of the excipients

Breast-feeding during treatment with gemcitabine

In combination with yellow fever vaccine (see section 4.5)

4.4 Special warnings and precautions for use

Warnings:
Prolongation of the infusion time and reduction of the recommended interval between doses increase toxicity.

In rare cases kidney failure, including haemolytic uremic syndrome, have been reported. Treatment should be discontinued if signs of micro-angiopathic haemolytic anaemia, such as rapidly falling haemoglobin levels with concurrent thrombocytopenia, increase of serum bilirubin, serum creatinine, blood urea nitrogen or lactate dehydrogenase. The kidney failure can be irreversible, even if the treatment of gemcitabine have been discontinued, and may necessitate dialysis.

Pulmonary effects, sometimes severe (such as pulmonary oedema, interstitial pneumonitis, or adult respiratory distress syndrome), have been reported rarely in association with gemcitabine therapy, see section 4.8. The aetiology of these effects is unknown. If severe pulmonary effects develop, gemcitabine must be discontinued. Early use of supportive care measures may help ameliorate the condition. The risk of adverse pulmonary reaction appears to be higher in patients with lung cancer and lung metastases than with other tumour types, which should be taken into consideration when treating such patients.

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

Interaction between gemcitabine and radiotherapy, see section 4.5.

If extravasation occurs, the infusion must be stopped immediately and started again in another blood vessel. The patient should be monitored carefully after the administration.

Precautions:
Treatment with gemcitabine should be started by, or in consultation with, a physician with considerable experience in the use of cytotoxic medicinal products.

Patients receiving therapy with gemcitabine must be monitored closely. Laboratory facilities should be available to monitor patient status. Treatment for a patient compromised by toxicity may be required.

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.
Before each dose, thrombocyte, leucocyte and granulocyte counts must be checked, see section 4.2. Peripheral blood levels may continue to deteriorate after gemcitabine treatment has been stopped.

Gemcitabine must be used with caution in patients with renal impairment and hepatic impairment as there is insufficient information from clinical studies to allow clear dose recommendations for this group of patients.

Periodic checks of liver and kidney functions, including transaminases and serum creatinine, should also be performed in patients receiving gemcitabine.

Women of child-bearing potential should take steps to avoid pregnancy, see section 4.6.

Men being treated with gemcitabine are advised to use effective contraception, see section 4.6

4.5 Interaction with other medicinal products and other forms of interaction

Radiotherapy:
Concurrent (given together or ≤ 7 days apart): Based on the result of preclinical studies and clinical trials, gemcitabine has radiosensitising activity. In a single trial, where gemcitabine at a dose of 1000 mg/m^2 was administered concurrently for up to 6 consecutive weeks with therapeutic thoracic radiation to patients with non-small cell lung cancer, significant toxicity in the form of severe and potentially life-threatening mucositis, especially oesophagitis and pneumonitis, was observed, particularly in patients receiving large volumes of radiotherapy (median treatment volumes 4795 cm^3). Studies done subsequently have suggested that it is feasible to administer gemcitabine at lower doses with concurrent radiotherapy with predictable toxicity, such as a Phase II study in non-small cell lung cancer. Thoracic radiation doses of 66 Gy were administered with gemcitabine (600 mg/m^2, four times) and cisplatin (80 mg/m^2, twice) during 6 weeks. The optimum regimen for safe administration of gemcitabine with therapeutic doses of radiation has not yet been determined.

Sequential (given >7 days apart): Available information does not indicate any enhanced toxicity with administration of gemcitabine in patients who receive prior 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. Available information does not indicate any enhanced toxicity from radiation therapy following gemcitabine exposure.

Oral anticoagulants (e.g. Warfarin):
Increase frequency of INR (International Normalised Ratio) monitoring due to the potential for increased anticoagulant effects.

Yellow fever vaccine:
Contraindicated due to the potential risk of fatal systemic vaccinal disease.

Live attenuated vaccines (except yellow fever):
Concomitant use not recommended due to the risk of systemic, possible fatal, disease, particularly in immunosuppressed patients. Use of an inactivated vaccine is recommended where on exists (e.g. poliomyelitis).

Phenytoin:
Concomitant use is not recommended. Risk of exacerbation of convulsions due to decreased phenytoin gastrointestinal absorption. Risk of toxicity enhancement, or reduced efficacy of gemcitabine due to increased hepatic metabolism by phenytoin.

Ciclosporin, tacrolimus:
Excessive immunosuppression with risk of lymphoproliferation.

4.6 Pregnancy and lactation

Pregnancy:
There are no data on the use of gemcitabine in pregnant patients. Studies in animals have shown reproductive toxicity (see section 5.3). Based on results from animal studies and the mechanism of action of gemcitabine, this substance should not be used during pregnancy, especially during the first trimester, unless clearly necessary. The advantages of treatment should be weighed against the possible risk for the fetus in every individual case.

Women of childbearing potential and men should use effective contraception during and up to 3 months after treatment. Men should be advised to seek further advice regarding cryoconservation of sperm prior to treatment because of the possibility of infertility.

Lactation:
It is unknown if gemcitabine in excreted in human milk. Lactation is contraindicated due to the potential harmful effects to the newborn.

Fertility:
There are no human data on the effect of gemcitabine on fertility. In animals adverse effects of gemcitabine have been observed (see section 5.3).

4.7 Effects on ability to drive and use machines

Gemcitabine can cause mild to moderate tiredness. This is particularly the case in combination with alcohol. The ability to drive vehicles or operate machinery may be affected. Patients experiencing tiredness should not drive or operate machinery.

4.8 Undesirable effects

The most commonly reported adverse reactions associated with gemcitabine treatment include: nausea, with or without vomiting, and raised liver transaminases (aspartate aminotransferase/alanine aminotransferase) 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 occurring in approximately 25% of patients, and 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 platelet, leucocyte, and granulocyte counts (see section 4.2).

The following table of undesirable effects and frequencies is based on clinical trial and post-marketing spontaneous reports.

Frequencies: 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)

Blood and lymphatic system disorders	*Very common:* Leucopenia, thrombocytopenia, neutropenia (frequency of grade 3 is 19.3% and of grade 4 is 6%), anaemia Bone marrow suppression is usually mild to moderate and mostly affects the granulocyte count (see sections 4.2 and 4.4) *Common:* Febrile neutropenia *Very rare:* Thrombocythaemia
Immune system disorders	*Very Rare:* Anaphylactoid reaction
Metabolism and nutrition disorders	*Common:* Anorexia
Nervous system disorders	*Common:* Headache, somnolence, insomnia
Cardiac disorders	*Rare:* Myocardial infarct, cardiac insufficiency, arrhythmia (predominantly supraventricular in nature)
Vascular disorders	*Rare:* Hypotension *Very rare:* Clinical signs of peripheral vasculitis, gangrene
Respiratory, thoracic and mediastinal	*Very common:* Dyspnoea (usually mild and passes rapidly without treatment)

disorders	*Common:* Cough, rhinitis *Uncommon:* Pulmonary oedema, bronchospasm, interstitial pneumonitis together with pulmonary infiltrates (see section 4.4) *Rare:* Adult respiratory distress syndrome (see section 4.4)
Gastrointestinal disorders	*Very common:* Nausea, vomiting *Common:* Diarrhoea, constipation, stomatitis, ulceration of the mouth
Hepatobiliary disorders	*Very common:* Elevation of liver transaminases (aspartate aminotransferase and alanine aminotransferase) and alkaline phosphatase *Common:* Increased bilirubin *Rare:* Increased gamma glutamyl transferase *Very rare:* Serious hepatotoxicity, including liver failure and death (see sections 4.3 and 4.4)
Skin and subcutaneous tissue disorders	*Very common:* Allergic skin rash frequently associated with pruritus (the rash is usually mild, not dose-limiting and responsive to local therapy), alopecia (usually mild with minimal hair loss) *Common:* Sweating, itching *Rare:* Scaling, vesicle formation, ulceration *Very rare:* Severe skin reactions including ecdysis and bullous skin eruptions
Musculoskeletal and connective tissue disorders	*Common:* Myalgia, back pain
Renal and urinary disorders	*Very common:* Mild proteinurea, haematuria (rarely clinically significant, and not usually associated with any change in serum creatinine or blood urea nitrogen) *Rare:* Haemolytic uraemic syndrome, renal failure – may lead to death or require dialysis (see section 4.4)
General disorders and administration site	*Very common:* Oedema/peripheral oedema (the reaction is not associated with signs of cardiac,

conditions	hepatic or renal insufficiency and is usually reversible after stopping treatment), influenza-like symptoms (the most common symptoms are fever, headache, back pain, shivering, muscle pain, asthenia, malaise and anorexia. Cough, rhinitis, sweating and sleeping difficulties have also been reported) *Common:* Fever, asthenia, facial oedema Rare: Injection site reactions (mainly mild in nature)
Injury, poisoning and procedural complications	*Very common:* Radiation toxicity (see section 4.5)

Gemcitabine plus paclitaxel:

	Number (%) of Patients			
	Paclitaxel Arm (n= 259)		**Gemcitabine plus Paclitaxel Arm (n= 262)**	
	Grade 3	**Grade 4**	**Grade 3**	**Grade 4**
Blood and Lymphatic				
Haemoglobin	5 (1.9)	1 (0.4)	15 (5.7)	3 (1.1)
Platelets	0	0	14 (5.3)	1 (0.4)
Neutrophils/ granulocytes	11 (4.2)	17 (6.6)*	82 (31.3)	45 (17.2)*
Febrile neutropenia	3 (1.2)	0	12 (4.6)	1 (0.4)
General Disorders and Administration Site Conditions				
Fatigue	3 (1.2)	1 (0.4)	15 (5.7)	2 (0.8)
Gastro-intestinal Disorders				
Diarrhoea	5 (1.9)	0	8(3.1)	0
* 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.				

The increase in these adverse reactions is not associated with an increased incidence of infections of 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.

Gemcitabine plus cisplatin:
An increase of the following grade 3 and 4 effects (gemcitabine + cisplatin versus MVAC (methotrexate, vinblastine, doxorubicin and cisplatin)) have been observed.

Haematological toxicity:
haemoglobin (G3: 24% and 16% respectively; G4: 4% and 2% respectively);
thrombocytes (G3: 29% and 8% respectively; G4: 29% and 13% respectively).

Non-haematological toxicity:
Nausea and vomiting (G3: 22% and 19% respectively; G4: 0% and 2% respectively);
diarrhoea (G3: 3% and 8% respectively; G4: 0% and 1% respectively);
infection (G3: 2% and 10% respectively; G4: 1% and 5% respectively);
stomatitis (G3: 1% and 18% respectively; G4: 0% and 4% respectively).

Gemcitabine plus carboplatin:
An increase of the following grade3 and 4 effects (gemcitabine + carboplatin versus carboplatin alone) have been observed.

Haematological toxicity:
haemoglobin (G3: 22.3% and 5.7% respectively; G4: 5.1% and 2.3% respectively);
neutrophils (G3: 41.7% and 10.9% respectively; G4: 28.6% and 1.1% respectively);
thrombocytes (G3: 30.3% and 10.3% respectively; G4: 4.6% and 1.1% respectively).
Non-haematological toxicity:
bleeding (G3: 1.8% and 0% respectively; G4: 0% and 0% respectively);
neutropenia with fever (G3: 1.1% and 0% respectively; G4: 0% and 0% respectively);
infection without neutropenia (G3: 0.6% and 0% respectively; G4: 0% and 0% respectively)

4.9 Overdose
There is no antidote to gemcitabine. Single doses of up to 5.7 g/m^2 have been administered as intravenous infusions over 30 minutes every other week with clinically acceptable toxicity. The main toxicities observed were myelosuppression, paraesthesias and severe skin rash. If there is a suspicion of overdose then the patient's blood counts should be monitored and treatment given as required.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties
Pharmacotherapeutic group: pyrimidine analogue
ATC code: L01BC05

Cytotoxic Activity in Cell Culture Models:
Gemcitabine exhibits significant cytotoxicity activity against a variety of cultured murine and human tumour cells. It exhibits cell phase specificity, primarily killing cells

undergoing DNA synthesis (S-phase) and under certain conditions blocking the progression of cells through the G1/S-phase boundary. *In vitro* the cytotoxic action of gemcitabine is both concentration and time dependent.

Antitumour Activity in Preclinical Models:
In animal tumour models, the antitumour activity of gemcitabine is schedule dependent. Generally it was found that treatment at a 3 or 4 day interval was more effective and /or less toxic than daily administration of gemcitabine.

Cellular Metabolism and Mechanisms of Action:
Gemcitabine (dFdC) is metabolised intracellularly by nucleoside kinases to the active diphosphate (dFdCDP) and triphosphate (dFdCTP) nucleosides. The cytotoxic action of gemcitabine appears to be due to inhibition of DNA synthesis by two actions of dFdCDP and dFdCTP. First, dFdCDP inhibits ribonucleotide reductase, which is uniquely responsible for catalysing the reactions that generate the deoxynucleoside triphosphates (dCTP) for DNA synthesis. Inhibition of this enzyme by dFdCDP causes a reduction in the concentrations of deoxynucleosides in general, and especially in that of 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 reduction in the intracellular concentration of dCTP potentiates the incorporation of dFdCTP into DNA. DNA polymerase epsilon is essentially unable to remove gemcitabine and 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 then appears to induce the programmed cellular death process known as apoptosis.

Gemcitabine and Paclitaxel Combination:
The combination of gemcitabine and paclitaxel was shown to be synergistic in a Calu-6 human lung xenograft model, which compared single-agent gemcitabine or paclitaxel versus the combination. In this model, minimal activity was seen with the paclitaxel monotherapy, while synergy was demonstrated with the combination of gemcitabine and paclitaxel. There is pharmacodynamic evidence, when paclitaxel is administered prior to gemcitabine in patients with NSCLC, that paclitaxel increases accumulation of the active metabolite, gemcitabine triphosphate (dFdCTP). The increased concentration of dFdCTP allows the metabolite to be effectively incorporated into RNA, resulting in an increased apoptotic index. This study also identified an increase in ribonucleotide levels with the combination of gemcitabine and paclitaxel, in which the author suggests that paclitaxel may enhance the antitumour activity of gemcitabine.

5.2 Pharmacokinetic properties

Gemcitabine Pharmacokinetics:
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/m^2 that were infused from 0.4 to 1.2 hours.

Peak plasma concentrations (obtained within 5 minutes of the end of the infusion):
3.2 to 45.5 µg/ml.

Volume of distribution of the central compartment:
12.4 l/m^2 for women and 17.5 l/m^2 for men (inter-individual variability was 91.9%).
Volume of distribution of the peripheral compartment:
47.4 l/m^2. The volume of the peripheral compartment was not sensitive to gender.

Plasma protein binding:
Negligible.

Systemic clearance:
Ranged from 29.2 l/hr/m^2 to 92.2 l/hr/m^2 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/m^2 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 unchanged.

Renal clearance:
2 to 7 l/hr/m^2.

Half-life:
Ranged from 42 to 94 minutes depending on age and gender. For the recommended dosing schedule, gemcitabine elimination should be virtually complete within 5 to 11 hours of the start of the infusion. Gemcitabine does not accumulate when administered once weekly.

Metabolism:
Gemcitabine is rapidly metabolised by cytidine deaminase in the liver, kidney, blood, and other tissues.

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

dFdCTP Kinetics:

This metabolite can be found in peripheral blood mononuclear cells and the information below refers to these cells.

Half-life of terminal elimination:

0.7-12 hours.

Intracellular concentrations increase in proportion to gemcitabine doses of 35-350 mg/m^2/30 min, 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. Parent plasma concentrations following a dose of 1,000 mg/m^2/30 min 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.

dFdU Kinetics*:*

Peak plasma concentrations (3-15 minutes after end of 30 minute infusion, 1,000 mg/m^2):
28-52µg/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 hours).

Formation of dFdU from parent compound:
91%-98%.

Mean volume of distribution of central compartment:
18 l/m^2 (range 11-22 l/m^2).

Mean steady-state volume of distribution (Vss):
150 l/m^2 (range 96-228 l/m^2).

Tissue distribution:
Extensive.

Mean apparent clearance:
2.5 l/hr/m^2 (range 1-4 l/hr/m^2).

Urinary excretion:
All.

Overall Elimination:

Amount recovered in one week:
92%-98%, of which 99% is dFdU, 1% of the dose is excreted in faeces.

Gemcitabine and Carboplatin Combination Therapy:
When given in combination with carboplatin the pharmacokinetics of gemcitabine were not altered.

Gemcitabine and Paclitaxel Combination Therapy:

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

5.3 Preclinical safety data

In repeated dose studies of up to 6 months duration in mice and dogs, the principle finding was haematopoetic suppression. This effect is related to the cytotoxic properties of the active substance and was reversible when treatment was withdrawn. The effect was dose and dosage interval dependent. Gemcitabine showed mutagenic potential in in-vitro and in in-vivo tests. Long-term animal studies have not been conducted to evaluate the carcinogenic potential of gemcitabine.

In reproductive studies several species tertogenic and fetotoxic effects (cleft palate, fused pulmonary artery, absence of gallbladder, decreased foetal viability) have been observed at doses below the human therapeutic dose. Infertility studies, gemcitabine caused reversible, dose and dosage interval dependent hypospermatogenesis in male mice. No effect on the fertility of female mice has been detected.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Mannitol, E421
Sodium acetate trihydrate
Hydrochloric acid (for pH-adjustment)
Sodium hydroxide (for pH-adjustment)

6.2 Incompatibilities

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

6.3 Shelf life

As packaged for sale:
2 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. Solutions 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

1 g vial: Type I clear glass vial with bromobutyl stopper. Vials may be sheathed in protective ONCO-TAIN sleeves. Pack sizes: carton containing a single vial or packs of 5 single vial cartons. Not all pack sizes may be marketed.

6.6 Special precautions for disposal

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	Volume of sodium chloride 9 mg/ml (0.9%) solution for injection to be added	Displacement volume	Final concentration
200 mg	5 ml	0.26 ml	38 mg/ml
1 g	25 ml	1.3 ml	38 mg/ml
2 g	50 ml	2.6 ml	38 mg/ml

The appropriate amount of 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 eye 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 product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Mayne Pharma Plc
Queensway
Royal Leamington Spa
Warwickshire
CV31 3RW
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

PL 04515/0212

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

31/07/2007

10 DATE OF REVISION OF THE TEXT

31/07/2007

2 mg Strength:

1 NAME OF THE MEDICINAL PRODUCT

Gemcitabine 2 g Powder for Solution for Infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains 2 g gemcitabine (as hydrochloride)

Contains approximately 1.5 mmol (35 mg) sodium per 2 g vial

One ml of the reconstituted solution for infusion (see section 6.6) contains 38 mg gemcitabine (as hydrochloride).

For full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Powder for solution for infusion (powder for infusion)

White to off-white powder.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Bladder Cancer:
Locally advanced or metastatic bladder cancer in combination with cisplatin.

Breast Cancer:
Locally advanced or metastatic breast cancer in combination with paclitaxel in patients experiencing a relapse after adjuvant/neoadjuvant chemotherapy. The preceding chemotherapy should have included an anthracycline unless clinically contraindicated.

Non-Small Cell Lung Cancer:
Locally advanced or metastatic non-small cell lung cancer in combination with other cytostatic medicinal products. Palliative treatment of adult patients with locally advanced or metastatic non-small cell lung cancer.

Pancreatic Cancer:
Locally advanced or metastatic adenocarcinoma of the pancreas in patients who are in good general condition with adequate bone marrow reserves.

4.2 Posology and method of administration

For intravenous infusion, following reconstitution.
Upon reconstitution a colourless or slightly yellow solution is produced.

Bladder cancer (combination therapy):
Adults: The recommended dose for gemcitabine is 1000 mg/m^2, given as a 30 minute infusion. The dose should be given on day 1, 8, and 15 of each 28 day cycle in combination with cisplatin. Cisplatin is given at a dose of 70 mg/m^2 on day 1 following gemcitabine or day 2 of each 28 day cycle. This four week cycle is then repeated. Dosage reduction with each cycle or within a cycle may be applied based upon the amount of toxicity experienced by the patient.

Breast cancer (combination therapy):

Adults: It is recommended that gemcitabine is used together with paclitaxel according to the following procedure:

Paclitaxel (175 mg/m^2) is intravenously infused over 3 hours on day 1 followed by gemcitabine (1250 mg/m^2) intravenously infused for 30 minutes on days 1 and 8 of each 21 day treatment cycle. Dosage reduction with each cycle or within a cycle may be applied based upon the amount of toxicity experienced by the patient. The absolute granulocyte count should be at least 1.5 x 10^9/l before treatment with gemcitabine + paclitaxel combination.

Non-small cell lung cancer (combination therapy):
Adults: Gemcitabine, in combination with cisplatin, has been investigated using two dosing regimens. One regimen used a three week schedule and the other used a four week schedule.

The three week schedule used gemcitabine 1250 mg/m^2, given by 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 amount of toxicity experienced by the patient.

The four week schedule used gemcitabine 1000 mg/m^2, given by 30 minute intravenous infusion, on days 1, 8, and 15 of each 28 day cycle. Dosage reduction with each cycle or within a cycle may be applied based upon the amount of toxicity experienced by the patient.

Cisplatin has been used at doses between 75-100 mg/m^2 once every 3 or 4 weeks.

Non-small cell lung cancer (single agent use):
Adults: The recommended dose of gemcitabine is 1000 mg/m^2, given by 30 minute intravenous infusion. This should be repeated once weekly for three weeks, followed by a one week rest period. This four-week cycle is then repeated. Dosage reduction is applied based upon the amount of toxicity experienced by the patient.

Cancer of the pancreas:
Adults: The recommended dose of gemcitabine is 1000 mg/m^2, given by 30 minute intravenous infusion. This should be repeated once weekly for up to 7 weeks, followed by a one week rest period. Subsequent cycles should consist of gemcitabine infusions once weekly for 3 consecutive weeks, followed by a one week rest period. Dosage reduction with each cycle or within a cycle may be applied based upon the amount of toxicity experienced by the patient.

Dosage adjustment in the presence of haematological toxicity:
Patients must be monitored before each dose for platelet, leucocyte, and granulocyte counts. The dose of gemcitabine must be either reduced or withheld in the presence of haematological toxicity according to the dose modifications below.
Non-small cell lung cancer, bladder cancer and pancreatic cancer:
Table 1 provides recommendations on the dose modification of gemcitabine when used as a single agent or in combination with cisplatin. Dosage adjustments based upon the

following scale should occur at day 8 and/or day 15 within the 21 or 28 day cycle for non-small cell lung cancer and bladder cancer, and for any dose within the 7 or 3 week cycle for pancreatic cancer.

Table 1

Absolute Granulocyte Count (x 10^9/l)		Platelet Count (x 10^9/l)	% of Total Dose
>1	and	>100	100
0.5-1	or	50-100	75
<0.5	or	<50	Withhold*

*Treatment may be reinstated on day 1 of the next cycle.

For cisplatin dosage adjustment in combination therapy, see the manufacturers' prescribing information.

Breast cancer:
Table 2 provides recommendations on dose modification of gemcitabine when used in combination with paclitaxel. Dosage adjustments based upon the following scale should occur at day 8 within the 21 day cycle for breast cancer.

Table 2

Absolute Neutrophil Count (x 10^9/l)		Platelet Count (x 10^9/l)	% of Total Dose
≥1.2	and	>75	100
1-<1.2	or	50-75	75
0.7-<1	and	≥50	50
<0.7	or	<50	Withhold*

*Treatment may be reinstated on day 1 of the next cycle.

Dose adjustment of gemcitabine (in combination with paclitaxel) for subsequent cycles is based upon haematological toxicity. Patients who experienced sustained Grade 4 febrile neutropenia, required gemcitabine omission on days 8, or had a prolonged delay of the start of cycle (≥2 weeks) should receive 75% of the starting dose of the previous cycle. For day 8 dosing, gemcitabine will be administered at the same dose as day 1.

For paclitaxel dosage adjustment in combination therapy, see the manufacturers' prescribing information.

Elderly patients:
Gemcitabine has been well tolerated in patients over the age of 65. Although gemcitabine clearance and half-life is affected by age, there are no specific recommendations on dose adjustment for the elderly.

Children:
Gemcitabine has not been studied in children. Use in children is not recommended.

Hepatic and renal impairment:

No studies have been done in patients with significant hepatic or renal impairment, see section 4.4.

4.3 Contraindications

Hypersensitivity to gemcitabine or to any of the excipients

Breast-feeding during treatment with gemcitabine

In combination with yellow fever vaccine (see section 4.5)

4.4 Special warnings and precautions for use

Warnings:

Prolongation of the infusion time and reduction of the recommended interval between doses increase toxicity.

In rare cases kidney failure, including haemolytic uremic syndrome, have been reported. Treatment should be discontinued if signs of micro-angiopathic haemolytic anaemia, such as rapidly falling haemoglobin levels with concurrent thrombocytopenia, increase of serum bilirubin, serum creatinine, blood urea nitrogen or lactate dehydrogenase. The kidney failure can be irreversible, even if the treatment of gemcitabine have been discontinued, and may necessitate dialysis.

Pulmonary effects, sometimes severe (such as pulmonary oedema, interstitial pneumonitis, or adult respiratory distress syndrome), have been reported rarely in association with gemcitabine therapy, see section 4.8. The aetiology of these effects is unknown. If severe pulmonary effects develop, gemcitabine must be discontinued. Early use of supportive care measures may help ameliorate the condition. The risk of adverse pulmonary reaction appears to be higher in patients with lung cancer and lung metastases than with other tumour types, which should be taken into consideration when treating such patients.

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

Interaction between gemcitabine and radiotherapy, see section 4.5.

If extravasation occurs, the infusion must be stopped immediately and started again in another blood vessel. The patient should be monitored carefully after the administration.

Precautions:

Treatment with gemcitabine should be started by, or in consultation with, a physician with considerable experience in the use of cytotoxic medicinal products.

Patients receiving therapy with gemcitabine must be monitored closely. Laboratory facilities should be available to monitor patient status. Treatment for a patient compromised by toxicity may be required.

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.
Before each dose, thrombocyte, leucocyte and granulocyte counts must be checked, see section 4.2. Peripheral blood levels may continue to deteriorate after gemcitabine treatment has been stopped.

Gemcitabine must be used with caution in patients with renal impairment and hepatic impairment as there is insufficient information from clinical studies to allow clear dose recommendations for this group of patients.

Periodic checks of liver and kidney functions, including transaminases and serum creatinine, should also be performed in patients receiving gemcitabine.

Women of child-bearing potential should take steps to avoid pregnancy, see section 4.6.

Men being treated with gemcitabine are advised to use effective contraception, see section 4.6

4.5 Interaction with other medicinal products and other forms of interaction

Radiotherapy:
Concurrent (given together or ≤ 7 days apart): Based on the result of preclinical studies and clinical trials, gemcitabine has radiosensitising activity. In a single trial, where gemcitabine at a dose of 1000 mg/m^2 was administered concurrently for up to 6 consecutive weeks with therapeutic thoracic radiation to patients with non-small cell lung cancer, significant toxicity in the form of severe and potentially life-threatening mucositis, especially oesophagitis and pneumonitis, was observed, particularly in patients receiving large volumes of radiotherapy (median treatment volumes 4795 cm^3). Studies done subsequently have suggested that it is feasible to administer gemcitabine at lower doses with concurrent radiotherapy with predictable toxicity, such as a Phase II study in non-small cell lung cancer. Thoracic radiation doses of 66 Gy were administered with gemcitabine (600 mg/m^2, four times) and cisplatin (80 mg/m^2, twice) during 6 weeks. The optimum regimen for safe administration of gemcitabine with therapeutic doses of radiation has not yet been determined.

Sequential (given >7 days apart): Available information does not indicate any enhanced toxicity with administration of gemcitabine in patients who receive prior 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. Available information does not indicate any enhanced toxicity from radiation therapy following gemcitabine exposure.

Oral anticoagulants (e.g. Warfarin):
Increase frequency of INR (International Normalised Ratio) monitoring due to the potential for increased anticoagulant effects.

Yellow fever vaccine:
Contraindicated due to the potential risk of fatal systemic vaccinal disease.

Live attenuated vaccines (except yellow fever):
Concomitant use not recommended due to the risk of systemic, possible fatal, disease, particularly in immunosuppressed patients. Use of an inactivated vaccine is recommended where on exists (e.g. poliomyelitis).

Phenytoin:
Concomitant use is not recommended. Risk of exacerbation of convulsions due to decreased phenytoin gastrointestinal absorption. Risk of toxicity enhancement, or reduced efficacy of gemcitabine due to increased hepatic metabolism by phenytoin.

Ciclosporin, tacrolimus:
Excessive immunosuppression with risk of lymphoproliferation.

4.6 Pregnancy and lactation

Pregnancy:
There are no data on the use of gemcitabine in pregnant patients. Studies in animals have shown reproductive toxicity (see section 5.3). Based on results from animal studies and the mechanism of action of gemcitabine, this substance should not be used during pregnancy, especially during the first trimester, unless clearly necessary. The advantages of treatment should be weighed against the possible risk for the fetus in every individual case.

Women of childbearing potential and men should use effective contraception during and up to 3 months after treatment. Men should be advised to seek further advice regarding cryoconservation of sperm prior to treatment because of the possibility of infertility.

Lactation:
It is unknown if gemcitabine in excreted in human milk. Lactation is contraindicated due to the potential harmful effects to the newborn.

Fertility:
There are no human data on the effect of gemcitabine on fertility. In animals adverse effects of gemcitabine have been observed (see section 5.3).

4.7 Effects on ability to drive and use machines

Gemcitabine can cause mild to moderate tiredness. This is particularly the case in combination with alcohol. The ability to drive vehicles or operate machinery may be affected. Patients experiencing tiredness should not drive or operate machinery.

4.8 Undesirable effects

The most commonly reported adverse reactions associated with gemcitabine treatment include: nausea, with or without vomiting, and raised liver transaminases (aspartate aminotransferase/alanine aminotransferase) 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 occurring in approximately 25% of patients, and 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 platelet, leucocyte, and granulocyte counts (see section 4.2).

The following table of undesirable effects and frequencies is based on clinical trial and post-marketing spontaneous reports.

Frequencies: 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)

Blood and lymphatic system disorders	*Very common:* Leucopenia, thrombocytopenia, neutropenia (frequency of grade 3 is 19.3% and of grade 4 is 6%), anaemia Bone marrow suppression is usually mild to moderate and mostly affects the granulocyte count (see sections 4.2 and 4.4) *Common:* Febrile neutropenia *Very rare:* Thrombocythaemia
Immune system disorders	*Very Rare:* Anaphylactoid reaction
Metabolism and nutrition disorders	*Common:* Anorexia
Nervous system disorders	*Common:* Headache, somnolence, insomnia
Cardiac disorders	*Rare:* Myocardial infarct, cardiac insufficiency, arrhythmia (predominantly supraventricular in nature)
Vascular disorders	*Rare:* Hypotension *Very rare:* Clinical signs of peripheral vasculitis, gangrene
Respiratory, thoracic and mediastinal disorders	*Very common:* Dyspnoea (usually mild and passes rapidly without treatment) *Common:* Cough, rhinitis *Uncommon:* Pulmonary oedema, bronchospasm, interstitial pneumonitis together with pulmonary infiltrates (see section 4.4) *Rare:* Adult respiratory distress syndrome (see section 4.4)
Gastrointestinal disorders	*Very common:* Nausea, vomiting *Common:* Diarrhoea, constipation, stomatitis,

	ulceration of the mouth
Hepatobiliary disorders	*Very common:* Elevation of liver transaminases (aspartate aminotransferase and alanine aminotransferase) and alkaline phosphatase *Common:* Increased bilirubin *Rare:* Increased gamma glutamyl transferase *Very rare:* Serious hepatotoxicity, including liver failure and death (see sections 4.3 and 4.4)
Skin and subcutaneous tissue disorders	*Very common:* Allergic skin rash frequently associated with pruritus (the rash is usually mild, not dose-limiting and responsive to local therapy), alopecia (usually mild with minimal hair loss) *Common:* Sweating, itching *Rare:* Scaling, vesicle formation, ulceration *Very rare:* Severe skin reactions including ecdysis and bullous skin eruptions
Musculoskeletal and connective tissue disorders	*Common:* Myalgia, back pain
Renal and urinary disorders	*Very common:* Mild proteinurea, haematuria (rarely clinically significant, and not usually associated with any change in serum creatinine or blood urea nitrogen) *Rare:* Haemolytic uraemic syndrome, renal failure – may lead to death or require dialysis (see section 4.4)
General disorders and administration site conditions	*Very common:* Oedema/peripheral oedema (the reaction is not associated with signs of cardiac, hepatic or renal insufficiency and is usually reversible after stopping treatment), influenza-like symptoms (the most common symptoms are fever, headache, back pain, shivering, muscle pain, asthenia, malaise and anorexia. Cough, rhinitis, sweating and sleeping difficulties have also been reported) *Common:* Fever, asthenia, facial oedema Rare: Injection site reactions (mainly mild in nature)
Injury, poisoning and	*Very common:* Radiation toxicity (see section 4.5)

procedural complications	

Gemcitabine plus paclitaxel:

	Number (%) of Patients			
	Paclitaxel Arm (n= 259)		**Gemcitabine plus Paclitaxel Arm** (n= 262)	
	Grade 3	**Grade 4**	**Grade 3**	**Grade 4**
Blood and Lymphatic				
Haemoglobin	5 (1.9)	1 (0.4)	15 (5.7)	3 (1.1)
Platelets	0	0	14 (5.3)	1 (0.4)
Neutrophils/ granulocytes	11 (4.2)	17 (6.6)*	82 (31.3)	45 (17.2)*
Febrile neutropenia	3 (1.2)	0	12 (4.6)	1 (0.4)
General Disorders and Administration Site Conditions				
Fatigue	3 (1.2)	1 (0.4)	15 (5.7)	2 (0.8)
Gastro-intestinal Disorders				
Diarrhoea	5 (1.9)	0	8(3.1)	0
* 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.				

The increase in these adverse reactions is not associated with an increased incidence of infections of 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.

Gemcitabine plus cisplatin:
An increase of the following grade 3 and 4 effects (gemcitabine + cisplatin versus MVAC (methotrexate, vinblastine, doxorubicin and cisplatin)) have been observed.

Haematological toxicity:
haemoglobin (G3: 24% and 16% respectively; G4: 4% and 2% respectively);
thrombocytes (G3: 29% and 8% respectively; G4: 29% and 13% respectively).

Non-haematological toxicity:
Nausea and vomiting (G3: 22% and 19% respectively; G4: 0% and 2% respectively);

diarrhoea (G3: 3% and 8% respectively; G4: 0% and 1% respectively);
infection (G3: 2% and 10% respectively; G4: 1% and 5% respectively);
stomatitis (G3: 1% and 18% respectively; G4: 0% and 4% respectively).

Gemcitabine plus carboplatin:
An increase of the following grade3 and 4 effects (gemcitabine + carboplatin versus carboplatin alone) have been observed.

Haematological toxicity:
haemoglobin (G3: 22.3% and 5.7% respectively; G4: 5.1% and 2.3% respectively);
neutrophils (G3: 41.7% and 10.9% respectively; G4: 28.6% and 1.1% respectively);
thrombocytes (G3: 30.3% and 10.3% respectively; G4: 4.6% and 1.1% respectively).
Non-haematological toxicity:
bleeding (G3: 1.8% and 0% respectively; G4: 0% and 0% respectively);
neutropenia with fever (G3: 1.1% and 0% respectively; G4: 0% and 0% respectively);
infection without neutropenia (G3: 0.6% and 0% respectively; G4: 0% and 0% respectively).

4.9 Overdose
There is no antidote to gemcitabine. Single doses of up to 5.7 g/m^2 have been administered as intravenous infusions over 30 minutes every other week with clinically acceptable toxicity. The main toxicities observed were myelosuppression, paraesthesias and severe skin rash. If there is a suspicion of overdose then the patient's blood counts should be monitored and treatment given as required.

5 PHARMACOLOGICAL PROPERTIES
5.1 Pharmacodynamic properties
Pharmacotherapeutic group: pyrimidine analogue
ATC code: L01BC05
Cytotoxic Activity in Cell Culture Models:
Gemcitabine exhibits significant cytotoxicity activity against a variety of cultured murine and human tumour cells. It exhibits cell phase specificity, primarily killing cells undergoing DNA synthesis (S-phase) and under certain conditions blocking the progression of cells through the G1/S-phase boundary. *In vitro* the cytotoxic action of gemcitabine is both concentration and time dependent.

Antitumour Activity in Preclinical Models:
In animal tumour models, the antitumour activity of gemcitabine is schedule dependent. Generally it was found that treatment at a 3 or 4 day interval was more effective and /or less toxic than daily administration of gemcitabine.

Cellular Metabolism and Mechanisms of Action:
Gemcitabine (dFdC) is metabolised intracellularly by nucleoside kinases to the active diphosphate (dFdCDP) and triphosphate (dFdCTP) nucleosides. The cytotoxic action of gemcitabine appears to be due to inhibition of DNA synthesis by two actions of dFdCDP and dFdCTP. First, dFdCDP inhibits ribonucleotide reductase, which is uniquely responsible for catalysing the reactions that generate the deoxynucleoside triphosphates

(dCTP) for DNA synthesis. Inhibition of this enzyme by dFdCDP causes a reduction in the concentrations of deoxynucleosides in general, and especially in that of 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 reduction in the intracellular concentration of dCTP potentiates the incorporation of dFdCTP into DNA. DNA polymerase epsilon is essentially unable to remove gemcitabine and 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 then appears to induce the programmed cellular death process known as apoptosis.

Gemcitabine and Paclitaxel Combination:
The combination of gemcitabine and paclitaxel was shown to be synergistic in a Calu-6 human lung xenograft model, which compared single-agent gemcitabine or paclitaxel versus the combination. In this model, minimal activity was seen with the paclitaxel monotherapy, while synergy was demonstrated with the combination of gemcitabine and paclitaxel. There is pharmacodynamic evidence, when paclitaxel is administered prior to gemcitabine in patients with NSCLC, that paclitaxel increases accumulation of the active metabolite, gemcitabine triphosphate (dFdCTP). The increased concentration of dFdCTP allows the metabolite to be effectively incorporated into RNA, resulting in an increased apoptotic index. This study also identified an increase in ribonucleotide levels with the combination of gemcitabine and paclitaxel, in which the author suggests that paclitaxel may enhance the antitumour activity of gemcitabine.

5.2 Pharmacokinetic properties

Gemcitabine Pharmacokinetics:
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/m^2 that were infused from 0.4 to 1.2 hours.

Peak plasma concentrations (obtained within 5 minutes of the end of the infusion):
3.2 to 45.5 µg/ml.

Volume of distribution of the central compartment:
12.4 l/m^2 for women and 17.5 l/m^2 for men (inter-individual variability was 91.9%).
Volume of distribution of the peripheral compartment:
47.4 l/m^2. The volume of the peripheral compartment was not sensitive to gender.

Plasma protein binding:
Negligible.

Systemic clearance:
Ranged from 29.2 l/hr/m^2 to 92.2 l/hr/m^2 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/m^2 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 unchanged.

Renal clearance:
2 to 7 l/hr/m^2.

Half-life:
Ranged from 42 to 94 minutes depending on age and gender. For the recommended dosing schedule, gemcitabine elimination should be virtually complete within 5 to 11 hours of the start of the infusion. Gemcitabine does not accumulate when administered once weekly.

Metabolism:
Gemcitabine is rapidly metabolised by cytidine deaminase in the liver, kidney, blood, and other tissues.

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

dFdCTP Kinetics:

This metabolite can be found in peripheral blood mononuclear cells and the information below refers to these cells.

Half-life of terminal elimination:
0.7-12 hours.

Intracellular concentrations increase in proportion to gemcitabine doses of 35-350 mg/m^2/30 min, 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. Parent plasma concentrations following a dose of 1,000 mg/m^2/30 min 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.

dFdU Kinetics*:*

Peak plasma concentrations (3-15 minutes after end of 30 minute infusion, 1,000 mg/m^2):
28-52µg/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 hours).

Formation of dFdU from parent compound:
91%-98%.

Mean volume of distribution of central compartment:
18 l/m^2 (range 11-22 l/m^2).

Mean steady-state volume of distribution (Vss):
150 l/m^2 (range 96-228 l/m^2).

Tissue distribution:
Extensive.

Mean apparent clearance:
2.5 l/hr/m^2 (range 1-4 l/hr/m^2).

Urinary excretion:
All.

Overall Elimination:

Amount recovered in one week:
92%-98%, of which 99% is dFdU, 1% of the dose is excreted in faeces.

Gemcitabine and Carboplatin Combination Therapy:
When given in combination with carboplatin the pharmacokinetics of gemcitabine were not altered.

Gemcitabine and Paclitaxel Combination Therapy:
Combination therapy did not alter the pharmacokinetics of either gemcitabine or paclitaxel.

5.3 Preclinical safety data

In repeated dose studies of up to 6 months duration in mice and dogs, the principle finding was haematopoetic suppression. This effect is related to the cytotoxic properties of the active substance and was reversible when treatment was withdrawn. The effect was dose and dosage interval dependent. Gemcitabine showed mutagenic potential in in-vitro and in in-vivo tests. Long-term animal studies have not been conducted to evaluate the carcinogenic potential of gemcitabine.

In reproductive studies several species tertogenic and fetotoxic effects (cleft palate, fused pulmonary artery, absence of gallbladder, decreased foetal viability) have been observed at doses below the human therapeutic dose. Infertility studies, gemcitabine caused reversible, dose and dosage interval dependent hypospermatogenesis in male mice. No effect on the fertility of female mice has been detected.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Mannitol, E421
Sodium acetate trihydrate
Hydrochloric acid (for pH-adjustment)
Sodium hydroxide (for pH-adjustment)

6.2 Incompatibilities

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

6.3 Shelf life

As packaged for sale:
2 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. Solutions 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

2 g vial: Type I clear glass vial with bromobutyl stopper. Vials may be sheathed in protective ONCO-TAIN sleeves. Pack sizes: carton containing a single vial or packs of 5 single vial cartons. Not all pack sizes may be marketed.

6.6 Special precautions for disposal

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	Volume of sodium chloride 9 mg/ml (0.9%) solution for injection to be added	Displacement volume	Final concentration
200 mg	5 ml	0.26 ml	38 mg/ml
1 g	25 ml	1.3 ml	38 mg/ml
2 g	50 ml	2.6 ml	38 mg/ml

The appropriate amount of 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 eye 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 product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Mayne Pharma Plc

Queensway
Royal Leamington Spa
Warwickshire
CV31 3RW
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

PL 04515/0211

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

31/07/2007

10 DATE OF REVISION OF THE TEXT

31/07/2007

Module 3

Product Information Leaflet

PACKAGE LEAFLET: INFORMATION FOR THE USER

GEMCITABINE 200 mg POWDER FOR SOLUTION FOR INFUSION

GEMCITABINE 1 g POWDER FOR SOLUTION FOR INFUSION

GEMCITABINE 2 g POWDER FOR SOLUTION FOR INFUSION

Gemcitabine

Read all of this leaflet carefully before you start using this medicine.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or healthcare staff.

In this leaflet:

1. WHAT GEMCITABINE POWDER FOR SOLUTION FOR INFUSION IS AND WHAT IT IS USED FOR

Gemcitabine Powder for Solution for Infusion is an anti-cancer medicinal product.

It is used in the treatment of a number of types of cancer including breast cancer, bladder cancer, a type of lung cancer (non-small cell lung cancer) and cancer of the pancreas.

Gemcitabine may be used in combination with other anti-cancer medicines.

2. BEFORE YOU USE GEMCITABINE POWDER FOR SOLUTION FOR INFUSION

Do not use Gemcitabine Powder for Solution for Infusion

- If you are allergic to gemcitabine or any of the other ingredients of Gemcitabine Powder for Solution for Infusion
- If you are breast-feeding
- In combination with yellow fever vaccine

Tell the doctor if you think any of the above applies to you.

Take special care with Gemcitabine Powder for Solution for Infusion

- If your blood cell levels are low or your body is unable to replace blood cells at a normal rate (this will be checked through blood tests)
- If you are to have radiotherapy whilst using gemcitabine or you have had radiotherapy within the last 7 days
- If you have kidney problems
- If you have liver problems
- If you have lung cancer or spread of cancer from elsewhere to the lungs

The use of gemcitabine in children is not recommended.

Taking and using other medicines

The following drugs may be affected by taking gemcitabine:
- Anticoagulants e.g. warfarin. Gemcitabine may increase the anticoagulant effect so that blood tests (INR) may need to be done more frequently
- Vaccines. There is a risk of the disease developing. Your doctor will choose to use a particular type of vaccine (inactivated) if there is one available
- Phenytoin (an anti-epileptic medicine). There is an increased risk of convulsions or reduced effectiveness of gemcitabine if the drugs are taken together
- Ciclosporin and tacrolimus (immunosuppressants). There is a risk of increased immunosuppression

Please tell your doctor if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.

Pregnancy and breast-feeding

Ask your doctor or pharmacist for advice before taking any medicine.

You must not use gemcitabine during pregnancy unless clearly indicated by your doctor.

You must not breast-feed while you are treated with gemcitabine.

If you are a woman of childbearing age you should take steps to avoid pregnancy during and up to 3 months after treatment with gemcitabine. If pregnancy occurs during treatment, you must immediately inform your doctor.

If you are a man, you should avoid fathering a child during treatment with gemcitabine and for 3 months after treatment has stopped. There is a risk that treatment with gemcitabine will lead to male infertility and you may wish to seek advice about sperm storage before the treament starts.

Driving and using machines

Gemcitabine treatment can make you feel drowsy. Alcohol can make this worse. If you feel drowsy you should not drive or operate machinery.

Important information about some of the ingredients of Gemcitabine Powder for Solution for Infusion

This medicinal product contains 35 mg (1.5 mmol) of sodium per 2 g dose. To be taken into consideration by patients on a controlled sodium diet.

3. HOW TO USE GEMCITABINE POWDER FOR SOLUTION FOR INFUSION

Gemcitabine will be prepared and given to you by healthcare staff under the supervision of a doctor with experience in the use of anti-cancer medicines.

This medicine will be made into a solution and given to you as an infusion (slow injection via a drip) over 30 minutes into a vein.

Your initial dose of gemcitabine will be calculated by the doctor. It will depend on the type of cancer you have and your body surface area in square metres (m^2). Typically, the dose will be between 1 g/m^2 and 1.25 g/m^2.

A number of follow up doses will be given. The dose may change depending on your blood cell levels, which will be checked using blood tests, and any side effects you get. The number of doses and the days when the doses are given will be decided by the doctor.

As gemcitabine will be given to you under the supervision of a doctor, it is unlikely that you will receive an incorrect dose. However, if you have any concerns about the dose you receive, please tell your doctor or healthcare staff.

If you have any further questions on the use of this product, ask your doctor or healthcare staff.

4. POSSIBLE SIDE EFFECTS

Like all medicines, Gemcitabine Powder for Solution for Infusion can cause side effects, although not everybody gets them.

If any of the following happen, tell your doctor immediately:
- Severe allergic reaction - you may experience a sudden itchy rash (hives), swelling of the hands, feet, ankles, face, lips, mouth

or throat (which may cause difficulty in swallowing or breathing), and you may feel you are going to faint
- Severe chest pains possibly radiating to the jaw or arm, sweating, breathlessness and nausea
- Severe breathing difficulty
- Yellowing of the skin and eyes because of liver problems (jaundice)
- Kidney failure (the doctor will monitor blood and urine tests for this)

These are all serious side effects. You may need urgent medical attention. These serious side effects are rare (less than 1 in 1,000 patients but more than 1 in 10,000) or very rare (less than 1 in 10,000 patients).

Tell the doctor or healthcare staff immediately if you notice any pain at the injection site during the infusion. Pain around the injection site could mean the needle has not been properly inserted into the vein.

If you receive radiation treatment and gemcitabine within 7 days of each other and you notice any of the following, tell the doctor immediately:
- Mouth soreness
- Swallowing difficulty or pain on swallowing

Tell the doctor as soon as possible if you notice any of the following side effects:

Very common (more than 1 in 10 patients):
- Blood in the urine
- Swelling (particularly of the ankles or hands)
- Flu like symptoms (fever, shivering aches and pains)
- Skin rash
- Itchy skin
- Hair loss
- Mild breathing difficulty
- Nausea
- Vomiting

Common (less than 1 in 10 patients but more than 1 in 100):
- Anorexia
- Headache
- Drowsiness
- Difficulty sleeping
- Cough
- Runny nose or nasal congestion
- Diarrhoea
- Constipation
- Mouth soreness
- Ulceration of the mouth
- Sweating
- Muscle pain
- Back pain
- Weakness
- Facial swelling
- Itching

Uncommon (less than 1 in 100 patients but more than 1 in 1,000):
- Wheezing
- Cough with pink frothy sputum/phlegm

Rare (less than 1 in 1,000 patients but more than 1 in 10,000):
- Heart problems, including an abnormal heart beat
- Low blood pressure
- Skin shedding
- Skin blisters
- Skin sores (ulcers)
- Soreness at the injection site after the injection

Very rare (less than 1 in 10,000 patients):
- Problems with blood flow to the limbs (may give tingling, coldness or pain in the hands and feet)
- If this is severe or lasts a long time, the hands or feet may become dead and black (gangrene)

Blood samples will be taken to check for changes in liver function and changes in blood cell levels, which are very common side effects of gemcitabine treatment. Blood and urine tests will be performed to check for changes in kidney function. Severe kidney problems are rare.

It is possible that a man may not be able to father a child after treatment with gemcitabine.

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or healthcare staff.

5. HOW TO STORE GEMCITABINE POWDER FOR SOLUTION FOR INFUSION

Keep out of the reach and sight of children.

Do not use Gemcitabine Powder for Solution for Infusion after the expiry date which is stated on the vial and carton. The expiry date refers to the last day of that month.

This medicinal product does not require any special storage conditions.

After reconstitution:

This medicine may be stored for 35 days at 25°C. From a microbiological point of view however, it is advised that the product is used immediately.

The reconstituted solution should not be refrigerated.

The prepared solution for infusion should not be used if it contains particles or if it is strongly coloured.

This medicine will be prepared and administered to you by healthcare staff. Any unused medicine must be disposed of by the healthcare staff.

6. FURTHER INFORMATION

What Gemcitabine Powder for Solution for Infusion contains

- The active substance is gemcitabine (as hydrochloride)
- Vials contain either 200 mg, 1 g or 2 g gemcitabine (as hydrochloride)
- The other ingredients are mannitol, sodium acetate trihydrate, hydrochloric acid (for pH adjustment) and sodium hydroxide (for pH adjustment)
- One ml of the reconstituted solution for infusion contains 38 mg gemcitabine (as hydrochloride)

What Gemcitabine Powder for Solution for Infusion looks like and contents of the pack

This medicinal product is a powder for solution for infusion (a powder which is dissolved before being injected slowly via a drip into a vein). It can also be referred to as a 'powder for infusion'.

The powder is white to off-white and when dissolved ready for infusion, it produces a colourless or slightly yellow solution.

The 200 mg, 1 g and 2 g vials are sold separately as single packs or packs of 5. Not all pack sizes may be marketed. Vials may be sheathed in protective ONCO-TAIN® sleeves.

Marketing Authorisation Holder and Manufacturer

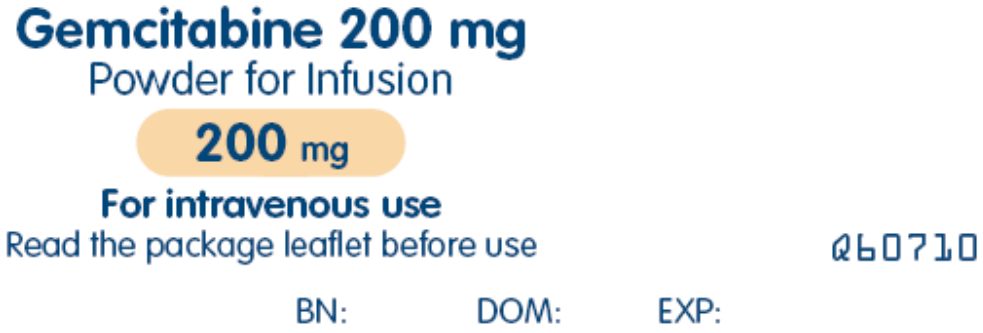
The marketing authorisation holder and manufacturer is Mayne Pharma Plc, Queensway, Royal Leamington Spa, Warwickshire, CV31 3RW, United Kingdom.

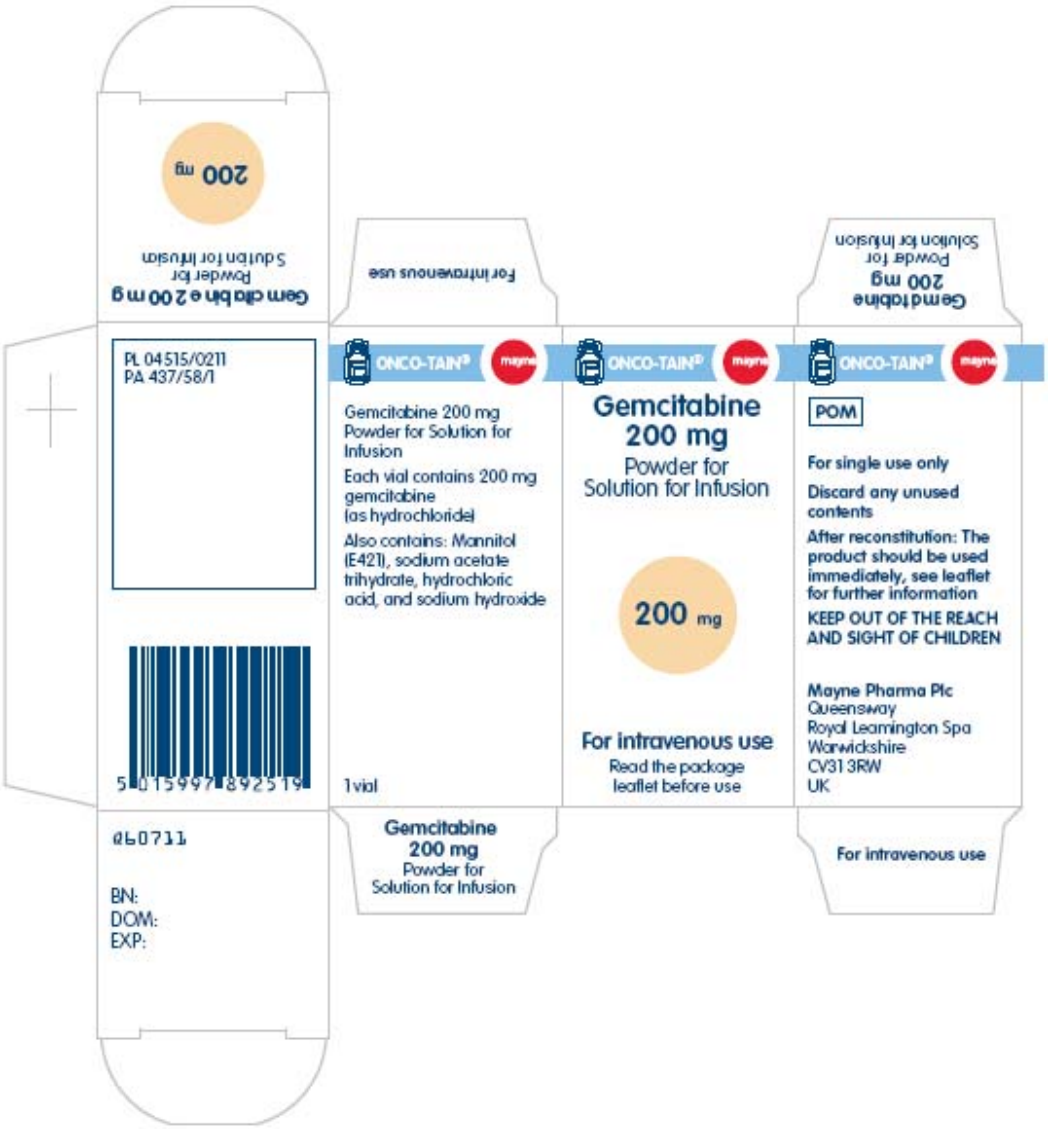
This leaflet was last approved in June 2007

Module 4

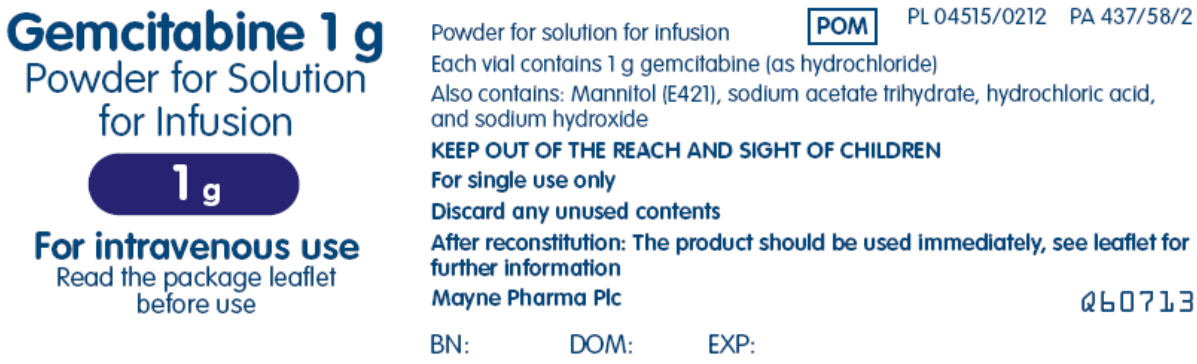
Labelling

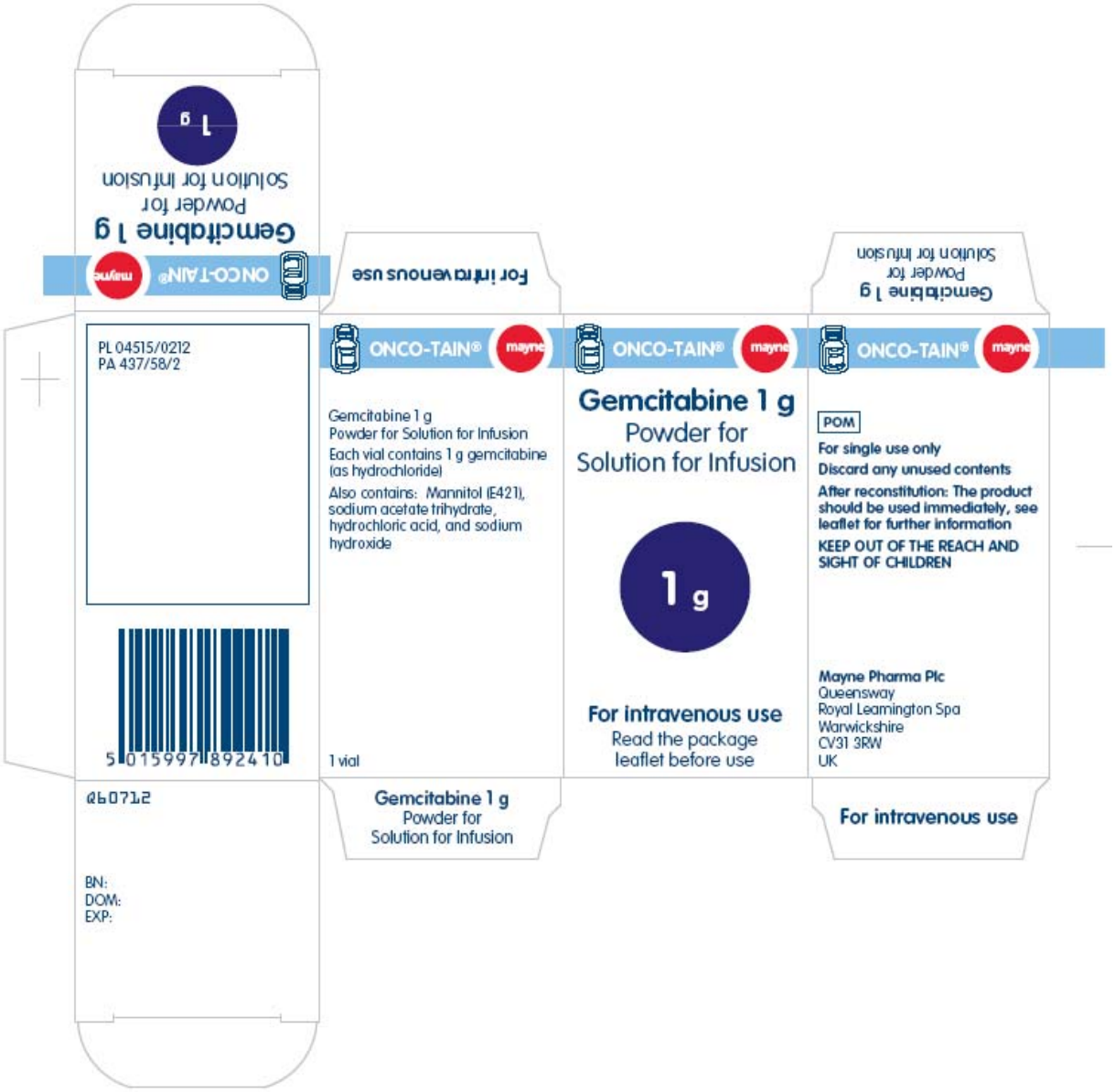
200 mg Strength:




200 mg
Gemcitabine 200 mg
Powder for
Solution for Infusion
For intravenous use
PL 04515/0211
PA 437/58/1
5 015997 892519
Q60711
BN:
DOM:
EXP:
ONCO-TAIN®
Gemcitabine 200 mg
Powder for Solution for Infusion
Each vial contains 200 mg gemcitabine (as hydrochloride)
Also contains: Mannitol (E421), sodium acetate trihydrate, hydrochloric acid, and sodium hydroxide
1 vial
Gemcitabine
200 mg
Powder for
Solution for Infusion
Read the package leaflet before use
POM
For single use only
Discard any unused contents
After reconstitution: The product should be used immediately, see leaflet for further information
KEEP OUT OF THE REACH AND SIGHT OF CHILDREN
Mayne Pharma Plc
Queensway
Royal Leamington Spa
Warwickshire
CV31 3RW
UK
For intravenous use

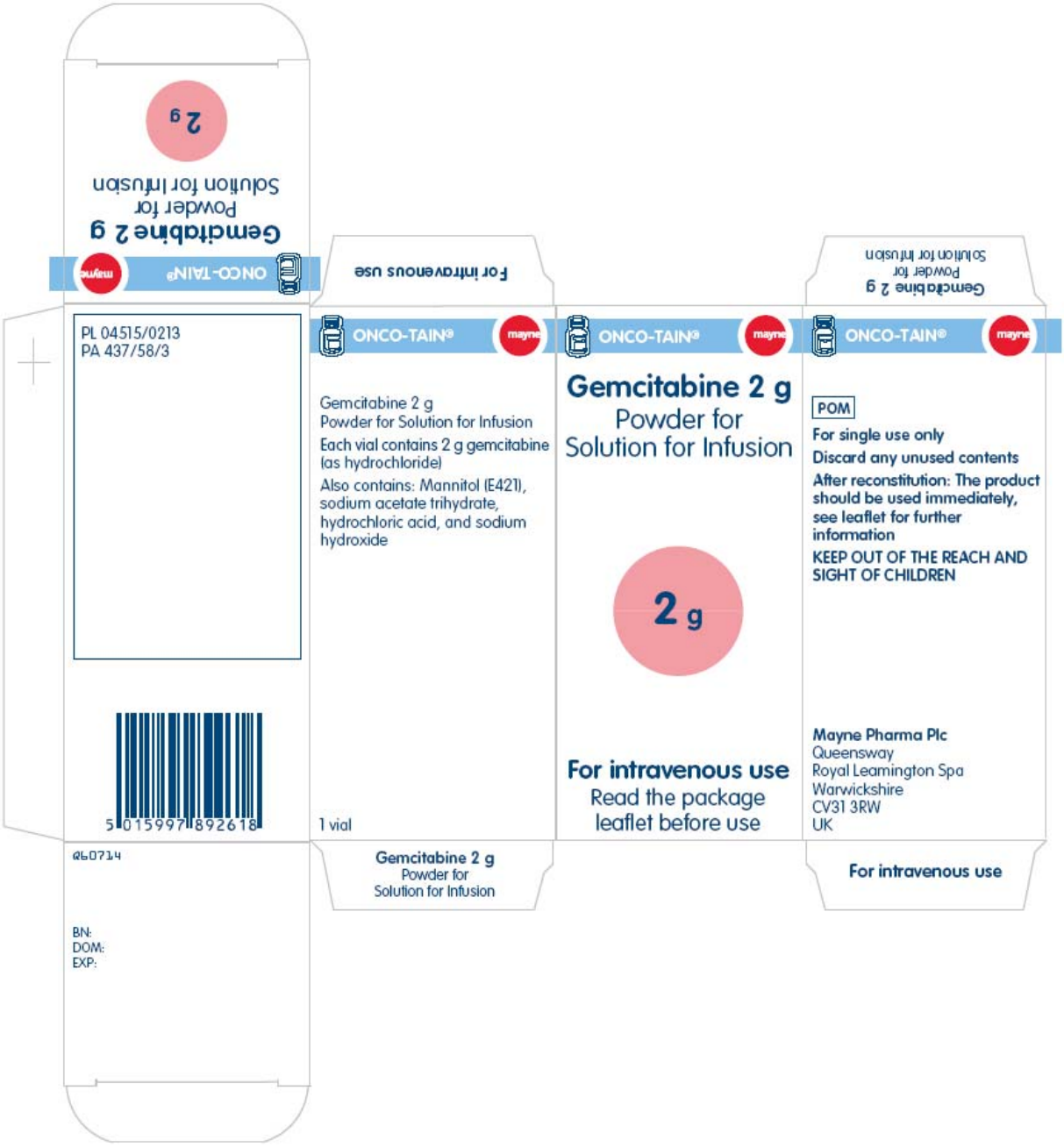
1 g Strength:


Gemcitabine 1 g
Powder for Solution for Infusion
1 g
For intravenous use
Read the package leaflet before use
Powder for solution for infusion
POM
PL 04515/0212 PA 437/58/2
Each vial contains 1 g gemcitabine (as hydrochloride)
Also contains: Mannitol (E421), sodium acetate trihydrate, hydrochloric acid, and sodium hydroxide
KEEP OUT OF THE REACH AND SIGHT OF CHILDREN
For single use only
Discard any unused contents
After reconstitution: The product should be used immediately, see leaflet for further information
Mayne Pharma Plc
Q60713
BN:
DOM:
EXP:


1 g
Gemcitabine 1 g
Powder for
Solution for Infusion
ONCO-TAIN®
mayne
For intravenous use
PL 04515/0212
PA 437/58/2
5 015997 892410
Q60712
BN:
DOM:
EXP:
Gemcitabine 1 g
Powder for Solution for Infusion
Each vial contains 1 g gemcitabine (as hydrochloride)
Also contains: Mannitol (E421), sodium acetate trihydrate, hydrochloric acid, and sodium hydroxide
1 vial
Read the package leaflet before use
POM
For single use only
Discard any unused contents
After reconstitution: The product should be used immediately, see leaflet for further information
KEEP OUT OF THE REACH AND SIGHT OF CHILDREN
Mayne Pharma Plc
Queensway
Royal Leamington Spa
Warwickshire
CV31 3RW
UK

2 g Strength:


Gemcitabine 2 g
Powder for Solution for Infusion
2 g
For intravenous use
Read the package leaflet before use
POM
PL 04515/0213 PA 437/58/3
Powder for solution for infusion
Each vial contains 2 g gemcitabine (as hydrochloride)
Also contains: Mannitol (E421), sodium acetate trihydrate, hydrochloric acid, and sodium hydroxide
KEEP OUT OF THE REACH AND SIGHT OF CHILDREN
For single use only
Discard any unused contents
After reconstitution: The product should be used immediately, see leaflet for further information
Mayne Pharma Plc
Q60715
BN:
DOM:
EXP:


2 g
Gemcitabine 2 g
Powder for
Solution for Infusion
ONCO-TAIN®
For intravenous use
Gemcitabine 2 g
Powder for
Solution for Infusion
PL 04515/0213
PA 437/58/3
5 015997 892618
Q60714
BN:
DOM:
EXP:
ONCO-TAIN®
Gemcitabine 2 g
Powder for Solution for Infusion
Each vial contains 2 g gemcitabine (as hydrochloride)
Also contains: Mannitol (E421), sodium acetate trihydrate, hydrochloric acid, and sodium hydroxide
1 vial
Gemcitabine 2 g
Powder for
Solution for Infusion
ONCO-TAIN®
Gemcitabine 2 g
Powder for
Solution for Infusion
2 g
For intravenous use
Read the package leaflet before use
ONCO-TAIN®
POM
For single use only
Discard any unused contents
After reconstitution: The product should be used immediately, see leaflet for further information
KEEP OUT OF THE REACH AND SIGHT OF CHILDREN
Mayne Pharma Plc
Queensway
Royal Leamington Spa
Warwickshire
CV31 3RW
UK
Gemcitabine 2 g
Powder for
Solution for Infusion
For intravenous use

Module 5

Scientific discussion during initial procedure

I. RECOMMENDATION

Based on the review of the data and the Applicant's responses to questions raised by the RMS and CMSs on quality, safety and efficacy, the RMS considers that the applications for Gemcitabine 200 mg, 1 g and 2 g Powder for Solution for Infusion are approvable in the treatment of the following indications:

"- Locally advanced or metastatic bladder cancer in combination with other cytostatic medicinal products.
- Locally advanced or metastatic breast cancer in combination with paclitaxel in patients experiencing a relapse after adjuvant/neoadjuvant chemotherapy. The preceding chemotherapy should have included an anthracycline unless clinically contraindicated.
- Locally advanced or metastatic non-small cell lung cancer in combination with other cytostatic medicinal products. Palliative treatment of adult patients with locally advanced or metastatic nonsmall cell lung cancer.
- Locally advanced or metastatic adenocarcinoma of the pancreas in patients who are in good general condition with adequate bone marrow reserves. Patients with 5-fluorouracil refractory pancreatic cancer."

II. EXECUTIVE SUMMARY

II.1 Problem statement

This abridged decentralised application concerns a generic version of gemcitabine submitted under Directive 2001/83/EC, as amended, Article 10.3. The originator product is Gemzar 200 mg Powder for Solution for Infusion, authorised to Eli Lilly UK on 26 October 1995. The legal basis is satisfactory.

With the UK as the Reference Member State in this Decentralised Procedure, Mayne Pharma plc is applying for the Marketing Authorisations for Gemcitabine 200 mg, 1 g and 2 g Powder for Solution for Infusion in AT, BE, CY, CZ, DE, DK, EE, EL, ES, FI, FR, HU, IE, IS, IT, LT, LU, LV, NL, NO, PL, PT, SE and SK.

The proposed product has three presentations (200 mg, 1 g and 2 g powder for solution for infusion), whereas the innovator product has only two presentations (200 mg and 1 g). However, the 2 g presentation is reconstituted prior to administration to exactly the same concentration as the reference product and the proposed dosage regimens are identical to those currently registered for the reference product.

II.2 About the product

Gemcitabine (2',2'-difluorodeoxycytidine), a pyrimidine antimetabolite, is a deoxycytidine analogue with two fluorine substitutes for the two hydrogen atoms in the 2' position of the deoxyribose moiety. After entering the cell, gemcitabine is phosphorylated to the active forms, such as gemcitabine diphosphate and triphosphate. The triphosphate form of gemcitabine is recognised by DNA polymerases and incorporated into the growing DNA strand. This process is followed by the incorporation of one or more natural nucleotides, resulting in an arrest in DNA polymerisation. Gemcitabine not only acts on the DNA, but is also incorporated into RNA. This action is called 'masked termination' and apparently locks the drug into the DNA, as the proof reading enzymes are unable to remove gemcitabine from this position. The inhibition of DNA synthesis by gemcitabine may lead to induction of DNA single- and double-strand breaks and may cause cell-death.

Gemcitabine is used clinically for the treatment of non-small-cell lung cancer, pancreatic cancer, breast cancer, and bladder cancer.

II.3 General comments on the submitted dossier

The dossier is of good quality. The applicant submitted the overviews and summaries in CTD format and these were found to be helpful.

II.4 General comments on compliance with GMP, GLP, GCP and agreed ethical principles

The product manufacturing site
The manufacturer of the drug product is approved by the UK authority for GMP compliance for sterile products. Copies of current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place have been provided.

GLP and GCP compliance
Since no additional non-clinical and clinical studies are performed for this generic application, there are no GLP and GCP issues to be discussed.

III. SCIENTIFIC OVERVIEW AND DISCUSSION

III.1 Quality aspects

Drug substance

The chemical-pharmaceutical documentation and Expert Report in relation to Gemcitabine 200 mg, 1 g and 2 g Powder for Solution for Infusion are of sufficient quality in view of current European regulatory requirements. Gemcitabine hydrochloride is the subject of a monograph in the USP and Ph Eur. The drug substance specification is acceptable. Stability studies have been performed with the drug substance. No significant changes in any parameters were observed. The proposed retest period of 24 months is acceptable.

Drug Product

The development of the product has been described, the choice of excipients is justified and their functions explained. The product specifications cover appropriate parameters for this dosage form. Validations of the analytical methods have been presented. Batch analysis results show that the finished products meet the specifications proposed. The conditions used in the stability studies are according to the ICH stability guideline. The proposed shelf-life of 24 months is acceptable.

III.2 Non clinical aspects

Critical evaluation of the Non-Clinical Overview and Summary

The pharmacodynamic, pharmacokinetic and toxicological properties of gemcitabine are well known. As gemcitabine is a well known active substance, the applicant has not provided additional studies and further studies are not required. An overview based on the literature review is therefore appropriate and the overview was adequate.

The three presentations for this product are 10 ml, 50 ml and 100 ml glass vials containing 200 mg, 1 g or 2 g of gemcitabine, respectively. The 200 mg and 1 g preparations are authorised for marketing in all the member states concerned by this application. The innovator does not have a marketing authorisation for a 2 g presentation, however the applicant considers that it would be more convenient for healthcare professionals in some circumstances. As dosing is performed on a mg/m^2 basis, the use of the proposed 2 g presentation does not result in the administration of a higher dose to the patient. The bulk formulation and manufacturing process of the 2 g preparation is stated to be identical to those of the proposed 200 mg and 1g presentations. Consequently no additional safety or efficacy studies are considered necessary to support the 2g presentation.

Section 4.6 of the SPC describes adequately the adverse treatment-related effects reported in the animal reproduction studies. Section 5.3 is acceptable.

Conclusions

There are no objections to the approval of Gemcitabine 200 mg, Gemcitabine 1g and Gemcitabine 2 g Powder for Solution for Infusion from a non-clinical point of view.

III.3 Clinical aspects

Pharmacokinetics

Gemcitabine 200 mg, 1 g and 2 g Powder for Solution for Infusion forms an aqueous solution for intravenous infusion containing the same active substance in the same concentration as the innovator product (Gemzar) that is marketed in most European countries. Therefore, no bioequivalence study is required and all data available for the original product also apply to this generic product.

Pharmacodynamics, clinical efficacy and clinical safety

The application contains an adequate review of the published clinical data. The Clinical Overview is of good quality. No new pharmacodynamic or clinical data were submitted for this application, and none were required. Regarding safety, no serious or unexpected adverse events were identified in the expert report.

The SPCs for Gemcitabine 200 mg, 1 g and 2 g Powder for Solution for Infusion have been updated in accordance with the RMS innovator's SPC and the comments made by the CMSs. It is, therefore, acceptable from a clinical point of view.

As for the 2 g presentation, there is no cause for concern as it is reconstituted prior to administration to exactly the same concentration as the reference product and the proposed dosage regimens are identical to those currently registered for the reference product.

IV. BENEFIT RISK ASSESSMENT

With regard to quality aspects, there are no potential serious risks to public health which need to be solved before a marketing authorisation can be granted.

There are no potential serious risks to public health from a non-clinical point of view.

With regard to clinical aspects, the application contains an adequate review of published clinical data. The reference medicinal product, Gemzar powder for solution for infusion 200 mg and 1g, contains the widely used and well-known active substance, gemcitabine hydrochloride, with an established favourable benefit-risk profile for the proposed indications in the updated SPC. As the 2 g dose is reconstituted to the same concentration as the reference product, there is no public health concern with the addition of this pack presentation.

The conclusion for the Benefit Risk Assessment is that the product approval could be recommended from the clinical point of view.

V. RECOMMENDED CONDITIONS FOR MARKETING AUTHORISATION AND PRODUCT INFORMATION

The RMS considers this product is approvable.

V.1 Conditions for the marketing authorisation

Legal Status

Prescription-only medicine

V.2 Summary of Product Characteristics (SPC)

The SPC has been updated to take account of RMS and CMS comments. The revised SPC is endorsed by the RMS

The applicant has provided a commitment, to update the current SPC following the Gemzar SPC harmonisation.

V.3 Package Leaflet (PL) and User Testing

The PL has been updated to take account of RMS and CMS comments. The revised PL is endorsed by the RMS

V.4 Labelling

The labelling has been updated to take account of RMS and CMS comments. The revised labelling is endorsed by the RMS

Overall conclusion

QUALITY

The important quality characteristics of Gemcitabine 200 mg, 1 g and 2 g Powder for Solution for Infusion are well defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

PRECLINICAL

The pharmacodynamic, pharmacokinetic and toxicological data submitted are satisfactory for an application of this type.

EFFICACY

Clinical studies have demonstrated the efficacy of gemcitabine hydrochloride in the treatment of pancreatic, bladder, breast or non-small cell lung cancer.

No new or unexpected safety concerns arise from these applications.

The SPC, PIL and labelling are satisfactory and consistent with that for the innovator product.

RISK BENEFIT ASSESSMENT

The quality of the product is acceptable and no new preclinical or clinical safety concerns have been identified.