

GEMCITABINE 200 MG POWDER FOR SOLUTION FOR INFUSION

GEMCITABINE 1G POWDER FOR SOLUTION FOR INFUSION

PL 20176/0048-9

UKPAR

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GEMCITABINE 200 MG POWDER FOR SOLUTION FOR INFUSION

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LAY SUMMARY

The Medicines and Healthcare products Regulatory Agency (MHRA) granted TechnoPharm Limited Marketing Authorisations (licences) for the medicinal products Gemcitabine 200 mg Powder for Solution for Infusion and Gemcitabine 1 g Powder for Solution for Infusion (Product Licence numbers: 20176/0048 and 20176/0049). These products are only available on prescription and should be administered by healthcare professionals.

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.

No new or unexpected safety concerns arose from these applications and it was, therefore, judged that the benefits of taking Gemcitabine 200 mg and 1 g Powder for Solution for Infusion outweigh the risks, hence Marketing Authorisations have been granted.

GEMCITABINE 200 MG POWDER FOR SOLUTION FOR INFUSION

GEMCITABINE 1G POWDER FOR SOLUTION FOR INFUSION

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SCIENTIFIC DISCUSSION

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INTRODUCTION

The UK granted marketing authorisations for the medicinal products Gemcitabine 200 mg and 1 g Powder for Solution for Infusion (PL 20176/0048-9) to TechnoPharm Limited on 24 January 2007. These are Prescription Only Medicines (POM).

These applications were submitted as complex abridged applications, according to Article 10(1) of EC Directive 2001/83/EC. The cross reference product is Gemzar 200 mg (PL00006/0301) and 1 g (PL00006/0302) Powder for Solution for Infusion, granted to Eli Lilly and Company Ltd on 26 October 1995.

PHARMACEUTICAL ASSESSMENT REPORT

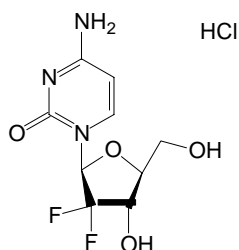
1. INTRODUCTION

These are abridged, complex applications submitted under Article 10(1) of Directive 2001/83/EC, as amended, as so called 'generic' applications. The original and reference products are Gemzar 200 mg (PL00006/0301) and 1g (PL00006/0302) Powder for Solution for Infusion, granted to Eli Lilly and Company Ltd on 26 October 1995.

2. ACTIVE SUBSTANCE

2.1 Gemcitabine hydrochloride

2.1.1 General information



Structure:

INN: Gemcitabine hydrochloride

Chemical names:

- i. 2'-deoxy-2',2'-difluorocytidine monohydrochloride (β -isomer)
- ii. Cytidine. 2'-deoxy-2',2'-difluoro-, monohydrochloride

Description: White or almost white crystalline powder

Molecular formula: $C_9H_{11}F_2N_3O_4.HCl$

Relative molecular mass: 299.66

3. MANUFACTURE

3.1 Manufacturer

The manufacturer of the active substance has provided a valid GMP certificate and a letter of access.

3.2 Manufacture

The manufacturing process is referenced to a drug master file (DMF).

3.3 Impurities

The specification limits for chemical impurities and residual solvents are appropriate. The chemical impurities are controlled to USP monographs.

3.4 Control of active substance

3.4.1 Specification

The specification used by the active substance manufacturer is controlled to the USP monograph, as supplemented by the DMF.

All tests and limits listed in the specification are satisfactory.

3.4.2 Analytical test methods

Suitable analytical tests are applied and satisfactory analytical validation data are provided.

3.4.3 Batch analyses

Satisfactory batch analyses data are provided by the active substance manufacturer.

3.4.4 Reference standards

Gemcitabine hydrochloride USP reference standard is procured from the USP. A working standard from an approved batch presented in batch analysis is used. A satisfactory certificate of analysis is provided.

3.4.5 Container closure system

Relevant specifications and satisfactory certificates of analysis are provided for the packaging components. The applicant has also submitted documentation that demonstrates the compliance of the primary packaging components with the food contact requirements of Directive 2002/72/EC.

3.4.6 Stability

Stability data are presented for batches that have undergone stability testing. The packaging conditions were also analysed. All data remain within specification.

The stability protocol for this active substance is satisfactory.

4. DRUG PRODUCT

4.1 Composition

The qualitative composition of the products is summarised in the following table. The products are powders for solution for infusion and are packed in colourless moulded glass vials (type I) with rubber stoppers and sealed with aluminium caps provided with PP covers.

Qualitative composition of gemcitabine 200 mg and 1 g powder for solution for infusion

Name of ingredient	Function	Ref Standard
Strength		
Gemcitabine HCl anhydrous (100%) (corresponds to gemcitabine)	API	USP
Mannitol 100%	Osmotically active	Ph. Eur.
Sodium acetate trihydrate	pH adjustment	Ph. Eur.
Sodium hydroxide and/or Hydrochloride acid up to pH	For additional pH adjustment	Ph. Eur.

4.2 Pharmaceutical Development

The development pharmaceuticals are well presented and the issues addressed include the rationale for the formulation and its subsequent evolution. Development studies on packaging materials are also provided.

4.3 Manufacture

4.3.1 Manufacturer(s)

A valid GMP certificate for the finished product manufacturer is provided.

A valid manufacturing authorisation is also provided.

4.3.2 Batch formula

A satisfactory batch formula is used in the manufacture of this product.

4.3.3 Manufacturing process and process controls

A flow diagram detailing the manufacturing process and in-process control testing has been provided. The manufacture of the product is relatively simple and uses conventional pharmaceutical methods. The account of the process is satisfactory.

4.3.4 Control of critical steps (in-process controls)

The in-process controls applied are appropriate and appear to give a reproducible product.

4.3.5 Process validation or evaluation

The process has been appropriately validated. The data generated are generally consistent and comply with the proposed control specification. The process appears to be under control and provides a reproducible bulk product.

Overall, the data demonstrate that the process is capable of producing sterile powder for solution for infusion of acceptable and consistent quality.

4.4 Control of excipients

4.4.1 Specification

All the excipients are controlled to Ph Eur monographs. Satisfactory specifications and certificates of analysis are provided.

A declaration is provided by the manufacturer stating that there are no excipients used in this product that are of animal origin.

4.5 Control of drug product

4.5.1 Specification

The finished product specification for the product has been provided; all tests and limits applied are satisfactory.

4.5.2 Analytical procedures

The product is tested according to the methods prescribed in the corresponding pharmacopoeial monographs.

4.5.3 Validation of analytical procedures

A satisfactory validation package, complying with ICH guidelines, has been provided.

4.5.4 Batch analyses

Certificates of batch analyses have been provided. Batches were all within specification and show a reasonable degree of comparability.

4.5.6 Reference standards

Satisfactory certificates of analysis for the reference standards are provided.

4.6 Container closure system

The product is filled in colourless vials made of type I glass. The 200 mg and 1 g strengths are filled in 10H and 50H vials, respectively, and are closed with rubber stoppers and capped with aluminium caps covered with a grey PP flip-off cover.

The vials and stoppers conform to Ph Eur monograph.

Specifications and dimensions of the primary packaging materials have been provided.

4.7 Stability

Full-scale production size batches of product manufactured at the intended site and stored in the intended packaging were subjected to stability testing.

The results obtained showed that there were no significant deviations from initial values and the product remained within the proposed release specification at all time points and temperatures.

Stability data from the test and the originator products (Gemzar) were compared and their impurity profiles were found to be almost identical.

Based on the stability data, a shelf-life of 24 months at a storage temperature below 30°C is acceptable.

5. CONCLUSIONS AND ADVICE

Marketing authorisations can be granted.

PRECLINICAL ASSESSMENT

No new preclinical data have been supplied with these applications and none are required for applications of this type.

CLINICAL ASSESSMENT

1. INTRODUCTION

1.1 Type of application and regulatory background

These national applications for Gemcitabine 200 mg and 1 g Powder for Solution for Infusion are submitted on behalf of TechnoPharm Ltd. These are generic applications made under Article 10(1) of Directive 2001/83/EC. The reference products are Gemzar 200 mg and 1 g Powder for Solution for Infusion (PL 00006/0301-2), marketed by Eli Lilly and Co. Ltd. The reference products have been marketed in the EEA since 26 October 1995. The applicant states that essential similarity has been demonstrated between the proposed and reference products. Please note that from here on, 'proposed product' refers to both the 200 mg and 1 g vials of Gemcitabine Powder for Solution for Infusion.

1.2 Clinical background

Gemcitabine (gemcitabine HCl) is a nucleoside analogue that exhibits antitumour activity. Gemcitabine HCl is 2'-deoxy-2',2'-difluorocytidine monohydrochloride (β -isomer). Gemcitabine exhibits cell phase specificity, primarily killing cells undergoing DNA synthesis (S-phase) and also blocking the progression of cells through the G1/S-phase boundary. Gemcitabine is metabolized intracellularly by nucleoside kinases to the active diphosphate (dFdCDP) and triphosphate (dFdCTP) nucleosides. The cytotoxic effect of gemcitabine is attributed to a combination of two actions of the diphosphate and the triphosphate nucleosides, which leads to inhibition of DNA synthesis:

- First, gemcitabine diphosphate inhibits ribonucleotide reductase, which is responsible for catalyzing the reactions that generate the deoxynucleoside triphosphates for DNA synthesis. Inhibition of this enzyme by the diphosphate nucleoside causes a reduction in the concentrations of deoxynucleotides, including dCTP.
- Second, gemcitabine triphosphate competes with dCTP for incorporation into DNA. The reduction in the intracellular concentration of dCTP (by the action of the diphosphate) enhances the incorporation of gemcitabine triphosphate into DNA (self-potentialiation).

1.3 Indications

From the SPC for the proposed product:

Non-Small Cell Lung Cancer:

Gemcitabine in combination with cisplatin is indicated as a first line treatment of patients with locally advanced (inoperable Stage IIIA or IIIB) or metastatic (Stage IV) non-small cell lung cancer.

Gemcitabine is indicated for the palliative treatment of adult patients with locally advanced or metastatic non-small cell lung cancer.

Pancreatic Cancer:

Gemcitabine is indicated for the treatment of adult patients with locally advanced or metastatic adenocarcinoma of the pancreas. Gemcitabine is indicated for patients with 5-FU refractory pancreatic cancer.

Bladder Cancer:

Gemcitabine is indicated for treatment of advanced bladder cancer (muscle invasive Stage IV tumours with or without metastases) in combination with cisplatin therapy.

Breast Cancer:

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

1.4 Dose and dose regimen

The dosing regime varies with indication and full details are provided in the SPC for the proposed product. Gemcitabine may also be given in a regime that includes cisplatin or paclitaxel therapy.

Gemcitabine is for intravenous infusion once reconstituted with sterile sodium chloride (see section 6.6 of the SPC for the proposed product).

1.5 GCP aspects

No new studies have been conducted by the applicant.

1.6 Orphan medicinal products

The proposed product does not have orphan status.

1.7 Paediatric development programme

No paediatric development programme has been submitted. The SPC for the proposed product states that ‘Gemcitabine has been studied in limited Phase I and II trials in children in a variety of tumour types. These studies did not provide sufficient data to establish the efficacy and safety of gemcitabine in children.’

1.8 Scientific advice

Not applicable.

1.9 Legal status

The proposed product’s legal status would be: POM.

2. CLINICAL PHARMACOLOGY

2.1 Pharmacokinetics

No new studies have been performed by the applicant. The SPC for the proposed product is almost identical to that for the reference product. The applicant’s dossier states that

‘gemcitabine is metabolised by cytidine deaminase to inactive uracil metabolite 2’2’-difluorodeoxyuridine (dFdU) and is excreted by kidney in urine.’

2.2 Bioequivalence

No bioequivalence studies have been performed. Essential similarity between the proposed product and reference product has been demonstrated:

- The proposed product has the same qualitative and quantitative composition (including identical impurity profile) to that of the reference product.
- The proposed product is reconstituted with saline to form an aqueous solution for intravenous administration (the same route as for the reference product).
- The proposed product is also indicated for the same conditions as the reference product.

2.3 Pharmacodynamics

No new studies have been performed by the applicant. The SPC for the proposed product is almost identical to that for the reference product.

3. CLINICAL EFFICACY

No new studies have been performed by the applicant. The applicant’s dossier states that products containing gemcitabine hydrochloride have been used in humans for about 15 years. Gemcitabine was first synthesized in the 1980s and put to clinical use in the 1990’s.

The clinical overview discusses studies showing a 17 to 24% response rate in non-small-cell lung cancer (NSCLC), an important limitation being mild haematologic toxicity. A twenty per cent remission rate in studies with neoadjuvant chemotherapy and local surgery has been shown. Randomised trials demonstrate that the combination of gemcitabine and cisplatin should be considered one of the more effective combinations in advanced NSCLC. In the elderly, gemcitabine is an example of a single agent of choice in NSCLC.

The clinical overview adds that many chemotherapy drugs have been evaluated in pancreatic cancer and that the results have been disappointing. Gemcitabine has been found to be more effective than 5-FU in palliation of patients with advanced pancreatic cancer. It is stated that gemcitabine is regarded as a standard treatment for unresectable disease with 17 to 28% survival in phase III studies. Combination therapy (including gemcitabine) has demonstrated significantly better progression-free survival at 4 months.

The clinical overview goes on to say that gemcitabine treatment has also been shown to result in a 17% remission rate in ovarian cancer patients with resistance to cisplatin or paclitaxel therapy. There is currently no standard care for metastatic breast cancer and gemcitabine, as a single agent, may be used. Gemcitabine can also be useful in soft tissue sarcoma.

In addition, the applicant's dossier states that 'the effects of significant renal or hepatic insufficiency on the disposition of gemcitabine have not been assessed'. The SPCs for the reference and proposed products advise caution in these contexts as 'there is insufficient information from clinical studies to allow clear dose recommendation for this patient population'.

4. CLINICAL SAFETY

4.1 Introduction

As a cytotoxic therapy, gemcitabine is associated with adverse effects. The applicant's dossier states that 'the principal dose-limiting toxicity with gemcitabine therapy is myelosuppression. Therefore, there is a need to have facilities to monitor haematological indices in patients undergoing therapy.'

4.2 Patient exposure

The applicant's dossier states that "gemcitabine is a deoxycytidine analogue which was originally investigated for its antiviral effects but has since been developed as an anticancer therapy. Gemcitabine was approved for clinical use in 1996. Since that time it has been approved for use in more than 90 countries worldwide. It is the worldwide standard for care of pancreatic cancer and in many parts of the world for non-small cell lung, bladder and breast cancers. Gemcitabine is approved in more than 75 countries as a single agent for the treatment of locally advanced or metastatic pancreatic cancer. It is also approved, in combination with paclitaxel, in more than 60 countries for the treatment of metastatic breast cancer. In most European countries, gemcitabine is approved as a single agent or in combination with cisplatin for the treatment of advanced non-small cell lung cancer. Gemcitabine, in combination with carboplatin, is approved in several European markets for the treatment of recurrent epithelial ovarian cancer. Most recently, gemcitabine was approved in Mexico for cervical cancer, making it the first approval for this disease."

4.3 Deaths

From the Physician's Desk Reference: 'Serious hepatotoxicity, including liver failure and death, has been reported very rarely in patients receiving gemcitabine alone or in combination with other potentially hepatotoxic drugs. In a study comparing gemcitabine plus cisplatin and cisplatin only in NSCLC, deaths occurred due to myelosuppression/infection and renal failure in the combined arm only. In a further study involving the combination of gemcitabine and cisplatin versus etoposide, a single death due to neutropenia associated with renal failure occurred in the combined arm.'

The Physician's Desk Reference also notes that some patients experienced (during post-marketing) the onset of pulmonary symptoms up to 2 weeks after the last dose of gemcitabine. Respiratory failure and death occurred very rarely in some patients, despite discontinuation of therapy. Renal failure leading to death (or dialysis) despite discontinuation of gemcitabine has also been rarely reported. The majority of the cases of renal failure leading to death involved haemolytic-uraemic syndrome.

4.4 Serious adverse events

The table below is included in the clinical overview and originates from the Physician's Desk Reference entry on gemcitabine.

- These data are based on 979 patients receiving gemcitabine as a single-agent administered weekly as a 30-minute infusion for treatment of a wide variety of malignancies.
- Gemcitabine starting doses ranged from 800 to 1250 mg/m².
- There was a 10% discontinuation rate and non-laboratory adverse events (causality not assessed) in the table occurred for at least 10% of patients.
- The SPC for the proposed product describes undesirable effects and frequencies based on clinical trial data and post-marketing reports for gemcitabine.

2.5.5. OVERVIEW OF SAFETY

The principal dose-limiting toxicity with gemcitabine therapy is myelosuppression. (1)

Table 4
Selected WHO-Graded Adverse Events in Patients Receiving Single-Agent Gemcitabine. WHO Grades (% incidence) (1)

	All Patients*			Pancreatic Cancer Patients**			Discontinuation% All Patients(n=979)
	All Grades	Grade 3	Grade 4	All Grades	Grade 3	Grade 4	
Laboratory***							
<i>Hematologic</i>							
Anemia	68	7	1	73	8	2	<1
Leukopenia	62	9	<1	64	8	1	<1
Neutropenia	63	19	6	61	17	7	-
Thrombocytopenia	24	4	1	36	7	<1	<1
<i>Hepatic</i>							
ALT	68	8	2	72	10	1	
AST	67	6	2	78	12	5	
ALP	55	7	2	77	16	4	
Bilirubin	13	2	<1	26	6	2	
<i>Renal</i>							
Proteinuria	45	<1	0	32	<1	0	<1
Hematuria	35	<1	0	23	0	0	
BUN	16	0	0	15	0	0	
Creatinine	8	<1	0	6	0	0	
Non-laboratory****							
Nausea/vomiting	69	13	1	71	10	2	<1
Pain	48	9	<1	42	6	<1	<1
Fever	41	2	0	38	2	0	<1
Rash	30	<1	0	28	<1	0	<1
Dyspnea	23	3	<1	10	0	<1	<1
Constipation	23	1	<1	31	3	<1	0
Diarrhea	19	1	0	30	3	0	0
Hemorrhage	17	<1	<1	4	2	<1	<1
Infection	16	1	<1	10	2	<1	<1
Alopecia	15	<1	0	16	0	0	0
Stomatitis	11	<1	0	10	<1	0	<1
Somnolence	11	<1	<1	11	2	<1	<1
Paresthesias	10	<1	0	10	<1	0	0

*N =699-974; all patients with laboratory or non-laboratory data

**N=161-241; all pancreatic cancer patients with laboratory or non-laboratory data

*** Regardless of causality

****Table includes non-laboratory data with incidence for all patients $\geq 10\%$. For approximately 60% of the patients the laboratory events were graded only if assessed to be possible drug-related

4.5 Common adverse events

Please refer to the above table (Section 4.4 of this report).

4.6 Discontinuation due to adverse events

Please refer to Section 4.4 of this report.

4.7 Laboratory findings

Please refer to Section 4.4 of this report.

4.8 Safety in special populations

Caution is advised in patients with hepatic or renal impairment. Gemcitabine is contraindicated in pregnancy or breast-feeding. The elderly may be treated with gemcitabine, although the Physician's Desk Reference does note that gemcitabine clearance is affected by age and Grade 3/4 thrombocytopenia is more common in the elderly. The efficacy and safety of gemcitabine has not been established in children.

4.9 Drug-specific safety considerations

Please refer to Section 4.4 of this report.

4.10 Safety related to interactions

The SPCs for the proposed product and reference product state that 'no interactions have been reported' for gemcitabine.

4.11 Post marketing experience

Please refer to Section 4.4 of this report.

4.12 Proposals for post marketing surveillance / STUDIES

No proposals for post-marketing surveillance have been submitted by the applicant.

4.13 Assessor's overall conclusions on clinical safety

The use of gemcitabine is well-established and it is noted that many of the indications for treatment with gemcitabine do not have a good prognosis. A range of toxicities are found with this cytotoxic drug and, therefore, careful monitoring of patients receiving gemcitabine is required.

5. EXPERT REPORTS

The clinical overview provides a brief overview of the salient points regarding the safety and efficacy of gemcitabine and the rationale for this generic application. Detailed references are provided.

6. PRODUCT LITERATURE

6.1 SPC

The SPCs for these products are satisfactory.

6.2 Patient information leaflet

The PIL for these products is satisfactory.

6.3 Label

All labelling for these products is satisfactory.

6.4 Application form

The application forms submitted with these applications are satisfactory.

7. OVERALL CONCLUSION

7.1 Pharmacokinetics

No new studies have been performed by the applicant. The SPC for the proposed product is almost identical to that for the reference product.

7.2 Pharmacodynamics

No new studies have been performed by the applicant. The SPC for the proposed product is almost identical to that for the reference product.

7.3 Efficacy

Essential similarity between the proposed product and reference product has been demonstrated. No new studies have been performed by the applicant. Products containing gemcitabine hydrochloride have been used in humans for about 15 years. Gemcitabine was first synthesized in the 1980s and was put to clinical use in the 1990's.

7.4 Safety

The use of gemcitabine is well-established and it is noted that many of the indications for treatment with gemcitabine do not have a good prognosis. A range of toxicities are found with this cytotoxic drug and, therefore, careful monitoring of patients receiving gemcitabine is required.

7.5 Risk benefit

Please refer to Section 7.4 (above) in this report.

7.6 Recommended conditions for Marketing Authorisation

Marketing authorisations can be recommended.

OVERALL CONCLUSION AND RISK BENEFIT ASSESSMENT

QUALITY

The important quality characteristics of the products 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

No new preclinical data were submitted and none are required for applications of this type.

EFFICACY AND SAFETY

The efficacy of gemcitabine powder for solution for infusion has been well documented in the past. No new or unexpected safety concerns arise from these applications.

The SPCs, PILs and labelling are satisfactory.

RISK BENEFIT ASSESSMENT

The quality of the products is acceptable and no new preclinical or clinical safety concerns have been identified. The risk benefit ratio is considered to be positive.

GEMCITABINE 200 MG POWDER FOR SOLUTION FOR INFUSION

GEMCITABINE 1G POWDER FOR SOLUTION FOR INFUSION

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STEPS TAKEN FOR ASSESSMENT

- 1** The MHRA received the marketing authorisation application on 23 December 2005
- 2** Following assessment of the application the MHRA requested further information relating to the quality dossier on 24 February 2006 and relating to the clinical dossier on 27 July 2006
- 3** The applicant responded to the MHRA's requests, providing further information on 23 August 2006
- 4** Following assessment of the response the MHRA requested further information relating to the clinical dossier on 16 October 2006
- 5** The applicant responded to the MHRA's request, providing further information on 7 January 2007
- 6** The application was determined on 24 January 2007

SUMMARY OF PRODUCT CHARACTERISTICS

PL 20176/0048:

1 NAME OF THE MEDICINAL PRODUCT

Gemcitabine 200mg Powder for Solution for Infusion.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Gemcitabine (as hydrochloride) 200mg.

Excipients: For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Vial containing powder for solution for infusion.

White lyophilised powder.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Non-Small Cell Lung Cancer:

Gemcitabine in combination with cisplatin is indicated as a first line treatment of patients with locally advanced (inoperable Stage IIIA or IIIB) or metastatic (Stage IV) non-small cell lung cancer.

Gemcitabine is indicated for the palliative treatment of adult patients with locally advanced or metastatic non-small cell lung cancer.

Pancreatic Cancer:

Gemcitabine is indicated for the treatment of adult patients with locally advanced or metastatic adenocarcinoma of the pancreas. Gemcitabine is indicated for patients with 5-FU refractory pancreatic cancer.

Bladder Cancer:

Gemcitabine is indicated for treatment of advanced bladder cancer (muscle invasive Stage IV tumours with or without metastases) in combination with cisplatin therapy.

Breast Cancer:

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

4.2 Posology and method of administration

Please refer to Section 6.6 for details of how to reconstitute gemcitabine powder for solution for infusion.

Non-Small Cell Lung Cancer:

Combination use: 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 1,250 mg/m², 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 1,000 mg/m², 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/m² once every 3 or 4 weeks.

Single-agent use: Adults: The recommended dose of gemcitabine is 1,000 mg/m², 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.

Pancreatic Cancer:

Adults: The recommended dose of gemcitabine is 1,000 mg/m², given by 30 minute intravenous infusion. This should be repeated once weekly for up to 7 weeks, followed by a week of rest. Subsequent cycles should consist of injections once weekly for 3 consecutive weeks out of every 4 weeks. Dosage reduction is applied based upon the amount of toxicity experienced by the patient.

Bladder Cancer:

Combination use: Adults: The recommended dose for gemcitabine is 1,000 mg/m², given by 30 minute infusion. The dose should be given on days 1, 8, and 15 of each 28 day cycle in combination with cisplatin. Cisplatin is given at a recommended dose of 70 mg/m² on day 1 following gemcitabine or day 2 of each 28 day cycle. This 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. A clinical trial showed more myelosuppression when cisplatin was used in doses of 100 mg/m².

Breast Cancer:

Combination use: Adults: Gemcitabine in combination with paclitaxel is recommended using paclitaxel (175 mg/m²) administered on day 1 over 3 hours as an intravenous infusion, followed by gemcitabine (1,250mg/m²) as a 30-60 minute intravenous infusion on days 1 and 8 of each 21 day cycle. Dose reduction with each cycle or within a cycle may be applied based upon the amount of toxicity experienced by the patient. Patients should have an absolute granulocyte count of at least 1,500 (x 10⁶/l) prior to initiation of gemcitabine + paclitaxel combination.

Patients receiving gemcitabine should be monitored prior to each dose for platelet, leucocyte, and granulocyte counts, and, if necessary, the dose of gemcitabine may be either reduced or withheld in the presence of haematological toxicity, according to the following scale:

Absolute granulocyte count (x 10 ⁶ /l)		Platelet count (x 10 ⁶ /l)	% of full dose
>1,000	and	>100,000	100
500 -1,000	or	50,000 -100,000	75
<500	or	<50,000	hold

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

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

Gemcitabine is well tolerated during the infusion, with only a few cases of injection site reaction reported. There have been no reports of injection site necrosis. Gemcitabine can be easily administered on an outpatient basis.

Elderly patients: Gemcitabine has been well tolerated in patients over the age of 65.

There is no evidence to suggest that dose adjustments are necessary in the elderly, although gemcitabine clearance and half-life are affected by age.

Children: Gemcitabine has been studied in limited Phase I and II trials in children in a variety of tumour types. These studies did not provide sufficient data to establish the efficacy and safety of gemcitabine in children.

Hepatic and renal impairment: Gemcitabine should be used with caution in patients with hepatic insufficiency or with impaired renal function as there is insufficient information from clinical studies to allow clear dose recommendation for this patient population.

4.3 Contraindications

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

4.4 Special warnings and precautions for use

Warnings:

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

Gemcitabine can suppress bone marrow function as manifested by leucopenia, thrombocytopenia, and anaemia. However, myelosuppression is short lived and usually does not result in dose reductions and rarely in discontinuation (see sections 4.2 and 4.8). Gemcitabine should be discontinued at the first signs of any evidence of microangiopathic haemolytic anaemia, such as rapidly falling haemoglobin with concomitant thrombocytopenia, elevation of serum bilirubin, serum creatinine, blood urea nitrogen, or LDH, which may indicate development of haemolytic uraemic syndrome (see section 4.8). Renal failure may not be reversible, even with discontinuation of therapy, and dialysis may be required.

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 1,000 mg/m² was administered concurrently for up to 6 consecutive weeks with therapeutic thoracic radiation to patients with non-small cell lung cancer, significant toxicity in the form of severe and potentially life-threatening mucositis, especially oesophagitis, and pneumonitis was observed, particularly in patients receiving large volumes of radiotherapy (median treatment volumes 4,795 cm³). Studies done subsequently have suggested that it is feasible to administer gemcitabine at lower doses with concurrent radiotherapy with predictable toxicity, such as a Phase II study in non-small cell lung cancer. Thoracic radiation doses of 66Gy were administered with gemcitabine (600 mg/m², four times) and cisplatin (80 mg/m², twice) during 6 weeks. The optimum regimen for safe administration of gemcitabine with therapeutic doses of radiation has not yet been determined.

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.

Precautions:

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

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

Laboratory tests: Therapy should be started cautiously in patients with compromised bone marrow function. As with other oncolytics, the possibility of cumulative bone marrow suppression when using combination or sequential chemotherapy should be considered.

Patients receiving gemcitabine should be monitored prior to each dose for platelet, leucocyte, and granulocyte counts. Suspension or modification of therapy should be considered when drug-induced marrow depression is detected. Guidelines regarding dose modifications are provided in section 4.2 above. Peripheral blood counts may continue to fall after the drug is stopped.

4.5 Interaction with other medicinal products and other forms of interaction

No interactions have been reported.

4.6 Pregnancy and lactation

The safety of this medicinal product for use in human pregnancy has not been established. Evaluation of experimental animal studies has shown reproductive toxicity, eg, birth defects or other effects on the development of the embryo or foetus, the course

of gestation, or perinatal and postnatal development. The use of gemcitabine should be avoided in pregnant or nursing women because of the potential hazard to the foetus or infant.

4.7 Effects on ability to drive and use machines

Gemcitabine has been reported to cause mild to moderate somnolence. Patients should be cautioned against driving or operating machinery until it is established that they do not become somnolent.

4.8 Undesirable effects

The most commonly reported adverse drug reactions associated with gemcitabine treatment include: nausea with or without vomiting, raised liver transaminases (AST/ALT) and alkaline phosphatase, reported in approximately 60% of patients; proteinuria and haematuria reported in approximately 50% patients; dyspnoea reported in 10-40% of patients (highest incidence in lung cancer patients); allergic skin rashes occur in approximately 25% of patients and are associated with itching in 10% of patients. The frequency and severity of the adverse reactions are affected by the dose, infusion rate, and intervals between doses (see section 4.4). Dose-limiting adverse reactions are reductions in thrombocyte, leucocyte, and granulocyte counts (see section 4.2). The following table of undesirable effects and frequencies is based on clinical trial and post-marketing spontaneous reports.

Blood and Lymphatic System Disorders

Very common (>1/10):

- Leucopenia
- Thrombocytopenia
- Neutropenia - frequency of Grade 3 is 19.3%, and of Grade 4 6%. Bone-marrow suppression is usually mild to moderate and mostly affects the granulocyte count (see section 4.2).
- Anaemia

Common (>1/100, <1/10):

- Febrile neutropenia

Very rare (<1/10,000):

- Thrombocythaemia

Immune System Disorders

Very rare (<1/10,000):

- Anaphylactoid reaction

Nervous System Disorders

Common (>1/100, <1/10):

- Somnolence

Cardiac Disorders

Very rare (<1/10,000):

- Myocardial infarct
- Congestive heart failure
- Arrhythmia - predominantly supraventricular in nature

Vascular Disorders

Rare (>1/10,000, <1/1000):

- Hypotension

Very Rare (<1/10,000):

Clinical signs of peripheral vasculitis and gangrene

Respiratory, Thoracic, and Mediastinal Disorders

Very common (>1/10):

- Dyspnoea - usually mild and passes rapidly without treatment

Uncommon (<1/100, >1/1000):

- Bronchospasm - usually mild and transient but may require parenteral treatment

Rare (>1/10,000, <1/1000):

- Adult respiratory distress syndrome (ARDS)
- Interstitial pneumonitis together with pulmonary infiltrates - symptoms may be relieved with steroid treatment

- Pulmonary oedema

In the event of ARDS, interstitial pneumonitis, or pulmonary oedema, gemcitabine treatment must be stopped. Initiating supportive treatment early may improve the situation.

Gastro-intestinal Disorders

Very common (>1/10):

- Nausea
- Vomiting

Common (>1/100, <1/10):

- Stomatitis and ulceration of mouth
- Diarrhoea
- Constipation

Hepatobiliary Disorders

Very Common (>1/10):

- Elevation of liver transaminases (AST and ALT) and alkaline phosphatase.

Common (>1/100, <1/10):

- Increased bilirubin

Rare (>1/10,000, <1/1,000):

- Increased gamma-glutamyl transferase (GGT).

Very Rare (<1/10,000):

- Serious hepatotoxicity, including liver failure and death – in patients receiving gemcitabine alone or in combination with other potentially hepatotoxic drugs.

Gemcitabine should be given with caution to patients with impaired hepatic function.

Skin and Subcutaneous Tissue Disorders

Very common (>1/10):

- Allergic skin rash often associated with pruritus
- Alopecia - usually mild with minimal hair loss

Rare (>1/10,000, <1/1000):

- Vesicle formation and ulceration
- Scaling

Very Rare (<1/10,000):

Severe desquamative and bullous skin eruptions.

Renal and Urinary Disorders

Very common (>1/10):

- Haematuria
- Proteinuria

Rarely of clinical importance and do not usually change serum creatinine or urea levels.

Rare (>1/10,000, <1/1000):

- Renal failure, aetiology unknown
- Haemolytic uraemic syndrome

Gemcitabine should be administered with caution to patients with impaired renal function (see section 4.4).

Gemcitabine treatment should be withdrawn if there is any sign of microangiopathic haemolytic anaemia, such as rapidly falling haemoglobin levels with simultaneous thrombocytopenia, elevation of serum bilirubin, serum creatinine, urea or LDH. Renal failure may be irreversible despite withdrawal of the gemcitabine treatment and may require dialysis.

General Disorders and Administration Site Conditions

Very common (>1/10):

- Oedema/peripheral oedema - reported in approximately 30% of patients. A few cases of facial oedema have been reported. 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 commonly reported symptoms include fever, headache, back pain, shivering, muscle pain, asthenia, and anorexia. Cough, rhinitis, malaise, perspiration, and sleeping difficulties have also been reported.

<p><i>Common (>1/100, <1/10):</i></p> <ul style="list-style-type: none"> • Fever • Asthenia <p><i>Rare (>1/10,000, <1/1,000):</i></p> <p>Injection site reactions - mainly mild in nature.</p>
<p>Injury and Poisoning</p> <ul style="list-style-type: none"> • Radiation toxicity (see section 4.4).

Haemolytic-uraemic syndrome (HUS) and/or thrombotic thrombocytopenic purpura and/or renal failure have been reported following one or more doses of gemcitabine. Renal failure leading to death or requiring dialysis, despite discontinuation of therapy, has been rarely reported. The majority of the cases of renal failure leading to death were due to HUS.

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

A few cases of facial oedema have occurred.

Combination Use in Breast Cancer:

The frequency of Grade 3 and 4 haematological toxicities, particularly neutropenia, increases when gemcitabine is used in combination with paclitaxel. However, the increase in these adverse reactions is not associated with an increased incidence of infections or haemorrhagic events.

Fatigue and febrile neutropenia occur more frequently when gemcitabine is used in combination with paclitaxel. Fatigue, which is not associated with anaemia, usually resolves after the first cycle.

**Grade 3 and 4 Adverse Events
Paclitaxel Versus Gemcitabine Plus Paclitaxel**

	Number (%) of Patients			
	Paclitaxel Arm (n = 259)		Gemcitabine Plus Paclitaxel Arm (n = 262)	
	Grade 3	Grade 4	Grade 3	Grade 4

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.				

4.9 Overdose

There is no antidote for overdosage of gemcitabine. Single doses as high as 5.7g/m² have been administered by IV infusion over 30 minutes every two weeks with clinically acceptable toxicity. In the event of suspected overdose, the patient should be monitored with appropriate blood counts and should receive supportive therapy, as necessary.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antineoplastic agents - antimetabolites, ATC code: L01BC 05

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. When administered daily, gemcitabine causes death in animals with minimal antitumour activity. However, when an every third or fourth day dosing schedule is used, gemcitabine can be given at non-lethal doses that have excellent antitumour activity against a broad range of mouse tumours.

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 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-potential). 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/m² 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/m² for women and 17.5 l/m² for men (inter-individual variability was 91.9%). Volume of distribution of the peripheral compartment: 47.4 l/m². The volume of the peripheral compartment was not sensitive to gender.

Plasma protein binding: Negligible.

Systemic clearance: Ranged from 29.2 l/hr/m² to 92.2 l/hr/m² depending on gender and age (inter-individual variability was 52.2%). Clearance for women is approximately 25% lower than the values for men. Although rapid, clearance for both men and women appears to decrease with age. For the recommended gemcitabine dose of 1,000 mg/m² given as a 30 minute infusion, lower clearance values for women and men should not necessitate a decrease in the gemcitabine dose.

Urinary excretion: Less than 10% is excreted as unchanged drug.

Renal clearance: 2 to 7 l/hr/m².

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/m²/30 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/m²/30 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/m²): 28-52 µg/ml.

Trough concentration following once weekly dosing: 0.07-1.12 µg/ml, with no apparent accumulation.

Triphasic plasma concentration versus time curve, mean half-life of terminal phase - 65 hours (range 33-84 hr).

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

Mean volume of distribution of central compartment: 18 l/m² (range 11-22 l/m²).

Mean steady state volume of distribution (V_{ss}): 150 l/m² (range 96-228 l/m²).

Tissue distribution: Extensive.

Mean apparent clearance: 2.5 l/hr/m² (range 1-4 l/hr/m²).

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 Paclitaxel Combination Therapy:

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

5.3 Preclinical safety data

In repeat dose studies of up to 6 months in duration in mice and dogs, the principal finding was haematopoietic suppression. These effects were related to the cytotoxic properties of the drug and were reversible when treatment was withdrawn. The degree of the effect was schedule and dose-dependent.

Carcinogenesis, Mutagenesis, Fertility:

Cytogenetic damage has been produced by gemcitabine in an *in vivo* assay. Gemcitabine induced forward mutation *in vitro* in a mouse lymphoma (L5178Y) assay. Gemcitabine caused a reversible, dose and schedule dependent hypospermatogenesis in male mice.

Although animal studies have shown an effect of gemcitabine on male fertility, no effect has been seen on female fertility. Long-term animal studies have not been conducted to evaluate the carcinogenic potential of gemcitabine.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Mannitol

Sodium Acetate

Hydrochloric Acid (for pH adjustment)

Sodium Hydroxide (for pH adjustment)

6.2 Incompatibilities

Gemcitabine should only be reconstituted with sterile Sodium Chloride for Injection BP (see Section 6.6). Compatibility with other drugs has not been studied.

6.3 Shelf life

Lyophilised powder: 2 years

Reconstituted solution:

Chemical and physical in-use stability has been demonstrated for 24 hours at 30°C. From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 25°C, unless reconstitution/dilution (etc) has taken place in controlled and aseptic conditions. Solutions should not be refrigerated, as crystallisation may occur.

6.4 Special precautions for storage

Do not store above 30°C. Store in the original package.
For storage conditions of the reconstituted medicinal product, see section 6.3.

6.5 Nature and contents of container

The product is contained in a 10ml sterile colourless vial Type I glass, which meets the requirements of the PhEur, and is closed with a rubber stopper and sealed with an aluminium seal with a polypropylene cap.
1 vial per pack.

6.6 Special precautions for disposal

Reconstitution:

Gemcitabine has only been shown to be compatible with Sodium Chloride Injection BP. Accordingly, only this diluent should be used for reconstitution. Compatibility with other drugs has not been studied; therefore, it is not recommended to mix Gemcitabine with other drugs when reconstituted. Due to solubility considerations, the maximum concentration for gemcitabine upon reconstitution is 40mg/ml. Reconstitution at concentrations greater than 40mg/ml may result in incomplete dissolution, and should be avoided.

To reconstitute, add 5ml of Sodium Chloride Injection BP to the 200mg vial. Shake to dissolve. These dilutions each yield a gemcitabine concentration of 38mg/ml, which includes accounting for the displacement volume of the lyophilised powder (0.26ml for the 200mg vial). The total volume upon reconstitution will be 5.26ml. Complete withdrawal of the vial contents will provide 200mg gemcitabine. The appropriate amount of drug may be administered as prepared or further diluted with Sodium Chloride Injection BP. Reconstituted solutions should be used immediately or may be stored for 24 hours if prepared in an appropriately controlled aseptic environment.

Parenteral drugs should be inspected visually for particulate matter and discolouration, prior to administration, whenever solution and container permit.

Guidelines for the Safe Handling of Antineoplastic Agents:

Cytotoxic preparations should not be handled by pregnant staff. Trained personnel should reconstitute the drug. This should be performed in a designated area. The work surface should be covered with disposable plastic-backed absorbent paper.

Adequate protective gloves, masks, and clothing should be worn. Precautions should be taken to avoid the drug accidentally coming into contact with the eyes. If accidental contamination occurs, the eye should be washed with water thoroughly and immediately.

Use Luer-lock fittings on all syringes and sets. 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.

Adequate care and precaution should be taken in the disposal of items used to reconstitute gemcitabine. 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 excess drug solution should be flushed directly into a drain with copious amounts of water.

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

7 MARKETING AUTHORISATION HOLDER

TechnoPharm Limited
Chapelizod
Dublin 20
Republic of Ireland

8 MARKETING AUTHORISATION NUMBER(S)

PL 20176/0048

9 DATE OF FIRST AUTHORISATION

24/01/2007

10 DATE OF REVISION OF THE TEXT

24/01/2007

PL 20176/0049:

1 NAME OF THE MEDICINAL PRODUCT

Gemcitabine 1g Powder for Solution for Infusion.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Gemcitabine (as hydrochloride) 1g.

Excipients: For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Vial containing powder for solution for infusion.

White lyophilised powder.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Non-Small Cell Lung Cancer:

Gemcitabine in combination with cisplatin is indicated as a first line treatment of patients with locally advanced (inoperable Stage IIIA or IIIB) or metastatic (Stage IV) non-small cell lung cancer.

Gemcitabine is indicated for the palliative treatment of adult patients with locally advanced or metastatic non-small cell lung cancer.

Pancreatic Cancer:

Gemcitabine is indicated for the treatment of adult patients with locally advanced or metastatic adenocarcinoma of the pancreas. Gemcitabine is indicated for patients with 5-FU refractory pancreatic cancer.

Bladder Cancer:

Gemcitabine is indicated for treatment of advanced bladder cancer (muscle invasive Stage IV tumours with or without metastases) in combination with cisplatin therapy.

Breast Cancer:

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

4.2 Posology and method of administration

Please refer to Section 6.6 for details of how to reconstitute gemcitabine powder for solution for infusion.

Non-Small Cell Lung Cancer:

Combination use: 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 1,250 mg/m², 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 1,000 mg/m², 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/m² once every 3 or 4 weeks.

Single-agent use: Adults: The recommended dose of gemcitabine is 1,000 mg/m², 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.

Pancreatic Cancer:

Adults: The recommended dose of gemcitabine is 1,000 mg/m², given by 30 minute intravenous infusion. This should be repeated once weekly for up to 7 weeks, followed by a week of rest. Subsequent cycles should consist of injections once weekly for 3 consecutive weeks out of every 4 weeks. Dosage reduction is applied based upon the amount of toxicity experienced by the patient.

Bladder Cancer:

Combination use: Adults: The recommended dose for gemcitabine is 1,000 mg/m², given by 30 minute infusion. The dose should be given on days 1, 8, and 15 of each 28 day cycle in combination with cisplatin. Cisplatin is given at a recommended dose of 70 mg/m² on day 1 following gemcitabine or day 2 of each 28 day cycle. This 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. A clinical trial showed more myelosuppression when cisplatin was used in doses of 100 mg/m².

Breast Cancer:

Combination use: Adults: Gemcitabine in combination with paclitaxel is recommended using paclitaxel (175 mg/m²) administered on day 1 over 3 hours as an intravenous infusion, followed by gemcitabine (1,250mg/m²) as a 30-60 minute intravenous infusion on days 1 and 8 of each 21 day cycle. Dose reduction with each cycle or within a cycle may be applied based upon the amount of toxicity experienced by the patient. Patients should have an absolute granulocyte count of at least 1,500 (x 10⁶/l) prior to initiation of gemcitabine + paclitaxel combination.

Patients receiving gemcitabine should be monitored prior to each dose for platelet, leucocyte, and granulocyte counts, and, if necessary, the dose of gemcitabine may be either reduced or withheld in the presence of haematological toxicity, according to the following scale:

Absolute granulocyte count (x 10 ⁶ /l)		Platelet count (x 10 ⁶ /l)	% of full dose
>1,000	and	>100,000	100
500 -1,000	or	50,000 -100,000	75

<500	or	<50,000	hold
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For cisplatin dosage adjustment in combination therapy, see the manufacturers' prescribing information.

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

Gemcitabine is well tolerated during the infusion, with only a few cases of injection site reaction reported. There have been no reports of injection site necrosis. Gemcitabine can be easily administered on an outpatient basis.

Elderly patients: Gemcitabine has been well tolerated in patients over the age of 65.

There is no evidence to suggest that dose adjustments are necessary in the elderly, although gemcitabine clearance and half-life are affected by age.

Children: Gemcitabine has been studied in limited Phase I and II trials in children in a variety of tumour types. These studies did not provide sufficient data to establish the efficacy and safety of gemcitabine in children.

Hepatic and renal impairment: Gemcitabine should be used with caution in patients with hepatic insufficiency or with impaired renal function as there is insufficient information from clinical studies to allow clear dose recommendation for this patient population.

4.3 Contraindications

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

4.4 Special warnings and precautions for use

Warnings:

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

Gemcitabine can suppress bone marrow function as manifested by leucopenia, thrombocytopenia, and anaemia. However, myelosuppression is short lived and usually does not result in dose reductions and rarely in discontinuation (see sections 4.2 and 4.8). Gemcitabine should be discontinued at the first signs of any evidence of microangiopathic haemolytic anaemia, such as rapidly falling haemoglobin with concomitant thrombocytopenia, elevation of serum bilirubin, serum creatinine, blood urea nitrogen, or LDH, which may indicate development of haemolytic uraemic syndrome (see section 4.8). Renal failure may not be reversible, even with discontinuation of therapy, and dialysis may be required.

Radiotherapy:

Concurrent (given together or \leq 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 1,000 mg/m² was administered concurrently for up to 6 consecutive weeks with therapeutic thoracic radiation to patients with non-small cell lung cancer, significant toxicity in the form of severe and potentially life-threatening mucositis, especially oesophagitis, and pneumonitis was observed, particularly in patients receiving large volumes of radiotherapy (median treatment volumes 4,795 cm³). Studies done subsequently have suggested that it is feasible to administer gemcitabine at lower doses with concurrent

radiotherapy with predictable toxicity, such as a Phase II study in non-small cell lung cancer. Thoracic radiation doses of 66Gy were administered with gemcitabine (600 mg/m², four times) and cisplatin (80 mg/m², twice) during 6 weeks. The optimum regimen for safe administration of gemcitabine with therapeutic doses of radiation has not yet been determined.

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.

Precautions:

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

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

Laboratory tests: Therapy should be started cautiously in patients with compromised bone marrow function. As with other oncolytics, the possibility of cumulative bone marrow suppression when using combination or sequential chemotherapy should be considered.

Patients receiving gemcitabine should be monitored prior to each dose for platelet, leucocyte, and granulocyte counts. Suspension or modification of therapy should be considered when drug-induced marrow depression is detected. Guidelines regarding dose modifications are provided in section 4.2 above. Peripheral blood counts may continue to fall after the drug is stopped.

4.5 Interaction with other medicinal products and other forms of interaction

No interactions have been reported.

4.6 Pregnancy and lactation

The safety of this medicinal product for use in human pregnancy has not been established. Evaluation of experimental animal studies has shown reproductive toxicity, eg, birth defects or other effects on the development of the embryo or foetus, the course of gestation, or perinatal and postnatal development. The use of gemcitabine should be avoided in pregnant or nursing women because of the potential hazard to the foetus or infant.

4.7 Effects on ability to drive and use machines

Gemcitabine has been reported to cause mild to moderate somnolence. Patients should be cautioned against driving or operating machinery until it is established that they do not become somnolent.

4.8 Undesirable effects

The most commonly reported adverse drug reactions associated with gemcitabine treatment include: nausea with or without vomiting, raised liver transaminases (AST/ALT) and alkaline phosphatase, reported in approximately 60% of patients; proteinuria and haematuria reported in approximately 50% patients; dyspnoea reported in 10-40% of patients (highest incidence in lung cancer patients); allergic skin rashes occur in approximately 25% of patients and are associated with itching in 10% of patients. The frequency and severity of the adverse reactions are affected by the dose, infusion rate, and intervals between doses (see section 4.4). Dose-limiting adverse reactions are reductions in thrombocyte, leucocyte, and granulocyte counts (see section 4.2). The following table of undesirable effects and frequencies is based on clinical trial and post-marketing spontaneous reports.

<p>Blood and Lymphatic System Disorders</p> <p><i>Very common (>1/10):</i></p> <ul style="list-style-type: none">• Leucopenia• Thrombocytopenia• Neutropenia - frequency of Grade 3 is 19.3%, and of Grade 4 6%. Bone-marrow suppression is usually mild to moderate and mostly affects the granulocyte count (see section 4.2).• Anaemia <p><i>Common (>1/100, <1/10):</i></p> <ul style="list-style-type: none">• Febrile neutropenia <p><i>Very rare (<1/10,000):</i></p> <ul style="list-style-type: none">• Thrombocythaemia
<p>Immune System Disorders</p> <p><i>Very rare (<1/10,000):</i></p> <ul style="list-style-type: none">• Anaphylactoid reaction
<p>Nervous System Disorders</p> <p><i>Common (>1/100, <1/10):</i></p> <ul style="list-style-type: none">• Somnolence

Cardiac Disorders

Very rare (<1/10,000):

- Myocardial infarct
- Congestive heart failure
- Arrhythmia - predominantly supraventricular in nature

Vascular Disorders

Rare (>1/10,000,<1/1000):

- Hypotension

Very Rare (<1/10,000):

Clinical signs of peripheral vasculitis and gangrene

Respiratory, Thoracic, and Mediastinal Disorders

Very common (>1/10):

- Dyspnoea - usually mild and passes rapidly without treatment

Uncommon (<1/100,>1/1000):

- Bronchospasm - usually mild and transient but may require parenteral treatment

Rare (>1/10,000,<1/1000):

- Adult respiratory distress syndrome (ARDS)
- Interstitial pneumonitis together with pulmonary infiltrates - symptoms may be relieved with steroid treatment
- Pulmonary oedema

In the event of ARDS, interstitial pneumonitis, or pulmonary oedema, gemcitabine treatment must be stopped. Initiating supportive treatment early may improve the situation.

Gastro-intestinal Disorders

Very common (>1/10):

- Nausea
- Vomiting

Common (>1/100, <1/10):

- Stomatitis and ulceration of mouth
- Diarrhoea
- Constipation

Hepatobiliary Disorders

Very Common (>1/10):

- Elevation of liver transaminases (AST and ALT) and alkaline phosphatase.

Common (>1/100, <1/10):

- Increased bilirubin

Rare (>1/10,000, <1/1,000):

- Increased gamma-glutamyl transferase (GGT).

Very Rare (<1/10,000):

- Serious hepatotoxicity, including liver failure and death – in patients receiving gemcitabine alone or in combination with other potentially hepatotoxic drugs.

Gemcitabine should be given with caution to patients with impaired hepatic function.

Skin and Subcutaneous Tissue Disorders

Very common (>1/10):

- Allergic skin rash often associated with pruritus
- Alopecia - usually mild with minimal hair loss

Rare (>1/10,000, <1/1000):

- Vesicle formation and ulceration
- Scaling

Very Rare (<1/10,000):

Severe desquamative and bullous skin eruptions.

Renal and Urinary Disorders

Very common (>1/10):

- Haematuria

- Proteinuria

Rarely of clinical importance and do not usually change serum creatinine or urea levels.

Rare (>1/10,000, <1/1000):

- Renal failure, aetiology unknown
- Haemolytic uraemic syndrome

Gemcitabine should be administered with caution to patients with impaired renal function (see section 4.4).

Gemcitabine treatment should be withdrawn if there is any sign of microangiopathic haemolytic anaemia, such as rapidly falling haemoglobin levels with simultaneous thrombocytopenia, elevation of serum bilirubin, serum creatinine, urea or LDH. Renal failure may be irreversible despite withdrawal of the gemcitabine treatment and may require dialysis.

General Disorders and Administration Site Conditions

Very common (>1/10):

- Oedema/peripheral oedema - reported in approximately 30% of patients. A few cases of facial oedema have been reported. 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 commonly reported symptoms include fever, headache, back pain, shivering, muscle pain, asthenia, and anorexia. Cough, rhinitis, malaise, perspiration, and sleeping difficulties have also been reported.

Common (>1/100, <1/10):

- Fever
- Asthenia

Rare (>1/10,000, <1/1,000):

Injection site reactions - mainly mild in nature.

Injury and Poisoning

- Radiation toxicity (see section 4.4).

Haemolytic-uraemic syndrome (HUS) and/or thrombotic thrombocytopenic purpura and/or renal failure have been reported following one or more doses of gemcitabine.

Renal failure leading to death or requiring dialysis, despite discontinuation of therapy, has been rarely reported. The majority of the cases of renal failure leading to death were due to HUS.

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

A few cases of facial oedema have occurred.

Combination Use in Breast Cancer:

The frequency of Grade 3 and 4 haematological toxicities, particularly neutropenia, increases when gemcitabine is used in combination with paclitaxel. However, the increase in these adverse reactions is not associated with an increased incidence of infections or haemorrhagic events.

Fatigue and febrile neutropenia occur more frequently when gemcitabine is used in combination with paclitaxel. Fatigue, which is not associated with anaemia, usually resolves after the first cycle.

**Grade 3 and 4 Adverse Events
Paclitaxel Versus Gemcitabine Plus Paclitaxel**

	Number (%) of Patients			
	Paclitaxel Arm (n = 259)		Gemcitabine Plus Paclitaxel Arm (n = 262)	
	Grade 3	Grade 4	Grade 3	Grade 4
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.				

4.9 Overdose

There is no antidote for overdosage of gemcitabine. Single doses as high as 5.7g/m² have been administered by IV infusion over 30 minutes every two weeks with clinically acceptable toxicity. In the event of suspected overdose, the patient should be monitored with appropriate blood counts and should receive supportive therapy, as necessary.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antineoplastic agents - antimetabolites, 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. When administered daily, gemcitabine causes death in animals with minimal antitumour activity. However, when an every third or fourth day dosing schedule is used, gemcitabine can be given at non-lethal doses that have excellent antitumour activity against a broad range of mouse tumours.

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

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-potential). 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/m² 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/m² for women and 17.5 l/m² for men (inter-individual variability was 91.9%). Volume of distribution of the peripheral compartment: 47.4 l/m². The volume of the peripheral compartment was not sensitive to gender.

Plasma protein binding: Negligible.

Systemic clearance: Ranged from 29.2 l/hr/m² to 92.2 l/hr/m² depending on gender and age (inter-individual variability was 52.2%). Clearance for women is approximately 25% lower than the values for men. Although rapid, clearance for both men and women appears to decrease with age. For the recommended gemcitabine dose of 1,000 mg/m² given as a 30 minute infusion, lower clearance values for women and men should not necessitate a decrease in the gemcitabine dose.

Urinary excretion: Less than 10% is excreted as unchanged drug.

Renal clearance: 2 to 7 l/hr/m².

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/m²/30 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/m²/30 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/m²): 28-52 µg/ml.

Trough concentration following once weekly dosing: 0.07-1.12 µg/ml, with no apparent accumulation.

Triphasic plasma concentration versus time curve, mean half-life of terminal phase - 65 hours (range 33-84 hr).

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

Mean volume of distribution of central compartment: 18 l/m² (range 11-22 l/m²).

Mean steady state volume of distribution (V_{ss}): 150 l/m² (range 96-228 l/m²).

Tissue distribution: Extensive.

Mean apparent clearance: 2.5 l/hr/m² (range 1-4 l/hr/m²).

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 Paclitaxel Combination Therapy:

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

5.3 Preclinical safety data

In repeat dose studies of up to 6 months in duration in mice and dogs, the principal finding was haematopoietic suppression. These effects were related to the cytotoxic properties of the drug and were reversible when treatment was withdrawn. The degree of the effect was schedule and dose-dependent.

Carcinogenesis, Mutagenesis, Fertility:

Cytogenetic damage has been produced by gemcitabine in an *in vivo* assay. Gemcitabine induced forward mutation *in vitro* in a mouse lymphoma (L5178Y) assay. Gemcitabine caused a reversible, dose and schedule dependent hypospermatogenesis in male mice. Although animal studies have shown an effect of gemcitabine on male fertility, no effect has been seen on female fertility. Long-term animal studies have not been conducted to evaluate the carcinogenic potential of gemcitabine.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Mannitol
Sodium Acetate
Hydrochloric Acid (for pH adjustment)
Sodium Hydroxide (for pH adjustment)

6.2 Incompatibilities

Gemcitabine should only be reconstituted with sterile Sodium Chloride for Injection BP (see Section 6.6). Compatibility with other drugs has not been studied.

6.3 Shelf life

Lyophilised powder: 2 years
Reconstituted solution:
Chemical and physical in-use stability has been demonstrated for 24 hours at 30°C. From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 25°C, unless reconstitution/dilution (etc) has taken place in controlled and aseptic conditions. Solutions should not be refrigerated, as crystallisation may occur.

6.4 Special precautions for storage

Do not store above 30°C. Store in the original package.
For storage conditions of the reconstituted medicinal product, see section 6.3.

6.5 Nature and contents of container

The product is contained in a 50ml sterile colourless vial Type I glass, which meets the requirements of the PhEur, and is closed with a rubber stopper and sealed with an aluminium seal with a polypropylene cap.

1 vial per pack.

6.6 Special precautions for disposal

Reconstitution:

Gemcitabine has only been shown to be compatible with Sodium Chloride Injection BP. Accordingly, only this diluent should be used for reconstitution. Compatibility with other drugs has not been studied; therefore, it is not recommended to mix Gemcitabine with other drugs when reconstituted. Due to solubility considerations, the maximum concentration for gemcitabine upon reconstitution is 40mg/ml. Reconstitution at concentrations greater than 40mg/ml may result in incomplete dissolution, and should be avoided.

To reconstitute, add 25ml of Sodium Chloride Injection BP to the 1g vial. Shake to dissolve. These dilutions each yield a gemcitabine concentration of 38mg/ml, which includes accounting for the displacement volume of the lyophilised powder (1.3ml for the 1g vial). The total volume upon reconstitution will be 26.3ml. Complete withdrawal of the vial contents will provide 1g gemcitabine. The appropriate amount of drug may be administered as prepared or further diluted with Sodium Chloride Injection BP.

Reconstituted solutions should be used immediately or may be stored for 24 hours if prepared in an appropriately controlled aseptic environment.

Parenteral drugs should be inspected visually for particulate matter and discolouration, prior to administration, whenever solution and container permit.

Guidelines for the Safe Handling of Antineoplastic Agents:

Cytotoxic preparations should not be handled by pregnant staff. Trained personnel should reconstitute the drug. This should be performed in a designated area. The work surface should be covered with disposable plastic-backed absorbent paper.

Adequate protective gloves, masks, and clothing should be worn. Precautions should be taken to avoid the drug accidentally coming into contact with the eyes. If accidental contamination occurs, the eye should be washed with water thoroughly and immediately. Use Luer-lock fittings on all syringes and sets. 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.

Adequate care and precaution should be taken in the disposal of items used to reconstitute gemcitabine. 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 excess drug solution should be flushed directly into a drain with copious amounts of water.

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

7 MARKETING AUTHORISATION HOLDER

TechnoPharm Limited
Chapelizod
Dublin 20
Republic of Ireland

8 MARKETING AUTHORISATION NUMBER(S)

PL 20176/0049

9 DATE OF FIRST AUTHORISATION

24/01/2007

10 DATE OF REVISION OF THE TEXT

24/01/2007

PATIENT INFORMATION LEAFLET

PACKAGE LEAFLET: INFORMATION FOR THE USER **Gemcitabine 200mg Powder for Solution for Infusion** **Gemcitabine 1g Powder for Solution for Infusion**

Read all of this leaflet carefully before you are given this medicine

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- 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 pharmacist.
- If you are being treated as an outpatient, it is important that you go to the clinic for all of your appointments.

In this leaflet:

1. What Gemcitabine is and what it is used for
2. Before you are given Gemcitabine
3. How Gemcitabine is given
4. Possible side effects
5. How to store Gemcitabine
6. Further information.

1. What Gemcitabine is and what it is used for

Gemcitabine is one of a group of medicines called cytotoxics. These are substances which kill cells that are dividing, including cancer cells.

Gemcitabine is used to treat breast cancer, bladder cancer, cancer of the pancreas and lung cancer (of the 'non-small cell' type).

2. Before you are given Gemcitabine

Your doctor will make sure that it is safe for you to receive Gemcitabine. Children should not have Gemcitabine.

You must not receive Gemcitabine

- if you are allergic (hypersensitive) to Gemcitabine or any of the other ingredients of Gemcitabine.
- if you are pregnant or breast-feeding.

Take special care while receiving Gemcitabine

If any of the following apply to you, tell your doctor, nurse or pharmacist as soon as possible:

- if you have liver or kidney problems
- if you have a long infusion time or a lot of injections (more than once a week)
- if you are receiving radiotherapy

Your doctor will check that your kidneys and liver are working properly using blood tests while you are undergoing treatment with Gemcitabine.

Gemcitabine may act on cells that are dividing but that are not cancer cells, e.g. bone marrow. Your doctor will use blood tests to check that your blood cell counts are not too low. Your doctor may decide to change the dose or put off treating you if your blood cell counts are too low. Your blood cell counts soon improve as your bone marrow makes new cells.

Taking other medicines

Gemcitabine is not known to interact with other medicines.

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

Pregnancy and breast-feeding

Gemcitabine should not be given to you if you are pregnant or breast-feeding.

Driving and using machines

Do not drive or use any tools or machines if you feel tired or sleepy when you have been given Gemcitabine.

3. How Gemcitabine is given

Gemcitabine is a powder for solution for infusion which is given using a drip, into a vein. It is diluted with sterile sodium chloride solution (salt water) before it is given to you. If you need further information about Gemcitabine or the liquid used to dilute it, ask the doctor or nurse who will be giving, or who has given you the infusion.

The dose of Gemcitabine that you are given is calculated using your weight and your height (body surface area). The usual dose is 1000mg to 1250mg per square metre of your body's surface area. The infusion will be given through a vein over 30 minutes to one hour. The frequency and length of the injections depends on what you are being treated for. The usual dose or the frequency of injections may be reduced if you have severe side effects.

You will be given Gemcitabine once weekly at set times over a number of weeks, followed by a gap in treatment. This is known as a treatment cycle. The details of the treatment cycle(s) will depend on which condition you are being treated for and whether you are also receiving other treatments for this condition.

Breast cancer

You will receive Gemcitabine once a week for two weeks followed by a one week gap in treatment. You will also be given another medicinal product called Paclitaxel while you are being treated with Gemcitabine.

Bladder cancer

You will receive Gemcitabine once a week for three weeks followed by a one week gap in treatment. You will also be given another medicinal product called Cisplatin while you are being treated with Gemcitabine.

Cancer of the pancreas

For your first treatment cycle you will receive Gemcitabine once a week for up to 7 weeks followed by a one week gap in treatment. For further treatment cycles you will receive Gemcitabine once a week for three weeks followed by a one week gap in treatment.

Lung cancer

You may be given Gemcitabine on its own or with another medicinal product called Cisplatin.

If you are given Gemcitabine on its own you will receive Gemcitabine once a week for three weeks followed by a one week gap in treatment.

If you are given Gemcitabine with Cisplatin you will receive Gemcitabine once a week for either two or three weeks followed by a one week gap in treatment.

If you are given more Gemcitabine than is recommended

It is extremely unlikely that you will be given too much injection. However if you think you have been given too much Gemcitabine, you should talk to your nurse or doctor.

If you forget to attend your hospital for treatment

It is very important that you receive every infusion in your treatment cycle. If you are being treated as an out patient you must attend every appointment you are given.

4. Possible side effects

Like all medicines, Gemcitabine can cause side effects, although not everybody gets them.

Side effects may be more severe and more frequent if you are given a higher dose, if the infusion is given over a long time or you receive Gemcitabine more often. If the levels of certain blood cells fall too low your doctor may decide to reduce the dose of Gemcitabine that you are receiving.

Very Common side effects (occurring in more than 1 in 10 patients) include:

Low blood cell counts (these may cause symptoms such as fever, a sore throat, rash, nose bleeds or bruising); shortness of breath; feeling or being sick; losing some of your hair (usually mild with minimal hair loss); skin rashes (some may be itchy, but they are usually mild – more serious allergic reactions are very rare); kidney test changes (you may get protein or blood in your urine – but kidney failure is rare); fluid retention (swelling in your hands, feet, legs); a flu-like condition which doesn't last long (fever, headache, pains and so on); changes in your liver test results.

Common side effects (occurring in more than 1 in 100 patients but in less than 10 in 100 patients):

Feeling tired or sleepy; feeling feverish or shivery; diarrhoea; constipation; sore mouth, lips or tongue, mouth ulcers; fever.

Uncommon side effects (occurring in more than 1 in 1000 patients but in less than 10 in 1000 patients):

Wheezing.

Rare side effects (occurring in more than 1 in 10,000 patients but in less than 10 in 10,000 patients):

More serious effects on your breathing; skin rashes/ulcers; redness, swelling or itching around the area of the injection; kidney failure; liver enzyme test changes (you may get increased levels of certain liver enzymes); low blood pressure (feeling faint).

Very rare side effects (occurring in less than 1 in 10,000 patients):

Severe peeling or inflammation of the skin; serious allergic reactions (the symptoms of an allergic reaction may include rash, changes in blood pressure, swelling and increased fluid in tissues, an increased heart rate, difficulty with breathing and collapse); liver failure; increase in blood platelets; heart failure, fast or irregular heart beat, heart attack; problems with blood flow to the limbs (this can be felt as numbness, tingling, coldness or loss of sensation). If this is particularly bad or lasts for a long time, permanent damage to the tissues can result.

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 pharmacist.

5. How to store Gemcitabine

Keep out of the reach and sight of children.

Gemcitabine should not be used after the expiry date which is stated on the label after expiry date. The expiry date refers to the last day of that month.

The doctor or nurse responsible for giving you the drip will ensure it has been stored and reconstituted correctly before giving it to you. The infusion will have been stored at room temperature (below 25°C) before use and will be given to you within 24 hours of it being mixed and diluted for use. Once Gemcitabine has been prepared for use it should be stored below 25°C. It should NOT be kept in a fridge.

Medicines should not be disposed of via wastewater or household waste. Your doctor, nurse or pharmacist will dispose of medicines no longer required. These measures will help to protect the environment.

6. Further Information.

What Gemcitabine contains

- The active substance is gemcitabine hydrochloride. Gemcitabine 200mg Powder for Solution for Infusion contains 200mg gemcitabine (as hydrochloride). Gemcitabine 1g Powder for Solution for Infusion contains 1g gemcitabine (as hydrochloride).
- The other ingredients are mannitol and sodium acetate. Small amounts of sodium hydroxide or hydrochloric acid (or both) may also have been added during manufacturing.

What Gemcitabine looks like and contents of the pack

Gemcitabine is a Powder for Solution for Infusion and is available in packs containing one glass vial.

Marketing Authorisation Holder

TechnoPharm Limited, Chapelizod, Dublin 20, Republic of Ireland

Manufacturer

PLIVA-Lachema a.s., Karásek 1, 621 33 Brno, Czech Republic.

This leaflet was last approved in MM/YYYY

LABELLING

200 mg:

Label




Gemcitabine 200mg Powder for Solution for Infusion

gemcitabine (as hydrochloride). Each vial contains 200mg gemcitabine.
One vial containing 200mg gemcitabine (as hydrochloride). Also contains mannitol, sodium acetate, hydrochloric acid (for pH adj.), sodium hydroxide (for pH adj.). **FOR INTRAVENOUS USE.** Read the package leaflet before use. **ITEM CODE**
Do not store above 30°C. Store in the original package. After reconstitution: 24 hours below 25°C. Do not refrigerate.
KEEP OUT OF THE REACH AND SIGHT OF CHILDREN. TechnoPharm Ltd, Chapelizod, Dublin, Republic of Ireland.

PL 20176/0048 **[POM]**

Batch:
Expiry date:

Carton

<p>FOR INTRAVENOUS USE</p> <p>Each vial contains 200mg gemcitabine (as hydrochloride)</p> <ul style="list-style-type: none"> • Also contains mannitol, sodium acetate, hydrochloric acid (for pH adj.), sodium hydroxide (for pH adj.) • Do not store above 30°C. Store in the original package. After reconstitution: 24 hours below 25°C. Do not refrigerate. • Read the package leaflet before use • Reconstitute with 5 ml Sodium Chloride Injection <p>POM ITEM CODE</p> <p>KEEP OUT OF THE REACH AND SIGHT OF CHILDREN</p> 	<p>Gemcitabine 200mg Powder for Solution for Infusion gemcitabine (as hydrochloride)</p> <p>BAR CODE</p>	
<p>Batch: Expiry date:</p>	<p>Gemcitabine 200mg Powder for Solution for Infusion gemcitabine (as hydrochloride) For Intravenous use One vial containing 200mg gemcitabine (as hydrochloride)</p> 	 <p>Gemcitabine 200mg Powder for Solution for Infusion Gemcitabine (as hydrochloride) One vial containing 200mg gemcitabine (as hydrochloride)</p>
<p>MA Holder: TechnoPharm Ltd, Chapelizod, Dublin Republic of Ireland PL 20176/0048</p>		

1g:
Label

Gemcitabine 1g Powder for Solution for Infusion


gemcitabine (as hydrochloride). Each vial contains 1g gemcitabine.
One vial containing 1g gemcitabine (as hydrochloride). Also contains mannitol, sodium acetate, hydrochloric acid (for pH adj.), sodium hydroxide (for pH adj.). **FOR INTRAVENOUS USE.** Read the package leaflet before use.

Do not store above 30°C. Store in the original package. After reconstitution: 24 hours below 25°C. Do not refrigerate. **KEEP OUT OF THE REACH AND SIGHT OF CHILDREN.** TechnoPharm Ltd, Chapelzod, Dublin, Republic of Ireland.

PL 20176/0049 **POM** ITEM CODE

Batch:
Expiry date:

Carton

<p>FOR INTRAVENOUS USE</p> <p>Each vial contains 1g gemcitabine (as hydrochloride)</p> <ul style="list-style-type: none"> • Also contains mannitol, sodium acetate, hydrochloric acid (for pH adj.), sodium hydroxide (for pH adj.) • Do not store above 30°C. Store in the original package. After reconstitution: 24 hours below 25°C. Do not refrigerate. • Read the package leaflet before use • Reconstitute with 25 ml Sodium Chloride Injection <p>POM ITEM CODE</p> <p>KEEP OUT OF THE REACH AND SIGHT OF CHILDREN</p> 	<p>Gemcitabine 1g Powder for Solution for Infusion gemcitabine (as hydrochloride)</p> <p>BAR CODE</p>	<p>Batch: Expiry date:</p>	<p>Gemcitabine 1g Powder for Solution for Infusion gemcitabine (as hydrochloride) For Intravenous use One vial containing 1g gemcitabine (as hydrochloride)</p> 	<p>Gemcitabine 1g Powder for Solution for Infusion Gemcitabine (as hydrochloride) One vial containing 1g gemcitabine (as hydrochloride)</p> 
<p>MA Holder: TechnoPharm Ltd, Chapelizod, Dublin Republic of Ireland PL 20176/0049</p>				