Public Assessment Report
Decentralised Procedure

Gemcitabine 200mg Powder for Solution for Infusion

Gemcitabine 1g Powder for Solution for Infusion

UK/H/1574/01-02/DC
UK/H/2439/01-02/DC

UK licence nos: PL 13621/0038-39
PL 13621/0050-51

Flynn Pharma Ltd
LAY SUMMARY

On 29th July 2009, the Medicines Healthcare products Regulatory Agency (MHRA) granted Flynn Pharma Limited Marketing Authorisations (licences) for the medicinal products Gemcitabine 200mg Powder for Solution for Infusion (PL 13621/0050) and Gemcitabine 1g Powder for Solution for Infusion (PL 13621/0051). On 31st July 2009, the Medicines Healthcare products Regulatory Agency (MHRA) granted Flynn Pharma Limited Marketing Authorisations (licences) for the medicinal products Gemcitabine 200mg Powder for Solution for Infusion (PL 13621/0038) and Gemcitabine 1g Powder for Solution for Infusion (PL 13621/0039). 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 200mg and 1g Powder for Solution for Infusion outweighs the risks, hence Marketing Authorisations have been granted.
# TABLE OF CONTENTS

<table>
<thead>
<tr>
<th>Module 1: Information about initial procedure</th>
<th>Page 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Module 2: Summary of Product Characteristics</td>
<td>Page 5</td>
</tr>
<tr>
<td>Module 3: Product Information Leaflet</td>
<td>Page 53</td>
</tr>
<tr>
<td>Module 4: Labelling</td>
<td>Page 62</td>
</tr>
<tr>
<td>Module 5: Scientific Discussion</td>
<td>Page 64</td>
</tr>
<tr>
<td>1 Introduction</td>
<td>Page 64</td>
</tr>
<tr>
<td>2 Quality aspects</td>
<td>Page 65</td>
</tr>
<tr>
<td>3 Pre-clinical aspects</td>
<td>Page 67</td>
</tr>
<tr>
<td>4 Clinical aspects</td>
<td>Page 67</td>
</tr>
<tr>
<td>5 Overall conclusions</td>
<td>Page 68</td>
</tr>
<tr>
<td>Module 6 Steps taken after initial procedure</td>
<td>Page 69</td>
</tr>
</tbody>
</table>
# Module 1

<table>
<thead>
<tr>
<th><strong>Product Name</strong></th>
<th>Gemcitabine 200mg and 1g Powder for solution for infusion</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Type of Application</strong></td>
<td>Generic, Article 10.1</td>
</tr>
<tr>
<td><strong>Active Substance</strong></td>
<td>Gemcitabine hydrochloride</td>
</tr>
<tr>
<td><strong>Form</strong></td>
<td>Powder for solution for infusion</td>
</tr>
<tr>
<td><strong>Strength</strong></td>
<td>200mg and 1g</td>
</tr>
<tr>
<td><strong>MA Holder</strong></td>
<td>Flynn Pharma Limited</td>
</tr>
<tr>
<td><strong>RMS</strong></td>
<td>UK</td>
</tr>
</tbody>
</table>
| **CMS** | UK/H/2439/001-2/DC – Austria, Germany and Spain  
UK/H/1574/001-2/DC- Ireland |
| **Procedure Number** | UK/H/1574/001-2/DC  
UK/H/2439/001-2/DC |
| **Timetable** | Day 210– 08.06.2009 |
Module 2
Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT
Gemcitabine 200 mg powder for solution for infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
One vial contains gemcitabine hydrochloride equivalent to 200 mg gemcitabine. After reconstitution, the solution contains 38 mg/ml of gemcitabine.
Excipients
Each 200 mg vial contains 3.5 mg (< 1 mmol) sodium.
For a full list of excipients see section 6.1.

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

4 CLINICAL PARTICULARS
4.1 Therapeutic indications
Gemcitabine is indicated for the treatment of locally advanced or metastatic bladder cancer in combination with cisplatin.
Gemcitabine is indicated for treatment of patients with locally advanced or metastatic adenocarcinoma of the pancreas.
Gemcitabine, in combination with cisplatin is indicated as first line treatment of patients with locally advanced or metastatic non-small cell lung cancer (NSCLC). Gemcitabine monotherapy can be considered in elderly patients or those with performance status 2.
Gemcitabine is indicated for the treatment of patients with locally advanced or metastatic epithelial ovarian carcinoma, in combination with carboplatin, in patients with relapsed disease following a recurrence-free interval of at least 6 months after platinum-based, first-line therapy.
Gemcitabine, in combination with paclitaxel, is indicated for the treatment of patients with unresectable, locally recurrent or metastatic breast cancer who have relapsed following adjuvant/neoadjuvant chemotherapy. Prior chemotherapy should have included an anthracycline unless clinically contraindicated.

4.2 Posology and method of administration
Gemcitabine should only be prescribed by a physician qualified in the use of anti-cancer chemotherapy.
Recommended posology
Bladder Cancer
Combination use
The recommended dose for gemcitabine is 1,000 mg/m², given by 30-minute infusion. The dose should be given on Days 1, 8, and 15 of each 28-day cycle in combination with cisplatin. Cisplatin is given at a recommended dose of 70 mg/m² on Day 1 following gemcitabine or Day 2 of each 28-day cycle. This 4-week cycle is then repeated. Dosage reduction with each cycle or within a cycle may be applied based upon the grade of toxicity experienced by the patient.

Pancreatic cancer
The recommended dose of gemcitabine is 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 with each cycle or within a cycle may be applied based upon the grade of toxicity experienced by the patient.

Non-small cell lung cancer
Monotherapy
The recommended dose of gemcitabine is 1,000 mg/m², given by 30-minute intravenous infusion. This should be repeated once weekly for 3 weeks, followed by a 1-week rest period. This 4-week cycle is then repeated. Dosage reduction with each cycle or within a cycle may be applied based upon the grade of toxicity experienced by the patient.

Combination use
The recommended dose for gemcitabine is 1,250 mg/m² body surface area given as a 30-minute intravenous infusion on Day 1 and 8 of the treatment cycle (21 days). Dosage reduction with each cycle or within a cycle may be applied based upon the grade of toxicity experienced by the patient. Cisplatin has been used at doses between 75-100 mg/m² once every 3 weeks.

**Breast Cancer**

**Combination use**

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

**Ovarian cancer**

**Combination use**

Gemcitabine in combination with carboplatin is recommended using gemcitabine 1,000 mg/m² administered on Days 1 and 8 of each 21-day cycle as a 30-minute intravenous infusion. After gemcitabine, carboplatin will be given on Day 1 consistent with a target Area under Curve (AUC) of 4.0 mg/ml·min. Dosage reduction with each cycle or within a cycle may be applied based upon the grade of toxicity experienced by the patient.

Monitoring for toxicity and dose modification due to toxicity

**Dose modification due to non-haematological toxicity**

Periodic physical examination and checks of renal and hepatic function should be made to detect non-haematological toxicity. Dosage reduction with each cycle or within a cycle may be applied based upon the grade of toxicity experienced by the patient. In general, for severe (Grade 3 or 4) non-haematological toxicity, except nausea/vomiting, therapy with gemcitabine should be withheld or decreased depending on the judgement of the treating physician. Doses should be withheld until toxicity has resolved in the opinion of the physician.

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

**Dose modification due to haematological toxicity**

**Initiation of a cycle**

For all indications, the patient must be monitored before each dose for platelet and granulocyte counts. Patients should have an absolute granulocyte count of at least 1,500 (x 10⁶/l) and platelet count of 100,000 (x 10⁶/l) prior to the initiation of a cycle.

**Within a cycle**

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

### Dose modification of gemcitabine within a cycle for bladder cancer, NSCLC and pancreatic cancer, given in monotherapy or in combination with cisplatin

<table>
<thead>
<tr>
<th>Absolute granulocyte count (x 10⁶/l)</th>
<th>Platelet count (x 10⁶/l)</th>
<th>Percentage of standard dose of gemcitabine (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 1,000 and</td>
<td>&gt; 100,000</td>
<td>100</td>
</tr>
<tr>
<td>500-1,000 or</td>
<td>50,000-100,000</td>
<td>75</td>
</tr>
<tr>
<td>&lt; 500 or</td>
<td>&lt; 50,000</td>
<td>Omit dose*</td>
</tr>
</tbody>
</table>

*Treatment omitted will not be re-instated within a cycle before the absolute granulocyte count reaches at least 500 (x 10⁶/l) and the platelet count reaches 50,000 (x 10⁶/l).*

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

<table>
<thead>
<tr>
<th>Absolute granulocyte count (x 10⁶/l)</th>
<th>Platelet count (x 10⁶/l)</th>
<th>Percentage of standard dose of gemcitabine (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 1,200 and</td>
<td>&gt; 75,000</td>
<td>100</td>
</tr>
<tr>
<td>1,000-&lt; 1,200 or</td>
<td>50,000-75,000</td>
<td>75</td>
</tr>
<tr>
<td>700-&lt; 1,000 and</td>
<td>≥ 50,000</td>
<td>50</td>
</tr>
<tr>
<td>&lt; 700 or</td>
<td>&lt; 50,000</td>
<td>Omit dose*</td>
</tr>
</tbody>
</table>

*Treatment omitted will not be re-instated within a cycle. Treatment will start on Day 1 of the next cycle once the absolute granulocyte count reaches at least 1,500 (x 10⁶/l) and the platelet count reaches 100,000 (x 10⁶/l).*
Dose modification of gemcitabine within a cycle for ovarian cancer, given in combination with carboplatin

<table>
<thead>
<tr>
<th>Absolute granulocyte count (x 10^6/l)</th>
<th>Platelet count (x 10^6/l)</th>
<th>Percentage of standard dose of gemcitabine (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 1,500 and</td>
<td>≥ 100,000</td>
<td>100</td>
</tr>
<tr>
<td>1,000-1,500 or</td>
<td>75,000-100,000</td>
<td>50</td>
</tr>
<tr>
<td>&lt; 1,000 or</td>
<td>&lt; 75,000</td>
<td>Omit dose*</td>
</tr>
</tbody>
</table>

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

*Dose modifications due to haematological toxicity in subsequent cycles, for all indications*

The gemcitabine dose should be reduced to 75% of the original cycle initiation dose, in the case of the following haematological toxicities:

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

Method of administration

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

For instructions on reconstitution, see section 6.6.

Special populations

Patients with renal or hepatic impairment

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

Elderly population (> 65 years)

Gemcitabine has been well tolerated in patients over the age of 65. There is no evidence to suggest that dose adjustments, other than those already recommended for all patients, are necessary in the elderly (see section 5.2).

Paediatric population (< 18 years)

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

4.3 Contraindications

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

Breast-feeding (see section 4.6).

4.4 Special warnings and precautions for use

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

Haematological toxicity

Gemcitabine can suppress bone marrow function as manifested by leucopaenia, thrombocytopenia and anaemia.

Patients receiving gemcitabine should be monitored prior to each dose for platelet, leucocyte and granulocyte counts. Suspension or modification of therapy should be considered when drug-induced bone marrow depression is detected (see section 4.2). However, myelosuppression is short lived and usually does not result in dose reduction and rarely in discontinuation.

Peripheral blood counts may continue to deteriorate after gemcitabine administration has been stopped. In patients with impaired bone marrow function, the treatment should be started with caution. As with other cytotoxic treatments, the risk of cumulative bone-marrow suppression must be considered when gemcitabine treatment is given together with other chemotherapy.

Hepatic insufficiency

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

Laboratory evaluation of renal and hepatic function (including virological tests) should be performed periodically.
Gemcitabine should be used with caution in patients with hepatic insufficiency or with impaired renal function as there is insufficient information from clinical studies to allow clear dose recommendation for this patient population (see section 4.2).

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

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

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

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

Renal
Clinical findings consistent with the haemolytic uraemic syndrome (HUS) were rarely reported in patients receiving gemcitabine (see section 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. Renal failure may not be reversible with discontinuation of therapy and dialysis may be required.

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

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

4.5 Interaction with other medicinal products and other forms of interaction
No specific interaction studies have been performed (see section 5.2).

Radiotherapy
Concurrent (given together or ≤ 7 days apart) - toxicity associated with this multimodality therapy is dependent on many different factors, including dose of gemcitabine, frequency of gemcitabine administration, dose of radiation, radiotherapy planning technique, the target tissue, and target volume. Pre-clinical and clinical studies have shown that gemcitabine has radiosensitising activity. In a single trial, where gemcitabine at a dose of 1,000 mg/m² was administered concurrently for up to 6 consecutive weeks with therapeutic thoracic radiation to patients with non-small cell lung cancer, significant toxicity in the form of severe, and potentially life threatening mucositis, especially oesophagitis, and pneumonitis was observed, particularly in patients receiving large volumes of radiotherapy [median treatment volumes 4,795 cm³]. Studies done subsequently have suggested that it is feasible to administer gemcitabine at lower doses with concurrent radiotherapy with predictable toxicity, such as a phase II study in non-small cell lung cancer, where thoracic radiation doses of 66 Gy were applied concomitantly with an administration with gemcitabine (600 mg/m², four times) and cisplatin (80 mg/m² twice) during 6 weeks. The optimum regimen for safe administration of gemcitabine with therapeutic doses of radiation has not yet been determined in all tumour types.

Non-concurrent (given > 7 days apart) - analysis of the data does not indicate any enhanced toxicity when gemcitabine is administered more than 7 days before or after radiation, other than radiation recall. Data suggest that gemcitabine can be started after the acute effects of radiation have resolved or at least one week after radiation.

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

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

#### Pregnancy

There are no adequate data from the use of gemcitabine in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3). Based on results from animal studies and the mechanism of action of gemcitabine, this substance should not be used during pregnancy unless clearly necessary. Women should be advised not to become pregnant during treatment with gemcitabine and to warn their attending physician immediately, should this occur after all.

#### Breast-feeding

It is not known whether gemcitabine is excreted in human milk and adverse effects on the suckling child cannot be excluded. Breast-feeding must be discontinued during gemcitabine therapy.

#### Fertility

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

### 4.7 Effects on ability to drive and use machines

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

### 4.8 Undesirable effects

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

#### Clinical trial data

Frequencies are defined as: Very common (≥ 1/10), Common (≥ 1/100 to < 1/10), Uncommon (≥ 1/1,000 to < 1/100), Rare (≥ 1/10,000 to < 1/1,000), Very Rare (< 1/10,000).

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

<table>
<thead>
<tr>
<th>System Organ Class</th>
<th>Frequency Grouping</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood and lymphatic system disorders</td>
<td>Very common</td>
</tr>
<tr>
<td></td>
<td>• Leucopaenia (Neutropaenia Grade 3 = 19.3%; Grade 4 = 6%).</td>
</tr>
<tr>
<td></td>
<td>Bone-marrow suppression is usually mild to moderate and mostly affects the granulocyte count (see section 4.2).</td>
</tr>
<tr>
<td></td>
<td>• Thrombocytopaenia</td>
</tr>
<tr>
<td></td>
<td>• Anaemia</td>
</tr>
<tr>
<td>Immune system disorders</td>
<td>Common</td>
</tr>
<tr>
<td></td>
<td>• Febrile neutropaenia</td>
</tr>
<tr>
<td></td>
<td>Very rare</td>
</tr>
<tr>
<td></td>
<td>• Thrombocytosis</td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td>Very rare</td>
</tr>
<tr>
<td></td>
<td>• Anaphylactoid reaction</td>
</tr>
<tr>
<td></td>
<td>Common</td>
</tr>
<tr>
<td></td>
<td>• Anorexia</td>
</tr>
<tr>
<td>System Organ Class</td>
<td>Frequency Grouping</td>
</tr>
<tr>
<td>------------------------------------------</td>
<td>------------------------------------------</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>Common</td>
</tr>
<tr>
<td></td>
<td>- Headache</td>
</tr>
<tr>
<td></td>
<td>- Insomnia</td>
</tr>
<tr>
<td></td>
<td>- Somnolence</td>
</tr>
<tr>
<td>Cardiac disorders</td>
<td>Rare</td>
</tr>
<tr>
<td></td>
<td>- Myocardial infarct</td>
</tr>
<tr>
<td>Vascular disorders</td>
<td>Rare</td>
</tr>
<tr>
<td></td>
<td>- Hypotension</td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal</td>
<td>Very common</td>
</tr>
<tr>
<td>disorders</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- Dyspnoea - usually mild and passes</td>
</tr>
<tr>
<td></td>
<td>rapidly without treatment</td>
</tr>
<tr>
<td></td>
<td>Common</td>
</tr>
<tr>
<td></td>
<td>- Cough</td>
</tr>
<tr>
<td></td>
<td>- Rhinitis</td>
</tr>
<tr>
<td></td>
<td>Uncommon</td>
</tr>
<tr>
<td></td>
<td>- Interstitial pneumonitis (see section 4.4)</td>
</tr>
<tr>
<td></td>
<td>- Bronchospasm - usually mild and</td>
</tr>
<tr>
<td></td>
<td>transient but may require parenteral</td>
</tr>
<tr>
<td></td>
<td>treatment</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>Very common</td>
</tr>
<tr>
<td></td>
<td>- Vomiting</td>
</tr>
<tr>
<td></td>
<td>- Nausea</td>
</tr>
<tr>
<td></td>
<td>Common</td>
</tr>
<tr>
<td></td>
<td>- Diarrhoea</td>
</tr>
<tr>
<td></td>
<td>- Stomatitis and ulceration of the mouth</td>
</tr>
<tr>
<td></td>
<td>- Constipation</td>
</tr>
<tr>
<td>Hepatobiliary disorders</td>
<td>Very common</td>
</tr>
<tr>
<td></td>
<td>- Elevation of liver transaminases (AST</td>
</tr>
<tr>
<td></td>
<td>and ALT) and alkaline phosphatase</td>
</tr>
<tr>
<td></td>
<td>Common</td>
</tr>
<tr>
<td></td>
<td>- Increased bilirubin</td>
</tr>
<tr>
<td></td>
<td>Rare</td>
</tr>
<tr>
<td></td>
<td>- Increased gamma-glutamyl transferase</td>
</tr>
<tr>
<td></td>
<td>(GGT)</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>Very common</td>
</tr>
<tr>
<td></td>
<td>- Allergic skin rash frequently associated with pruritus</td>
</tr>
<tr>
<td></td>
<td>- Alopecia</td>
</tr>
<tr>
<td></td>
<td>Common</td>
</tr>
<tr>
<td></td>
<td>- Itching</td>
</tr>
<tr>
<td></td>
<td>- Sweating</td>
</tr>
<tr>
<td></td>
<td>Rare</td>
</tr>
<tr>
<td></td>
<td>- Ulceration</td>
</tr>
<tr>
<td></td>
<td>- Vesicle and sore formation</td>
</tr>
<tr>
<td></td>
<td>- Scaling</td>
</tr>
<tr>
<td></td>
<td>Very rare</td>
</tr>
</tbody>
</table>
System Organ Class | Frequency Grouping
--- | ---
• Severe skin reactions, including desquamation and bullous skin eruptions
Musculoskeletal and connective tissue disorders | Common
• Back pain
• Myalgia
Renal and urinary disorders | Very common
• Haematuria
• Mild proteinuria
General disorders and administration site conditions | Very common
• Influenza-like symptoms - the most common symptoms are fever, headache, chills, myalgia, asthenia and anorexia. Cough, rhinitis, malaise, perspiration, and sleeping difficulties have also been reported.
• Oedema/peripheral oedema - including facial oedema. Oedema is usually reversible after stopping treatment.
Common
• Fever
• Asthenia
• Chills
Rare
• Injection site reactions - mainly mild in nature
Injury, poisoning and procedural complications | • Radiation toxicity (see section 4.5).

Postmarketing experience (spontaneous reports) frequency not known (can’t be estimated from the available data)

Nervous system disorders
Cerebrovascular accident

Cardiac disorders
Arrhythmias, predominantly supraventricular in nature
Heart failure

Vascular disorders
Clinical signs of peripheral vasculitis and gangrene

Respiratory, thoracic and mediastinal disorders
Pulmonary oedema
Adult respiratory distress syndrome (see section 4.4)

Gastrointestinal disorders
Ischaemic colitis

Hepatobiliary disorders
Serious hepatotoxicity, including liver failure and death

Skin and subcutaneous tissue disorders
Severe skin reactions, including desquamation and bullous skin eruptions, Lyell’s Syndrome, Steven-Johnson Syndrome

Renal and urinary disorders
Renal failure (see section 4.4)
Haemolytic uraemic syndrome (see section 4.4)
Injury, poisoning and procedural complications

Combination Use in Breast Cancer

The frequency of Grade 3 and 4 haematological toxicities, particularly neutropaenia, 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 neutropaenia occur more frequently when gemcitabine is used in combination with paclitaxel. Fatigue, which is not associated with anaemia, usually resolves after the first cycle.

<table>
<thead>
<tr>
<th>Grade 3 and 4 Adverse Events</th>
<th>Paclitaxel versus Gemcitabine plus Paclitaxel</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number (%) of Patients</td>
</tr>
<tr>
<td></td>
<td>Grade 3</td>
</tr>
<tr>
<td>Laboratory</td>
<td></td>
</tr>
<tr>
<td>Anaemia</td>
<td>5 (1.9)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>0</td>
</tr>
<tr>
<td>Neutropaenia</td>
<td>11 (4.2)</td>
</tr>
<tr>
<td>Non-laboratory</td>
<td></td>
</tr>
<tr>
<td>Febrile neutropaenia</td>
<td>3 (1.2)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>3 (1.2)</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>5 (1.9)</td>
</tr>
<tr>
<td>Motor neuropathy</td>
<td>2 (0.8)</td>
</tr>
<tr>
<td>Sensory neuropathy</td>
<td>9 (3.5)</td>
</tr>
</tbody>
</table>

* Grade 4 neutropaenia lasting for more than 7 days occurred in 12.6% of patients in the combination arm and 5.0% of patients in the paclitaxel arm.

Combination use in bladder cancer

<table>
<thead>
<tr>
<th>Grade 3 and 4 Adverse Events</th>
<th>MVAC versus Gemcitabine plus cisplatin</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number (%) of Patients</td>
</tr>
<tr>
<td></td>
<td>Grade 3</td>
</tr>
<tr>
<td>Laboratory</td>
<td></td>
</tr>
<tr>
<td>Anaemia</td>
<td>30 (16)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>15 (8)</td>
</tr>
<tr>
<td>Non-laboratory</td>
<td></td>
</tr>
<tr>
<td>Nausea and vomiting</td>
<td>37 (19)</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>15 (8)</td>
</tr>
<tr>
<td>Infection</td>
<td>19 (10)</td>
</tr>
<tr>
<td>Stomatitis</td>
<td>34 (18)</td>
</tr>
</tbody>
</table>

Combination use in ovarian cancer

<table>
<thead>
<tr>
<th>Grade 3 and 4 Adverse Events</th>
<th>Carboplatin versus Gemcitabine plus carboplatin</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number (%) of Patients</td>
</tr>
<tr>
<td></td>
<td>Grade 3</td>
</tr>
<tr>
<td>Laboratory</td>
<td></td>
</tr>
<tr>
<td>Anaemia</td>
<td>10 (5.7)</td>
</tr>
<tr>
<td>Neutropaenia</td>
<td>19 (10.9)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>18 (10.3)</td>
</tr>
<tr>
<td>Leucopaenia</td>
<td>11 (6.3)</td>
</tr>
<tr>
<td>Non-laboratory</td>
<td></td>
</tr>
<tr>
<td>Haemorrhage</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Febrile neutropaenia</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Infection without</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>
Sensory neuropathy was also more frequent in the combination arm than with single agent carboplatin.

4.9 Overdose
There is no known antidote for overdose of gemcitabine. Doses as high as 5,700 mg/m² have been administered by intravenous infusion over 30 minutes every 2 weeks with clinically acceptable toxicity. In the event of suspected overdose, the patient should be monitored with appropriate blood counts and receive supportive therapy, as necessary.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: pyrimidine analogues ATC code: L01BC05

Cytotoxic activity in cell cultures
Gemcitabine shows significant cytotoxic effects against a variety of cultured murine and human tumour cells. Its action is phase-specific such that gemcitabine primarily kills cells that are undergoing DNA synthesis (S-phase) and, under certain circumstances, blocks the progression of cells at the junction of the G1/S-phase boundary. In vitro, the cytotoxic effect of gemcitabine is dependent on both concentration and time.

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

Mechanism of action
Cellular metabolism and mechanism of action: gemcitabine (dFdC), which is a pyrimidine antimetabolite, is metabolised intracellularly by nucleoside kinase to the active diphosphate (dFdCDP) and triphosphate (dFdCTP) nucleosides. The cytotoxic effect of gemcitabine is due to inhibition of DNA synthesis by two mechanisms of action by dFdCDP and dFdCTP. First, dFdCDP inhibits ribonucleotide reductase, which is uniquely responsible for catalysing the reactions that produce deoxynucleoside triphosphates (dCTP) for DNA synthesis. Inhibition of this enzyme by dFdCDP reduces the concentration of deoxynucleosides in general and, in particular, dCTP. Second, dFdCTP competes with dCTP for incorporation into DNA (self-potentiation). Likewise, a small amount of gemcitabine may also be incorporated into RNA. Thus, the reduced intracellular concentration of dCTP potentiates the incorporation of dFdCTP into DNA. DNA polymerase epsilon lacks the ability to eliminate gemcitabine and to repair the growing DNA strands. After gemcitabine is incorporated into DNA, one additional nucleotide is added to the growing DNA strands. After this addition there is essentially a complete inhibition in further DNA synthesis (masked chain termination). After incorporation into DNA, gemcitabine appears to induce the programmed cell death process known as apoptosis.

Clinical data

Bladder cancer
A randomised phase III study of 405 patients with advanced or metastatic urothelial transitional cell carcinoma showed no difference between the two treatment arms, gemcitabine/cisplatin versus methotrexate/vinblastine/adriamycin/cisplatin (MVAC), in terms of median survival (12.8 and 14.8 months respectively, \( p=0.547 \)), time to disease progression (7.4 and 7.6 months respectively, \( p=0.842 \)) and response rate (49.4% and 45.7% respectively, \( p=0.512 \)). However, the combination of gemcitabine and cisplatin had a better toxicity profile than MVAC.

Pancreatic cancer
In a randomised phase III study of 126 patients with advanced or metastatic pancreatic cancer, gemcitabine showed a statistically significant higher clinical benefit response rate than 5-fluourouracil (23.8% and 4.8% respectively, \( p=0.0022 \)). Also, a statistically significant prolongation of the time to progression from 0.9 to 2.3 months (log-rank \( p<0.0002 \)) and a statistically significant prolongation of median survival from 4.4 to 5.7 months (log-rank \( p<0.0024 \)) was observed in patients treated with gemcitabine compared to patients treated with 5-fluourouracil.

Non-small cell lung cancer
In a randomised phase III study of 522 patients with inoperable, locally advanced or metastatic
NSCLC, gemcitabine in combination with cisplatin showed a statistically significant higher response rate than cisplatin alone (31.0% and 12.0%, respectively, p<0.0001). A statistically significant prolongation of the time to progression, from 3.7 to 5.6 months (log-rank p<0.0012) and a statistically significant prolongation of median survival from 7.6 months to 9.1 months (log-rank p<0.004) was observed in patients treated with gemcitabine/cisplatin compared to patients treated with cisplatin.

In another randomised phase III study of 135 patients with stage IIIB or IV NSCLC, a combination of gemcitabine and cisplatin showed a statistically significant higher response rate than a combination of cisplatin and etoposide (40.6% and 21.2%, respectively, p=0.025). A statistically significant prolongation of the time to progression, from 4.3 to 6.9 months (p=0.014) was observed in patients treated with gemcitabine/cisplatin compared to patients treated with etoposide/cisplatin. In both studies it was found that tolerability was similar in the two treatment arms.

**Ovarian carcinoma**

In a randomised phase III study, 356 patients with advanced epithelial ovarian carcinoma who had relapsed at least 6 months after completing platinum based therapy were randomised to therapy with gemcitabine and carboplatin (GCb), or carboplatin (Cb). A statistically significant prolongation of the time to progression of disease, from 5.8 to 8.6 months (log-rank p=0.0038) was observed in the patients treated with GCb compared to patients treated with Cb. Differences in response rate of 47.2% in the GCb arm versus 30.9% in the Cb arm (p=0.0016) and median survival 18 months (GCb) versus 17.3 (Cb) (p=0.73) favoured the GCb arm.

**Breast cancer**

In a randomised phase III study of 529 patients with inoperable, locally recurrent or metastatic breast cancer with relapse after adjuvant/neoadjuvant chemotherapy, gemcitabine in combination with paclitaxel showed a statistically significant prolongation of time to documented disease progression from 3.98 to 6.14 months (log-rank p=0.0002) in patients treated with gemcitabine/paclitaxel compared to patients treated with paclitaxel. After 377 deaths, the overall survival was 18.6 months versus 15.8 months (log rank p=0.0489, HR 0.82) in patients treated with gemcitabine/paclitaxel compared to patients treated with paclitaxel and the overall response rate was 41.4% and 26.2% respectively (p=0.0002).

### 5.2 Pharmacokinetic properties

The pharmacokinetics of gemcitabine have been examined in 353 patients in seven studies. The 121 women and 232 men ranged in age from 29 to 79 years. Of these patients, approximately 45% had non-small cell lung cancer and 35% were diagnosed with pancreatic cancer. The following pharmacokinetic parameters were obtained for doses ranging from 500 to 2,592 mg/m² that were infused from 0.4 to 1.2 hours.

Peak plasma concentrations (obtained within 5 minutes of the end of the infusion) were 3.2 to 45.5 µg/ml. Plasma concentrations of the parent compound following a dose of 1,000 mg/m²/30-minutes are greater than 5 µg/ml for approximately 30 minutes after the end of the infusion and greater than 0.4 µg/ml for an additional hour.

**Distribution**

The volume of distribution of the central compartment was 12.4 l/m² for women and 17.5 l/m² for men (inter-individual variability was 91.9%). The volume of distribution of the peripheral compartment: 47.4 l/m². The volume of the peripheral compartment was not sensitive to gender.

The plasma protein binding was considered to be negligible.

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

**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.

**Excretion**

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 men is approximately 25% lower than the values for women. 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 was 2 to 7 l/hr/m².
During the week following administration, 92 to 98% of the dose of gemcitabine administered is recovered, 99% in the urine, mainly in the form of dFdU and 1% of the dose is excreted in faeces.

dFdCTP kinetics
This metabolite can be found in peripheral blood mononuclear cells and the information below refers to these cells. Intracellular concentrations increase in proportion to gemcitabine doses of 35-350 mg/m²/30-minutes, which give steady state concentrations of 0.4-5 µg/ml. At gemcitabine plasma concentrations above 5 µg/ml, dFdCTP levels do not increase, suggesting that the formation is saturable in these cells.
Half-life of terminal elimination: 0.7-12 hours.
dFdU kinetics
Peak plasma concentrations (3-15 minutes after end of 30-minute infusion, 1,000 mg/m²): 28-52 µg/ml.
Trough concentration following once weekly dosing: 0.07-1.12 µg/ml, with no apparent accumulation.
Triphasic plasma concentration versus time curve, mean half-life of terminal phase - 65 hours (range 33-84 hr).
Formation of dFdU from parent compound: 91%-98%.
Mean volume of distribution of central compartment: 18 l/m² (range 11-22 l/m²).
Mean steady-state volume of distribution (Vss): 150 l/m² (range 96-228 l/m²).
Tissue distribution: extensive.
Mean apparent clearance: 2.5 l/hr/m² (range 1-4 l/hr/m²).
Urinary excretion: all.
Gemcitabine and paclitaxel combination therapy:
Combination therapy did not alter the pharmacokinetics of either gemcitabine or paclitaxel.
Gemcitabine and carboplatin combination therapy:
When given in combination with carboplatin the pharmacokinetics of gemcitabine were not altered.

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

5.3 Preclinical safety data
In repeat-dose studies of up to 6 months in duration in mice and dogs, the principal finding was schedule and dose-dependent haematopoietic suppression which was reversible.
Gemcitabine is mutagenic in an in vitro mutation test and an in vivo bone marrow micronucleus test.
Long term animal studies evaluating the carcinogenic potential have not been performed.
In fertility studies, gemcitabine caused reversible hypospermatogenesis in male mice. No effect on the fertility of females has been detected.
Evaluation of experimental animal studies has shown reproductive toxicity e.g. birth defects and other effects on the development of the embryo or foetus, the course of gestation or peri- and postnatal development.

6 PHARMACEUTICAL PARTICULARS
6.1 List of excipients
Gemcitabine 200 mg contains:
Mannitol (E421)
Sodium acetate (E262)
Hydrochloric acid (E507) (for pH adjustment)
Sodium hydroxide (E524) (for pH adjustment)

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

6.3 Shelf life
Unopened vials: 2 years.
Reconstituted solution:
Chemical and physical in-use stability has been demonstrated for 24 hours at 20-25°C. From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be
longer than 24 hours at room temperature, unless reconstitution (and further dilution, if applicable) has taken place in controlled and validated aseptic conditions.

Solutions of reconstituted gemcitabine should not be refrigerated, as crystallisation may occur.

6.4 Special precautions for storage
Unopened vials: this medicinal product does not require any special storage conditions.
For storage conditions of the reconstituted medicinal product see section 6.3.

6.5 Nature and contents of container
Type I clear glass vials, stoppered with a grey bromobutyl rubber stopper and sealed with an aluminium flip-off cap, combined with a polypropylene disk.
Each pack contains 1 vial.

6.6 Special precautions for disposal
Handling
The normal safety precautions for cytostatic agents must be observed when preparing and disposing of the infusion solution. Handling of the solution for infusion should be done in a safety box and protective coats and gloves should be used. If no safety box is available, the equipment should be supplemented with a mask and protective glasses.

If the preparation comes into contact with the eyes, this may cause serious irritation. The eyes should be rinsed immediately and thoroughly with water. If there is lasting irritation, a doctor should be consulted. If the solution is spilled on the skin, rinse thoroughly with water.

Instructions for reconstitution (and further dilution, if performed)
The only approved diluent for reconstitution of gemcitabine sterile powder is sodium chloride 9 mg/ml (0.9%) solution for injection (without preservative). Due to solubility considerations, the maximum concentration for gemcitabine upon reconstitution is 40 mg/ml. Reconstitution at concentrations greater than 40 mg/ml may result in incomplete dissolution and should be avoided.

1. Use aseptic technique during the reconstitution and any further dilution of gemcitabine for intravenous infusion administration.

2. To reconstitute, add 5 ml of sterile sodium chloride 9 mg/ml (0.9%) solution for injection, without preservative, to the 200 mg vial or 25 ml of sterile sodium chloride 9 mg/ml (0.9%) solution for injection, without preservative, to the 1,000 mg vial. The total volume after reconstitution is 5.26 ml (200 mg vial) or 26.3 ml (1,000 mg vial) respectively. This yields a gemcitabine concentration of 38 mg/ml, which includes accounting for the displacement volume of the lyophilised powder. Shake to dissolve. Further dilution with sterile sodium chloride 9 mg/ml (0.9%) solution for injection, without preservative can be done. Reconstituted solution is a clear colourless to light straw-coloured solution.

3. Parenteral medicinal drugs should be inspected visually for particulate matter and discolouration prior to administration. If particulate matter is observed, do not administer.

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

1 NAME OF THE MEDICINAL PRODUCT
Gemcitabine 1 g powder for solution for infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
One vial contains gemcitabine hydrochloride equivalent to 1,000 mg gemcitabine.
After reconstitution, the solution contains 38 mg/ml of gemcitabine.
Excipients
Each 1,000 mg vial contains 17.5 mg (< 1 mmol) sodium.
For a full list of excipients see section 6.1.

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

4 CLINICAL PARTICULARS
4.1 Therapeutic indications
Gemcitabine is indicated for the treatment of locally advanced or metastatic bladder cancer in combination with cisplatin.
Gemcitabine is indicated for treatment of patients with locally advanced or metastatic adenocarcinoma of the pancreas.
Gemcitabine, in combination with cisplatin is indicated as first line treatment of patients with locally advanced or metastatic non-small cell lung cancer (NSCLC). Gemcitabine monotherapy can be considered in elderly patients or those with performance status 2.
Gemcitabine is indicated for the treatment of patients with locally advanced or metastatic epithelial ovarian carcinoma, in combination with carboplatin, in patients with relapsed disease following a recurrence-free interval of at least 6 months after platinum-based, first-line therapy.
Gemcitabine, in combination with paclitaxel, is indicated for the treatment of patients with unresectable, locally recurrent or metastatic breast cancer who have relapsed following adjuvant/neoadjuvant chemotherapy. Prior chemotherapy should have included an anthracycline unless clinically contraindicated.

4.2 Posology and method of administration
Gemcitabine should only be prescribed by a physician qualified in the use of anti-cancer chemotherapy.
Recommended posology
**Bladder Cancer**
Combination use
The recommended dose for gemcitabine is 1,000 mg/m², given by 30-minute infusion. The dose should be given on Days 1, 8, and 15 of each 28-day cycle in combination with cisplatin. Cisplatin is given at a recommended dose of 70 mg/m² on Day 1 following gemcitabine or Day 2 of each 28-day cycle. This 4-week cycle is then repeated. Dosage reduction with each cycle or within a cycle may be applied based upon the grade of toxicity experienced by the patient.
**Pancreatic cancer**
The recommended dose of gemcitabine is 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 with each cycle or within a cycle may be applied based upon the grade of toxicity experienced by the patient.
**Non-small cell lung cancer**
Monotherapy
The recommended dose of gemcitabine is 1,000 mg/m², given by 30-minute intravenous infusion. This should be repeated once weekly for 3 weeks, followed by a 1-week rest period. This 4-week cycle is then repeated. Dosage reduction with each cycle or within a cycle may be applied based upon the grade of toxicity experienced by the patient.
Combination use
The recommended dose for gemcitabine is 1,250 mg/m² body surface area given as a 30-minute intravenous infusion on Day 1 and 8 of the treatment cycle (21 days). Dosage reduction with each cycle or within a cycle may be applied based upon the grade of toxicity experienced by the patient. Cisplatin has been used at doses between 75-100 mg/m² once every 3 weeks.
**Breast Cancer**

**Combination use**

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

**Ovarian cancer**

**Combination use**

Gemcitabine in combination with carboplatin is recommended using gemcitabine 1,000 mg/m² administered on Days 1 and 8 of each 21-day cycle as a 30-minute intravenous infusion. After gemcitabine, carboplatin will be given on Day 1 consistent with a target Area under Curve (AUC) of 4.0 mg/ml/min. Dosage reduction with each cycle or within a cycle may be applied based upon the grade of toxicity experienced by the patient.

**Monitoring for toxicity and dose modification due to toxicity**

**Dose modification due to non-haematological toxicity**

Periodic physical examination and checks of renal and hepatic function should be made to detect non-haematological toxicity. Dosage reduction with each cycle or within a cycle may be applied based upon the grade of toxicity experienced by the patient. In general, for severe (Grade 3 or 4) non-haematological toxicity, except nausea/vomiting, therapy with gemcitabine should be withheld or decreased depending on the judgement of the treating physician. Doses should be withheld until toxicity has resolved in the opinion of the physician. For cisplatin, carboplatin, and paclitaxel dosage adjustment in combination therapy, please refer to the corresponding Summary of Product Characteristics.

**Dose modification due to haematological toxicity**

**Initiation of a cycle**

For all indications, the patient must be monitored before each dose for platelet and granulocyte counts. Patients should have an absolute granulocyte count of at least 1,500 (x 10⁶/l) and platelet count of 100,000 (x 10⁶/l) prior to the initiation of a cycle.

**Within a cycle**

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

### Dose modification of gemcitabine within a cycle for bladder cancer, NSCLC and pancreatic cancer, given in monotherapy or in combination with cisplatin

<table>
<thead>
<tr>
<th>Absolute granulocyte count (x 10⁶/l)</th>
<th>Platelet count (x 10⁶/l)</th>
<th>Percentage of standard dose of gemcitabine (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 1,000 and</td>
<td>&gt; 100,000</td>
<td>100</td>
</tr>
<tr>
<td>500-1,000 or</td>
<td>50,000-100,000</td>
<td>75</td>
</tr>
<tr>
<td>&lt; 500 or</td>
<td>&lt; 50,000</td>
<td>Omit dose*</td>
</tr>
</tbody>
</table>

*Treatment omitted will not be re-instated within a cycle before the absolute granulocyte count reaches at least 500 (x 10⁶/l) and the platelet count reaches 50,000 (x 10⁶/l).

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

<table>
<thead>
<tr>
<th>Absolute granulocyte count (x 10⁶/l)</th>
<th>Platelet count (x 10⁶/l)</th>
<th>Percentage of standard dose of gemcitabine (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 1,200 and</td>
<td>&gt; 75,000</td>
<td>100</td>
</tr>
<tr>
<td>1,000-&lt; 1,200 or</td>
<td>50,000-75,000</td>
<td>75</td>
</tr>
<tr>
<td>700-&lt; 1,000 and</td>
<td>≥ 50,000</td>
<td>50</td>
</tr>
<tr>
<td>&lt; 700 or</td>
<td>&lt; 50,000</td>
<td>Omit dose*</td>
</tr>
</tbody>
</table>

*Treatment omitted will not be re-instated within a cycle. Treatment will start on Day 1 of the next cycle once the absolute granulocyte count reaches at least 1,500 (x 10⁶/l) and the platelet count reaches 100,000 (x 10⁶/l).
Dose modification of gemcitabine within a cycle for ovarian cancer, given in combination with carboplatin

<table>
<thead>
<tr>
<th>Absolute granulocyte count (x 10⁶/l)</th>
<th>Platelet count (x 10⁶/l)</th>
<th>Percentage of standard dose of gemcitabine (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 1,500 and</td>
<td>≥ 100,000</td>
<td>100</td>
</tr>
<tr>
<td>1,000-1,500 or</td>
<td>75,000-100,000</td>
<td>50</td>
</tr>
<tr>
<td>&lt; 1,000 or</td>
<td>&lt; 75,000</td>
<td>Omit dose*</td>
</tr>
</tbody>
</table>

*Treatment omitted will not be re-instated within a cycle. Treatment will start on Day 1 of the next cycle once the absolute granulocyte count reaches at least 1,500 (x 10⁶/l) and the platelet count reaches 100,000 (x 10⁶/l).

**Dose modifications due to haematological toxicity in subsequent cycles, for all indications**

The gemcitabine dose should be reduced to 75% of the original cycle initiation dose, in the case of the following haematological toxicities:

- Absolute granulocyte count < 500 x 10⁶/l for more than 5 days
- Absolute granulocyte count < 100 x 10⁶/l for more than 3 days
- Febrile neutropaenia
- Platelets < 25,000 x 10⁶/l
- Cycle delay of more than 1 week due to toxicity

**Method of administration**

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

For instructions on reconstitution, see section 6.6.

**Special populations**

*Patients with renal or hepatic impairment*

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

*Elderly population (> 65 years)*

Gemcitabine has been well tolerated in patients over the age of 65. There is no evidence to suggest that dose adjustments, other than those already recommended for all patients, are necessary in the elderly (see section 5.2).

*Paediatric population (< 18 years)*

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

4.3 **Contraindications**

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

Breast-feeding (see section 4.6).

4.4 **Special warnings and precautions for use**

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

**Haematological toxicity**

Gemcitabine can suppress bone marrow function as manifested by leucopaenia, thrombocytopenia and anaemia.

Patients receiving gemcitabine should be monitored prior to each dose for platelet, leucocyte and granulocyte counts. Suspension or modification of therapy should be considered when drug-induced bone marrow depression is detected (see section 4.2). However, myelosuppression is short lived and usually does not result in dose reduction and rarely in discontinuation.

Peripheral blood counts may continue to deteriorate after gemcitabine administration has been stopped. In patients with impaired bone marrow function, the treatment should be started with caution. As with other cytotoxic treatments, the risk of cumulative bone-marrow suppression must be considered when gemcitabine treatment is given together with other chemotherapy.

**Hepatic insufficiency**

Administration of gemcitabine in patients with concurrent liver metastases or a pre-existing medical history of hepatitis, alcoholism or liver cirrhosis may lead to exacerbation of the underlying hepatic insufficiency.
Laboratory evaluation of renal and hepatic function (including virological tests) should be performed periodically.

Gemcitabine should be used with caution in patients with hepatic insufficiency or with impaired renal function as there is insufficient information from clinical studies to allow clear dose recommendation for this patient population (see section 4.2).

Concomitant radiotherapy

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

Live vaccinations

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

Cardiovascular

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

Pulmonary

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

Renal

Clinical findings consistent with the haemolytic uraemic syndrome (HUS) were rarely reported in patients receiving gemcitabine (see section 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. Renal failure may not be reversible with discontinuation of therapy and dialysis may be required.

Fertility

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

Sodium

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

4.5 Interaction with other medicinal products and other forms of interaction

No specific interaction studies have been performed (see section 5.2).

Radiotherapy

Concurrent (given together or ≤ 7 days apart) - toxicity associated with this multimodality therapy is dependent on many different factors, including dose of gemcitabine, frequency of gemcitabine administration, dose of radiation, radiotherapy planning technique, the target tissue, and target volume. Pre-clinical and clinical studies have shown that gemcitabine has radiosensitising activity. In a single trial, where gemcitabine at a dose of 1,000 mg/m² was administered concurrently for up to 6 consecutive weeks with therapeutic thoracic radiation to patients with non-small cell lung cancer, significant toxicity in the form of severe, and potentially life threatening mucositis, especially oesophagitis, and pneumonitis was observed, particularly in patients receiving large volumes of radiotherapy [median treatment volumes 4,795 cm³]. Studies done subsequently have suggested that it is feasible to administer gemcitabine at lower doses with concurrent radiotherapy with predictable toxicity, such as a phase II study in non-small cell lung cancer, where thoracic radiation doses of 66 Gy were applied concomitantly with an administration with gemcitabine (600 mg/m², four times) and cisplatin (80 mg/m² twice) during 6 weeks. The optimum regimen for safe administration of gemcitabine with therapeutic doses of radiation has not yet been determined in all tumour types.

Non-concurrent (given > 7 days apart) - analysis of the data does not indicate any enhanced toxicity when gemcitabine is administered more than 7 days before or after radiation, other than radiation recall. Data suggest that gemcitabine can be started after the acute effects of radiation have resolved or at least one week after radiation.

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

Others

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

Pregnancy

There are no adequate data from the use of gemcitabine in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3). Based on results from animal studies and the mechanism of action of gemcitabine, this substance should not be used during pregnancy unless clearly necessary. Women should be advised not to become pregnant during treatment with gemcitabine and to warn their attending physician immediately, should this occur after all.

Breast-feeding

It is not known whether gemcitabine is excreted in human milk and adverse effects on the suckling child cannot be excluded. Breast-feeding must be discontinued during gemcitabine therapy.

Fertility

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

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

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

Clinical trial data

Frequencies are defined as: Very common (≥ 1/10), Common (≥ 1/100 to < 1/10), Uncommon (≥ 1/1,000 to < 1/100), Rare (≥ 1/10,000 to < 1/1,000), Very Rare (< 1/10,000).

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

<table>
<thead>
<tr>
<th>System Organ Class</th>
<th>Frequency Grouping</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood and lymphatic system disorders</td>
<td>Very common</td>
</tr>
<tr>
<td></td>
<td>• Leucopaenia (Neutropaenia Grade 3 = 19.3%; Grade 4 = 6%).</td>
</tr>
<tr>
<td></td>
<td>Bone-marrow suppression is usually mild to moderate and mostly affects the granulocyte count (see section 4.2).</td>
</tr>
<tr>
<td></td>
<td>• Thrombocytopaenia</td>
</tr>
<tr>
<td></td>
<td>• Anaemia</td>
</tr>
<tr>
<td></td>
<td>Common</td>
</tr>
<tr>
<td></td>
<td>• Febrile neutropaenia</td>
</tr>
<tr>
<td></td>
<td>Very rare</td>
</tr>
<tr>
<td></td>
<td>• Thrombocytosis</td>
</tr>
<tr>
<td>Immune system disorders</td>
<td>Very rare</td>
</tr>
<tr>
<td></td>
<td>• Anaphylactoid reaction</td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td>Common</td>
</tr>
<tr>
<td></td>
<td>• Anorexia</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>Common</td>
</tr>
<tr>
<td>System Organ Class</td>
<td>Frequency Grouping</td>
</tr>
<tr>
<td>-----------------------------------</td>
<td>-----------------------------------------------------------------------------------</td>
</tr>
<tr>
<td></td>
<td>• Headache</td>
</tr>
<tr>
<td></td>
<td>• Insomnia</td>
</tr>
<tr>
<td></td>
<td>• Somnolence</td>
</tr>
<tr>
<td>Cardiac disorders</td>
<td>Rare</td>
</tr>
<tr>
<td></td>
<td>• Myocardial infarct</td>
</tr>
<tr>
<td>Vascular disorders</td>
<td>Rare</td>
</tr>
<tr>
<td></td>
<td>• Hypotension</td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td>Very common</td>
</tr>
<tr>
<td></td>
<td>• Dyspnoea - usually mild and passes rapidly without treatment</td>
</tr>
<tr>
<td></td>
<td>Common</td>
</tr>
<tr>
<td></td>
<td>• Cough</td>
</tr>
<tr>
<td></td>
<td>• Rhinitis</td>
</tr>
<tr>
<td></td>
<td>Uncommon</td>
</tr>
<tr>
<td></td>
<td>• Interstitial pneumonitis (see section 4.4)</td>
</tr>
<tr>
<td></td>
<td>• Bronchospasm - usually mild and transient but may require parenteral treatment</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>Very common</td>
</tr>
<tr>
<td></td>
<td>• Vomiting</td>
</tr>
<tr>
<td></td>
<td>• Nausea</td>
</tr>
<tr>
<td></td>
<td>Common</td>
</tr>
<tr>
<td></td>
<td>• Diarrhoea</td>
</tr>
<tr>
<td></td>
<td>• Stomatitis and ulceration of the mouth</td>
</tr>
<tr>
<td></td>
<td>• Constipation</td>
</tr>
<tr>
<td>Hepatobiliary disorders</td>
<td>Very common</td>
</tr>
<tr>
<td></td>
<td>• Elevation of liver transaminases (AST and ALT) and alkaline phosphatase</td>
</tr>
<tr>
<td></td>
<td>Common</td>
</tr>
<tr>
<td></td>
<td>• Increased bilirubin</td>
</tr>
<tr>
<td></td>
<td>Rare</td>
</tr>
<tr>
<td></td>
<td>• Increased gamma-glutamyl transferase (GGT)</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>Very common</td>
</tr>
<tr>
<td></td>
<td>• Allergic skin rash frequently associated with pruritus</td>
</tr>
<tr>
<td></td>
<td>• Alopecia</td>
</tr>
<tr>
<td></td>
<td>Common</td>
</tr>
<tr>
<td></td>
<td>• Itching</td>
</tr>
<tr>
<td></td>
<td>• Sweating</td>
</tr>
<tr>
<td></td>
<td>Rare</td>
</tr>
<tr>
<td></td>
<td>• Ulceration</td>
</tr>
<tr>
<td></td>
<td>• Vesicle and sore formation</td>
</tr>
<tr>
<td>System Organ Class</td>
<td>Frequency Grouping</td>
</tr>
<tr>
<td>------------------------------------------------</td>
<td>-------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>• Scaling</td>
<td>Very rare</td>
</tr>
<tr>
<td>• Severe skin reactions, including desquamation and bullous skin eruptions</td>
<td></td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td>Common</td>
</tr>
<tr>
<td>• Back pain</td>
<td></td>
</tr>
<tr>
<td>• Myalgia</td>
<td></td>
</tr>
<tr>
<td>Renal and urinary disorders</td>
<td>Very common</td>
</tr>
<tr>
<td>• Haematuria</td>
<td></td>
</tr>
<tr>
<td>• Mild proteinuria</td>
<td></td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td>Very common</td>
</tr>
<tr>
<td>• Influenza-like symptoms - the most common symptoms are fever, headache, chills, myalgia, asthenia and anorexia. Cough, rhinitis, malaise, perspiration, and sleeping difficulties have also been reported.</td>
<td></td>
</tr>
<tr>
<td>• Oedema/peripheral oedema - including facial oedema. Oedema is usually reversible after stopping treatment.</td>
<td></td>
</tr>
<tr>
<td>Common</td>
<td></td>
</tr>
<tr>
<td>• Fever</td>
<td></td>
</tr>
<tr>
<td>• Asthenia</td>
<td></td>
</tr>
<tr>
<td>• Chills</td>
<td></td>
</tr>
<tr>
<td>Rare</td>
<td></td>
</tr>
<tr>
<td>• Injection site reactions - mainly mild in nature</td>
<td></td>
</tr>
<tr>
<td>Injury, poisoning and procedural complications</td>
<td>Radiation toxicity (see section 4.5).</td>
</tr>
</tbody>
</table>

Postmarketing experience (spontaneous reports) frequency not known (can’t be estimated from the available data)

*Nervous system disorders*
Cerebrovascular accident

*Cardiac disorders*
Arrhythmias, predominantly supraventricular in nature
Heart failure

*Vascular disorders*
Clinical signs of peripheral vasculitis and gangrene

*Respiratory, thoracic and mediastinal disorders*
Pulmonary oedema
Adult respiratory distress syndrome (see section 4.4)

*Gastrointestinal disorders*
Ischaemic colitis

*Hepatobiliary disorders*
Serious hepatotoxicity, including liver failure and death

*Skin and subcutaneous tissue disorders*
Severe skin reactions, including desquamation and bullous skin eruptions, Lyell’s Syndrome, Steven-
Johnson Syndrome

**Renal and urinary disorders**
Renal failure (see section 4.4)
Haemolytic uraemic syndrome (see section 4.4)

**Injury, poisoning and procedural complications**
Radiation recall

**Combination Use in Breast Cancer**
The frequency of Grade 3 and 4 haematological 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**

<table>
<thead>
<tr>
<th></th>
<th>Paclitaxel arm (n=259)</th>
<th>Gemcitabine plus Paclitaxel arm (n=262)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Laboratory</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anaemia</td>
<td>5 (1.9)</td>
<td>15 (5.7)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>0</td>
<td>14 (5.3)</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>11 (4.2)</td>
<td>82 (31.3)</td>
</tr>
<tr>
<td><strong>Non-laboratory</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Febrile neutropenia</td>
<td>3 (1.2)</td>
<td>12 (4.6)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>3 (1.2)</td>
<td>15 (5.7)</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>5 (1.9)</td>
<td>8 (3.1)</td>
</tr>
<tr>
<td>Motor neuropathy</td>
<td>2 (0.8)</td>
<td>6 (2.3)</td>
</tr>
<tr>
<td>Sensory neuropathy</td>
<td>9 (3.5)</td>
<td>14 (5.3)</td>
</tr>
</tbody>
</table>

* 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.

### Grade 3 and 4 Adverse Events
**MVAC versus Gemcitabine plus cisplatin**

<table>
<thead>
<tr>
<th></th>
<th>MVAC (methotrexate, vinblastine, doxorubicin and cisplatin) arm (N=196)</th>
<th>Gemcitabine plus cisplatin arm (N=200)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Laboratory</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anaemia</td>
<td>30 (16)</td>
<td>47 (24)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>15 (8)</td>
<td>57 (29)</td>
</tr>
<tr>
<td><strong>Non-laboratory</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea and vomiting</td>
<td>37 (19)</td>
<td>44 (22)</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>15 (8)</td>
<td>6 (3)</td>
</tr>
<tr>
<td>Infection</td>
<td>19 (10)</td>
<td>4 (2)</td>
</tr>
<tr>
<td>Stomatitis</td>
<td>34 (18)</td>
<td>2 (1)</td>
</tr>
</tbody>
</table>

### Grade 3 and 4 Adverse Events
**Carboplatin versus Gemcitabine plus carboplatin**

<table>
<thead>
<tr>
<th></th>
<th>Carboplatin arm (N=174)</th>
<th>Gemcitabine plus carboplatin arm (N=175)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Laboratory</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anaemia</td>
<td>10 (5.7)</td>
<td>39 (22.3)</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>19 (10.9)</td>
<td>73 (41.7)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>18 (10.3)</td>
<td>53 (30.3)</td>
</tr>
</tbody>
</table>
Sensory neuropathy was also more frequent in the combination arm than with single agent carboplatin.

4.9 Overdose
There is no known antidote for overdose of gemcitabine. Doses as high as 5,700 mg/m² have been administered by intravenous infusion over 30 minutes every 2 weeks with clinically acceptable toxicity. In the event of suspected overdose, the patient should be monitored with appropriate blood counts and receive supportive therapy, as necessary.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: pyrimidine analogues ATC code: L01BC05

Cytotoxic activity in cell cultures
Gemcitabine shows significant cytotoxic effects against a variety of cultured murine and human tumour cells. Its action is phase-specific such that gemcitabine primarily kills cells that are undergoing DNA synthesis (S-phase) and, under certain circumstances, blocks the progression of cells at the junction of the G1/S-phase boundary. In vitro, the cytotoxic effect of gemcitabine is dependent on both concentration and time.

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

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

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

Clinical data

Bladder cancer
A randomised phase III study of 405 patients with advanced or metastatic urothelial transitional cell carcinoma showed no difference between the two treatment arms, gemcitabine/cisplatin versus methotrexate/vinblastine/adriamycin/cisplatin (MVAC), in terms of median survival (12.8 and 14.8 months respectively, p=0.547), time to disease progression (7.4 and 7.6 months respectively, p=0.842) and response rate (49.4% and 45.7% respectively, p=0.512). However, the combination of gemcitabine and cisplatin had a better toxicity profile than MVAC.

Pancreatic cancer
In a randomised phase III study of 126 patients with advanced or metastatic pancreatic cancer, gemcitabine showed a statistically significant higher clinical benefit response rate than 5-fluorouracil (23.8% and 4.8% respectively, p=0.0022). Also, a statistically significant prolongation of the time to progression from 0.9 to 2.3 months (log-rank p<0.0002) and a statistically significant prolongation of median survival from 4.4 to 5.7 months (log-rank p<0.0024) was observed in patients treated with gemcitabine compared to patients treated with 5-fluorouracil.
**Non-small cell lung cancer**

In a randomised phase III study of 522 patients with inoperable, locally advanced or metastatic NSCLC, gemcitabine in combination with cisplatin showed a statistically significant higher response rate than cisplatin alone (31.0% and 12.0%, respectively, \( p< 0.0001 \)). A statistically significant prolongation of the time to progression, from 3.7 to 5.6 months (log-rank \( p< 0.0012 \)) and a statistically significant prolongation of median survival from 7.6 months to 9.1 months (log-rank \( p< 0.004 \)) was observed in patients treated with gemcitabine/cisplatin compared to patients treated with cisplatin.

In another randomised phase III study of 135 patients with stage IIIIB or IV NSCLC, a combination of gemcitabine and cisplatin showed a statistically significant higher response rate than a combination of cisplatin and etoposide (40.6% and 21.2%, respectively, \( p=0.025 \)). A statistically significant prolongation of the time to progression, from 4.3 to 6.9 months (\( p=0.014 \)) was observed in patients treated with gemcitabine/cisplatin compared to patients treated with etoposide/cisplatin.

In both studies it was found that tolerability was similar in the two treatment arms.

**Ovarian carcinoma**

In a randomised phase III study, 356 patients with advanced epithelial ovarian carcinoma who had relapsed at least 6 months after completing platinum based therapy were randomised to therapy with gemcitabine and carboplatin (GCb), or carboplatin (Cb). A statistically significant prolongation of the time to progression of disease, from 5.8 to 8.6 months (log-rank \( p=0.0038 \)) was observed in the patients treated with GCb compared to patients treated with Cb. Differences in response rate of 47.2% in the GCb arm versus 30.9% in the Cb arm (\( p=0.0016 \)) and median survival 18 months (GCb) versus 17.3 (Cb) (\( p=0.73 \)) favoured the GCb arm.

**Breast cancer**

In a randomised phase III study of 529 patients with inoperable, locally recurrent or metastatic breast cancer with relapse after adjuvant/neoadjuvant chemotherapy, gemcitabine in combination with paclitaxel showed a statistically significant prolongation of time to documented disease progression from 3.98 to 6.14 months (log-rank \( p=0.0002 \)) in patients treated with gemcitabine/paclitaxel compared to patients treated with paclitaxel. After 377 deaths, the overall survival was 18.6 months versus 15.8 months (log rank \( p=0.0489, \) HR 0.82) in patients treated with gemcitabine/paclitaxel compared to patients treated with paclitaxel and the overall response rate was 41.4% and 26.2% respectively (\( p=0.0002 \)).

### 5.2 Pharmacokinetic properties

The pharmacokinetics of gemcitabine have been examined in 353 patients in seven studies. The 121 women and 232 men ranged in age from 29 to 79 years. Of these patients, approximately 45% had non-small cell lung cancer and 35% were diagnosed with pancreatic cancer. The following pharmacokinetic parameters were obtained for doses ranging from 500 to 2,592 mg/m\(^2\) that were infused from 0.4 to 1.2 hours.

Peak plasma concentrations (obtained within 5 minutes of the end of the infusion) were 3.2 to 45.5 µg/ml. Plasma concentrations of the parent compound following a dose of 1,000 mg/m\(^2\)/30-minutes are greater than 5 µg/ml for approximately 30 minutes after the end of the infusion and greater than 0.4 µg/ml for an additional hour.

**Distribution**

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

The plasma protein binding was considered to be negligible.

**Half-life**

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

**Metabolism**

Gemcitabine is rapidly 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.

**Excretion**

Systemic clearance ranged from 29.2 l/hr/m\(^2\) to 92.2 l/hr/m\(^2\) depending on gender and age (inter-individual variability was 52.2%). Clearance for women is approximately 25% lower than the values for men. Although rapid, clearance for both men and women appears to decrease with age. For the
recommended gemcitabine dose of 1,000 mg/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 was 2 to 7 l/hr/m².  
During the week following administration, 92 to 98% of the dose of gemcitabine administered is recovered, 99% in the urine, mainly in the form of dFdU and 1% of the dose is excreted in faeces.  

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

**dFdU kinetics**  
Peak plasma concentrations (3-15 minutes after end of 30-minute infusion, 1,000 mg/m²²): 28-52 µg/ml.  
Trough concentration following once weekly dosing: 0.07-1.12 µg/ml, with no apparent accumulation.  
Triphasic plasma concentration versus time curve, mean half-life of terminal phase - 65 hours (range 33-84 hr).  
Formation of dFdU from parent compound: 91%-98%.  
Mean volume of distribution of central compartment: 18 l/m² (range 11-22 l/m²).  
Mean steady-state volume of distribution (Vss): 150 l/m² (range 96-228 l/m²).  
Tissue distribution: extensive.  
Mean apparent clearance: 2.5 l/hr/m² (range 1-4 l/hr/m²).  
Urinary excretion: all.  
Gemcitabine and paclitaxel combination therapy:  
Combination therapy did not alter the pharmacokinetics of either gemcitabine or paclitaxel.  
Gemcitabine and carboplatin combination therapy:  
When given in combination with carboplatin the pharmacokinetics of gemcitabine were not altered.  

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

### Preclinical safety data
In repeat-dose studies of up to 6 months in duration in mice and dogs, the principal finding was schedule and dose-dependent haematopoietic suppression which was reversible.  
Gemcitabine is mutagenic in an *in vitro* mutation test and an *in vivo* bone marrow micronucleus test.  
Long term animal studies evaluating the carcinogenic potential have not been performed.  
In fertility studies, gemcitabine caused reversible hypospermatogenesis in male mice. No effect on the fertility of females has been detected.  
Evaluation of experimental animal studies has shown reproductive toxicity e.g. birth defects and other effects on the development of the embryo or foetus, the course of gestation or peri- and postnatal development.

### PHARMACEUTICAL PARTICULARS

#### 6.1 List of excipients
Gemcitabine 1 g contains:  
Mannitol (E421)  
Sodium acetate (E262)  
Hydrochloric acid (E507) (for pH adjustment)  
Sodium hydroxide (E524) (for pH adjustment)

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

#### 6.3 Shelf life
Unopened vials: 2 years.  
Reconstituted solution:  
Chemical and physical in-use stability has been demonstrated for 24 hours at 20-25°C. From a microbiological point of view, the product should be used immediately. If not used immediately, in-use
storage times and conditions prior to use are the responsibility of the user and would normally not be
longer than 24 hours at room temperature, unless reconstitution (and further dilution, if applicable) has
taken place in controlled and validated aseptic conditions.
Solutions of reconstituted gemcitabine should not be refrigerated, as crystallisation may occur.

6.4 Special precautions for storage
Unopened vials: this medicinal product does not require any special storage conditions.
For storage conditions of the reconstituted medicinal product see section 6.3.

6.5 Nature and contents of container
Type I clear glass vials, stoppered with a grey bromobutyl rubber stopper and sealed with an
aluminium flip-off cap, combined with a polypropylene disk.
Each pack contains 1 vial.

6.6 Special precautions for disposal
Handling
The normal safety precautions for cytostatic agents must be observed when preparing and disposing of
the infusion solution. Handling of the solution for infusion should be done in a safety box and
protective coats and gloves should be used. If no safety box is available, the equipment should be
supplemented with a mask and protective glasses.
If the preparation comes into contact with the eyes, this may cause serious irritation. The eyes should
be rinsed immediately and thoroughly with water. If there is lasting irritation, a doctor should be
consulted. If the solution is spilled on the skin, rinse thoroughly with water.
Instructions for reconstitution (and further dilution, if performed)
The only approved diluent for reconstitution of gemcitabine sterile powder is sodium chloride 9 mg/ml
(0.9%) solution for injection (without preservative). Due to solubility considerations, the maximum
concentration for gemcitabine upon reconstitution is 40 mg/ml. Reconstitution at concentrations greater
than 40 mg/ml may result in incomplete dissolution and should be avoided.

4. Use aseptic technique during the reconstitution and any further dilution of gemcitabine for
intravenous infusion administration.

5. To reconstitute, add 5 ml of sterile sodium chloride 9 mg/ml (0.9%) solution for injection, without
preservative, to the 200 mg vial or 25 ml of sterile sodium chloride 9 mg/ml (0.9%) solution for
injection, without preservative, to the 1,000 mg vial. The total volume after reconstitution is
5.26 ml (200 mg vial) or 26.3 ml (1,000 mg vial) respectively. This yields a gemcitabine
concentration of 38 mg/ml, which includes accounting for the displacement volume of the
lyophilised powder. Shake to dissolve. Further dilution with sterile sodium chloride 9 mg/ml (0.9
%) solution for injection, without preservative can be done. Reconstituted solution is a clear
colourless to light straw-coloured solution.

6. Parenteral medicinal drugs should be inspected visually for particulate matter and discolouration
prior to administration. If particulate matter is observed, do not administer.

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

7 MARKETING AUTHORISATION HOLDER
Flynn Pharma Ltd
Alton House
4 Herbert Street
Dublin 2
Ireland

8 MARKETING AUTHORISATION NUMBER(S)
PL 13621/0039

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
31/07/2009

10 DATE OF REVISION OF THE TEXT
31/07/2009
SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT
Gemcitabine 200 mg powder for solution for infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
One vial contains gemcitabine hydrochloride equivalent to 200 mg gemcitabine.
After reconstitution, the solution contains 38 mg/ml of gemcitabine.
Excipients
Each 200 mg vial contains 3.5 mg (< 1 mmol) sodium.
For a full list of excipients see section 6.1.

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

4 CLINICAL PARTICULARS
4.1 Therapeutic indications
Gemcitabine is indicated for the treatment of locally advanced or metastatic bladder cancer in combination with cisplatin.
Gemcitabine is indicated for treatment of patients with locally advanced or metastatic adenocarcinoma of the pancreas.
Gemcitabine, in combination with cisplatin is indicated as first line treatment of patients with locally advanced or metastatic non-small cell lung cancer (NSCLC). Gemcitabine monotherapy can be considered in elderly patients or those with performance status 2.
Gemcitabine is indicated for the treatment of patients with locally advanced or metastatic epithelial ovarian carcinoma, in combination with carboplatin, in patients with relapsed disease following a recurrence-free interval of at least 6 months after platinum-based, first-line therapy.
Gemcitabine, in combination with paclitaxel, is indicated for the treatment of patients with unresectable, locally recurrent or metastatic breast cancer who have relapsed following adjuvant/neoadjuvant chemotherapy. Prior chemotherapy should have included an anthracycline unless clinically contraindicated.

4.2 Posology and method of administration
Gemcitabine should only be prescribed by a physician qualified in the use of anti-cancer chemotherapy.
Recommended posology
Bladder Cancer
Combination use
The recommended dose for gemcitabine is 1,000 mg/m², given by 30-minute infusion. The dose should be given on Days 1, 8, and 15 of each 28-day cycle in combination with cisplatin. Cisplatin is given at a recommended dose of 70 mg/m² on Day 1 following gemcitabine or Day 2 of each 28-day cycle. This 4-week cycle is then repeated. Dosage reduction with each cycle or within a cycle may be applied based upon the grade of toxicity experienced by the patient.
Pancreatic cancer
The recommended dose of gemcitabine is 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 with each cycle or within a cycle may be applied based upon the grade of toxicity experienced by the patient.
Non-small cell lung cancer
Monotherapy
The recommended dose of gemcitabine is 1,000 mg/m², given by 30-minute intravenous infusion. This should be repeated once weekly for 3 weeks, followed by a 1-week rest period. This 4-week cycle is then repeated. Dosage reduction with each cycle or within a cycle may be applied based upon the grade of toxicity experienced by the patient.
Combination use
The recommended dose for gemcitabine is 1,250 mg/m² body surface area given as a 30-minute intravenous infusion on Day 1 and 8 of the treatment cycle (21 days). Dosage reduction with each cycle or within a cycle may be applied based upon the grade of toxicity experienced by the patient. Cisplatin has been used at doses between 75-100 mg/m² once every 3 weeks.
**Breast Cancer**

**Combination use**

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

**Ovarian cancer**

**Combination use**

Gemcitabine in combination with carboplatin is recommended using gemcitabine 1,000 mg/m² administered on Days 1 and 8 of each 21-day cycle as a 30-minute intravenous infusion. After gemcitabine, carboplatin will be given on Day 1 consistent with a target Area under Curve (AUC) of 4.0 mg/ml·min. Dosage reduction with each cycle or within a cycle may be applied based upon the grade of toxicity experienced by the patient.

**Monitoring for toxicity and dose modification due to toxicity**

**Dose modification due to non-haematological toxicity**

Periodic physical examination and checks of renal and hepatic function should be made to detect non-haematological toxicity. Dosage reduction with each cycle or within a cycle may be applied based upon the grade of toxicity experienced by the patient. In general, for severe (Grade 3 or 4) non-haematological toxicity, except nausea/vomiting, therapy with gemcitabine should be withheld or decreased depending on the judgement of the treating physician. Doses should be withheld until toxicity has resolved in the opinion of the physician.

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

**Dose modification due to haematological toxicity**

**Initiation of a cycle**

For all indications, the patient must be monitored before each dose for platelet and granulocyte counts. Patients should have an absolute granulocyte count of at least 1,500 (x 10⁶/l) and platelet count of 100,000 (x 10⁶/l) prior to the initiation of a cycle.

**Within a cycle**

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

<table>
<thead>
<tr>
<th>Absolute granulocyte count(x 10⁶/l)</th>
<th>Platelet count (x 10⁶/l)</th>
<th>Percentage of standard dose of gemcitabine (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 1,000 and</td>
<td>&gt; 100,000</td>
<td>100</td>
</tr>
<tr>
<td>500-1,000 or</td>
<td>50,000-100,000</td>
<td>75</td>
</tr>
<tr>
<td>&lt; 500</td>
<td>&lt; 50,000</td>
<td>Omit dose*</td>
</tr>
</tbody>
</table>

*Treatment omitted will not be re-instated within a cycle before the absolute granulocyte count reaches at least 500 (x 10⁶/l) and the platelet count reaches 50,000 (x 10⁶/l).

<table>
<thead>
<tr>
<th>Absolute granulocyte count(x 10⁶/l)</th>
<th>Platelet count (x 10⁶/l)</th>
<th>Percentage of standard dose of gemcitabine (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 1,200 and</td>
<td>&gt; 75,000</td>
<td>100</td>
</tr>
<tr>
<td>1,000-&lt; 1,200 or</td>
<td>50,000-75,000</td>
<td>75</td>
</tr>
<tr>
<td>700-&lt; 1,000 and</td>
<td>≥ 50,000</td>
<td>50</td>
</tr>
<tr>
<td>&lt; 700</td>
<td>&lt; 50,000</td>
<td>Omit dose*</td>
</tr>
</tbody>
</table>

*Treatment omitted will not be re-instated within a cycle. Treatment will start on Day 1 of the next cycle once the absolute granulocyte count reaches at least 1,500 (x 10⁶/l) and the platelet count reaches 100,000 (x 10⁶/l).
Dose modification of gemcitabine within a cycle for ovarian cancer, given in combination with carboplatin

<table>
<thead>
<tr>
<th>Absolute granulocyte count (x 10^6/l)</th>
<th>Platelet count (x 10^6/l)</th>
<th>Percentage of standard dose of gemcitabine (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 1,500 and</td>
<td>≥ 100,000</td>
<td>100</td>
</tr>
<tr>
<td>1,000-1,500 or</td>
<td>75,000-100,000</td>
<td>50</td>
</tr>
<tr>
<td>&lt; 1,000 or</td>
<td>&lt; 75,000</td>
<td>Omit dose*</td>
</tr>
</tbody>
</table>

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

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

The gemcitabine dose should be reduced to 75% of the original cycle initiation dose, in the case of the following haematological toxicities:

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

Method of administration

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

For instructions on reconstitution, see section 6.6.

Special populations

*Patients with renal or hepatic impairment*

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

*Elderly population (> 65 years)*

Gemcitabine has been well tolerated in patients over the age of 65. There is no evidence to suggest that dose adjustments, other than those already recommended for all patients, are necessary in the elderly (see section 5.2).

*Paediatric population (< 18 years)*

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

4.3 Contraindications

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

Breast-feeding (see section 4.6).

4.4 Special warnings and precautions for use

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

Haematological toxicity

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

Patients receiving gemcitabine should be monitored prior to each dose for platelet, leucocyte and granulocyte counts. Suspension or modification of therapy should be considered when drug-induced bone marrow depression is detected (see section 4.2). However, myelosuppression is short lived and usually does not result in dose reduction and rarely in discontinuation.

Peripheral blood counts may continue to deteriorate after gemcitabine administration has been stopped. In patients with impaired bone marrow function, the treatment should be started with caution. As with other cytotoxic treatments, the risk of cumulative bone-marrow suppression must be considered when gemcitabine treatment is given together with other chemotherapy.

Hepatic insufficiency

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

Laboratory evaluation of renal and hepatic function (including virological tests) should be performed periodically.
Gemcitabine should be used with caution in patients with hepatic insufficiency or with impaired renal function as there is insufficient information from clinical studies to allow clear dose recommendation for this patient population (see section 4.2).

**Concomitant radiotherapy**

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

**Live vaccinations**

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

**Cardiovascular**

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

**Pulmonary**

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

**Renal**

Clinical findings consistent with the haemolytic uraemic syndrome (HUS) were rarely reported in patients receiving gemcitabine (see section 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. Renal failure may not be reversible with discontinuation of therapy and dialysis may be required.

**Fertility**

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

**Sodium**

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

### 4.5 Interaction with other medicinal products and other forms of interaction

No specific interaction studies have been performed (see section 5.2).

**Radiotherapy**

Concurrent (given together or ≤ 7 days apart) - toxicity associated with this multimodality therapy is dependent on many different factors, including dose of gemcitabine, frequency of gemcitabine administration, dose of radiation, radiotherapy planning technique, the target tissue, and target volume. Pre-clinical and clinical studies have shown that gemcitabine has radiosensitising activity. In a single trial, where gemcitabine at a dose of 1,000 mg/m² was administered concurrently for up to 6 consecutive weeks with therapeutic thoracic radiation to patients with non-small cell lung cancer, significant toxicity in the form of severe, and potentially life threatening mucositis, especially oesophagitis, and pneumonitis was observed, particularly in patients receiving large volumes of radiotherapy [median treatment volumes 4,795 cm³]. Studies done subsequently have suggested that it is feasible to administer gemcitabine at lower doses with concurrent radiotherapy with predictable toxicity, such as a phase II study in non-small cell lung cancer, where thoracic radiation doses of 66 Gy were applied concomitantly with an administration with gemcitabine (600 mg/m², four times) and cisplatin (80 mg/m² twice) during 6 weeks. The optimum regimen for safe administration of gemcitabine with therapeutic doses of radiation has not yet been determined in all tumour types.

Non-concurrent (given > 7 days apart) - analysis of the data does not indicate any enhanced toxicity when gemcitabine is administered more than 7 days before or after radiation, other than radiation recall. Data suggest that gemcitabine can be started after the acute effects of radiation have resolved or at least one week after radiation.

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

**Others**

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

Pregnancy

There are no adequate data from the use of gemcitabine in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3). Based on results from animal studies and the mechanism of action of gemcitabine, this substance should not be used during pregnancy unless clearly necessary. Women should be advised not to become pregnant during treatment with gemcitabine and to warn their attending physician immediately, should this occur after all.

Breast-feeding

It is not known whether gemcitabine is excreted in human milk and adverse effects on the suckling child cannot be excluded. Breast-feeding must be discontinued during gemcitabine therapy.

Fertility

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

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

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

Clinical trial data

Frequencies are defined as: Very common (≥ 1/10), Common (≥ 1/100 to < 1/10), Uncommon (≥ 1/1,000 to < 1/100), Rare (≥ 1/10,000 to < 1/1,000), Very Rare (< 1/10,000).

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

<table>
<thead>
<tr>
<th>System Organ Class</th>
<th>Frequency Grouping</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood and lymphatic system disorders</td>
<td>Very common</td>
</tr>
<tr>
<td></td>
<td>• Leucopaenia (Neutropaenia Grade 3 = 19.3%; Grade 4 = 6%).</td>
</tr>
<tr>
<td></td>
<td>Bone-marrow suppression is usually mild to moderate and mostly affects the granulocyte count (see section 4.2).</td>
</tr>
<tr>
<td></td>
<td>• Thrombocytopaenia</td>
</tr>
<tr>
<td></td>
<td>• Anaemia</td>
</tr>
<tr>
<td></td>
<td>Common</td>
</tr>
<tr>
<td></td>
<td>• Febrile neutropaenia</td>
</tr>
<tr>
<td></td>
<td>Very rare</td>
</tr>
<tr>
<td></td>
<td>• Thrombocytosis</td>
</tr>
<tr>
<td>Immune system disorders</td>
<td>Very rare</td>
</tr>
<tr>
<td></td>
<td>• Anaphylactoid reaction</td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td>Common</td>
</tr>
<tr>
<td></td>
<td>• Anorexia</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>Common</td>
</tr>
<tr>
<td>System Organ Class</td>
<td>Frequency Grouping</td>
</tr>
<tr>
<td>------------------------------------</td>
<td>--------------------------------------------------------</td>
</tr>
<tr>
<td></td>
<td>• Headache</td>
</tr>
<tr>
<td></td>
<td>• Insomnia</td>
</tr>
<tr>
<td></td>
<td>• Somnolence</td>
</tr>
<tr>
<td>Cardiac disorders</td>
<td>Rare</td>
</tr>
<tr>
<td></td>
<td>• Myocardial infarct</td>
</tr>
<tr>
<td>Vascular disorders</td>
<td>Rare</td>
</tr>
<tr>
<td></td>
<td>• Hypotension</td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td>Very common</td>
</tr>
<tr>
<td></td>
<td>• Dyspnoea - usually mild and passes rapidly without treatment</td>
</tr>
<tr>
<td></td>
<td>Common</td>
</tr>
<tr>
<td></td>
<td>• Cough</td>
</tr>
<tr>
<td></td>
<td>• Rhinitis</td>
</tr>
<tr>
<td></td>
<td>Uncommon</td>
</tr>
<tr>
<td></td>
<td>• Interstitial pneumonitis (see section 4.4)</td>
</tr>
<tr>
<td></td>
<td>• Bronchospasm - usually mild and transient but may require parenteral treatment</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>Very common</td>
</tr>
<tr>
<td></td>
<td>• Vomiting</td>
</tr>
<tr>
<td></td>
<td>• Nausea</td>
</tr>
<tr>
<td></td>
<td>Common</td>
</tr>
<tr>
<td></td>
<td>• Diarrhoea</td>
</tr>
<tr>
<td></td>
<td>• Stomatitis and ulceration of the mouth</td>
</tr>
<tr>
<td></td>
<td>• Constipation</td>
</tr>
<tr>
<td>Hepatobiliary disorders</td>
<td>Very common</td>
</tr>
<tr>
<td></td>
<td>• Elevation of liver transaminases (AST and ALT) and alkaline phosphatase</td>
</tr>
<tr>
<td></td>
<td>Common</td>
</tr>
<tr>
<td></td>
<td>• Increased bilirubin</td>
</tr>
<tr>
<td></td>
<td>Rare</td>
</tr>
<tr>
<td></td>
<td>• Increased gamma-glutamyl transferase (GGT)</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>Very common</td>
</tr>
<tr>
<td></td>
<td>• Allergic skin rash frequently associated with pruritus</td>
</tr>
<tr>
<td></td>
<td>• Alopecia</td>
</tr>
<tr>
<td></td>
<td>Common</td>
</tr>
<tr>
<td></td>
<td>• Itching</td>
</tr>
<tr>
<td></td>
<td>• Sweating</td>
</tr>
<tr>
<td></td>
<td>Rare</td>
</tr>
<tr>
<td></td>
<td>• Ulceration</td>
</tr>
<tr>
<td></td>
<td>• Vesicle and sore formation</td>
</tr>
<tr>
<td>System Organ Class</td>
<td>Frequency Grouping</td>
</tr>
<tr>
<td>---------------------------------------------------------</td>
<td>-----------------------------------------------------------------------------------</td>
</tr>
<tr>
<td></td>
<td>• Scaling</td>
</tr>
<tr>
<td></td>
<td>Very rare</td>
</tr>
<tr>
<td></td>
<td>Severe skin reactions, including desquamation and bullous skin eruptions</td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td>Common</td>
</tr>
<tr>
<td></td>
<td>Back pain</td>
</tr>
<tr>
<td></td>
<td>Myalgia</td>
</tr>
<tr>
<td>Renal and urinary disorders</td>
<td>Very common</td>
</tr>
<tr>
<td></td>
<td>Haematuria</td>
</tr>
<tr>
<td></td>
<td>Mild proteinuria</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td>Very common</td>
</tr>
<tr>
<td></td>
<td>Influenza-like symptoms - the most common symptoms are fever, headache, chills,</td>
</tr>
<tr>
<td></td>
<td>myalgia, asthenia and anorexia. Cough, rhinitis, malaise, perspiration, and</td>
</tr>
<tr>
<td></td>
<td>sleeping difficulties have also been reported.</td>
</tr>
<tr>
<td></td>
<td>Oedema/peripheral oedema - including facial oedema. Oedema is usually reversible</td>
</tr>
<tr>
<td></td>
<td>after stopping treatment.</td>
</tr>
<tr>
<td></td>
<td>Common</td>
</tr>
<tr>
<td></td>
<td>Fever</td>
</tr>
<tr>
<td></td>
<td>Asthenia</td>
</tr>
<tr>
<td></td>
<td>Chills</td>
</tr>
<tr>
<td></td>
<td>Rare</td>
</tr>
<tr>
<td></td>
<td>Injection site reactions - mainly mild in nature</td>
</tr>
<tr>
<td>Injury, poisoning and procedural complications</td>
<td>Radiation toxicity (see section 4.5).</td>
</tr>
</tbody>
</table>

Postmarketing experience (spontaneous reports) frequency not known (can’t be estimated from the available data)

**Nervous system disorders**  
Cerebrovascular accident

**Cardiac disorders**  
Arrhythmias, predominantly supraventricular in nature  
Heart failure

**Vascular disorders**  
Clinical signs of peripheral vasculitis and gangrene

**Respiratory, thoracic and mediastinal disorders**  
Pulmonary oedema  
Adult respiratory distress syndrome (see section 4.4)

**Gastrointestinal disorders**  
Ischaemic colitis

**Hepatobiliary disorders**  
Serious hepatotoxicity, including liver failure and death

**Skin and subcutaneous tissue disorders**  
Severe skin reactions, including desquamation and bullous skin eruptions, Lyell’s Syndrome, Steven-
Johnson Syndrome

**Renal and urinary disorders**
- Renal failure (see section 4.4)
- Haemolytic uraemic syndrome (see section 4.4)

**Injury, poisoning and procedural complications**
- Radiation recall

**Combination Use in Breast Cancer**
The frequency of Grade 3 and 4 haematological toxicities, particularly neutropaenia, 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 neutropaenia 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

<table>
<thead>
<tr>
<th></th>
<th>Paclitaxel arm (n=259)</th>
<th>Gemcitabine plus Paclitaxel arm (n=262)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Laboratory</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anaemia</td>
<td>5 (1.9)</td>
<td>1 (0.4)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Neutropaenia</td>
<td>11 (4.2)</td>
<td>17 (6.6)*</td>
</tr>
<tr>
<td><strong>Non-laboratory</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Febrile neutropaenia</td>
<td>3 (1.2)</td>
<td>0</td>
</tr>
<tr>
<td>Fatigue</td>
<td>3 (1.2)</td>
<td>1 (0.4)</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>5 (1.9)</td>
<td>0</td>
</tr>
<tr>
<td>Motor neuropathy</td>
<td>2 (0.8)</td>
<td>0</td>
</tr>
<tr>
<td>Sensory neuropathy</td>
<td>9 (3.5)</td>
<td>0</td>
</tr>
</tbody>
</table>

* Grade 4 neutropaenia 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.

### Grade 3 and 4 Adverse Events
#### MVAC versus Gemcitabine plus cisplatin

<table>
<thead>
<tr>
<th></th>
<th>MVAC (methotrexate, vinblastine, doxorubicin and cisplatin) arm (N=196)</th>
<th>Gemcitabine plus cisplatin arm (N=200)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Laboratory</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anaemia</td>
<td>30 (16)</td>
<td>47 (24)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>15 (8)</td>
<td>57 (29)</td>
</tr>
<tr>
<td><strong>Non-laboratory</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea and vomiting</td>
<td>37 (19)</td>
<td>44 (22)</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>15 (8)</td>
<td>6 (3)</td>
</tr>
<tr>
<td>Infection</td>
<td>19 (10)</td>
<td>4 (2)</td>
</tr>
<tr>
<td>Stomatitis</td>
<td>34 (18)</td>
<td>2 (1)</td>
</tr>
</tbody>
</table>

### Grade 3 and 4 Adverse Events
#### Carboplatin versus Gemcitabine plus carboplatin

<table>
<thead>
<tr>
<th></th>
<th>Carboplatin arm (N=174)</th>
<th>Gemcitabine plus carboplatin arm (N=175)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Laboratory</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anaemia</td>
<td>10 (5.7)</td>
<td>39 (22.3)</td>
</tr>
<tr>
<td>Neutropaenia</td>
<td>19 (10.9)</td>
<td>73 (41.7)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>18 (10.3)</td>
<td>53 (30.3)</td>
</tr>
</tbody>
</table>
4.9 Overdose
There is no known antidote for overdose of gemcitabine. Doses as high as 5,700 mg/m² have been administered by intravenous infusion over 30 minutes every 2 weeks with clinically acceptable toxicity. In the event of suspected overdose, the patient should be monitored with appropriate blood counts and receive supportive therapy, as necessary.

5 PHARMACOLOGICAL PROPERTIES

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

Cytotoxic activity in cell cultures
Gemcitabine shows significant cytotoxic effects against a variety of cultured murine and human tumour cells. Its action is phase-specific such that gemcitabine primarily kills cells that are undergoing DNA synthesis (S-phase) and, under certain circumstances, blocks the progression of cells at the junction of the G1/S-phase boundary. In vitro, the cytotoxic effect of gemcitabine is dependent on both concentration and time.

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

Mechanism of action
Cellular metabolism and mechanism of action: gemcitabine (dFdC), which is a pyrimidine antimetabolite, is metabolised intracellularly by nucleoside kinase to the active diphosphate (dFdCDP) and triphosphate (dFdCTP) nucleosides. The cytotoxic effect of gemcitabine is due to inhibition of DNA synthesis by two mechanisms of action by dFdCDP and dFdCTP. First, dFdCDP inhibits ribonucleotide reductase, which is uniquely responsible for catalysing the reactions that produce deoxynucleoside triphosphates (dCTP) for DNA synthesis. Inhibition of this enzyme by dFdCDP reduces the concentration of deoxynucleosides in general and, in particular, dCTP. Second, dFdCTP competes with dCTP for incorporation into DNA (self-potentiation). Likewise, a small amount of gemcitabine may also be incorporated into RNA. Thus, the reduced intracellular concentration of dCTP potentiates the incorporation of dFdCTP into DNA. DNA polymerase epsilon lacks the ability to eliminate gemcitabine and to repair the growing DNA strands. After gemcitabine is incorporated into DNA, one additional nucleotide is added to the growing DNA strands. After this addition there is essentially a complete inhibition in further DNA synthesis (masked chain termination). After incorporation into DNA, gemcitabine appears to induce the programmed cell death process known as apoptosis.

Clinical data

Bladder cancer
A randomised phase III study of 405 patients with advanced or metastatic urothelial transitional cell carcinoma showed no difference between the two treatment arms, gemcitabine/cisplatin versus methotrexate/vinblastine/adriamycin/cisplatin (MVAC), in terms of median survival (12.8 and 14.8 months respectively, p=0.547), time to disease progression (7.4 and 7.6 months respectively, p=0.842) and response rate (49.4% and 45.7% respectively, p=0.512). However, the combination of gemcitabine and cisplatin had a better toxicity profile than MVAC.

Pancreatic cancer
In a randomised phase III study of 126 patients with advanced or metastatic pancreatic cancer, gemcitabine showed a statistically significant higher clinical benefit response rate than 5-fluorouracil (23.8% and 4.8% respectively, p=0.0022). Also, a statistically significant prolongation of the time to progression from 0.9 to 2.3 months (log-rank p<0.0002) and a statistically significant prolongation of median survival from 4.4 to 5.7 months (log-rank p<0.0024) was observed in patients treated with gemcitabine compared to patients treated with 5-fluorouracil.

<p>| | | | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Leucopaenia</td>
<td>11 (6.3)</td>
<td>1 (0.6)</td>
<td>84 (48.0)</td>
<td>9 (5.1)</td>
</tr>
<tr>
<td>Non-laboratory</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Haemorrhage</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>3 (1.8)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Febrile neutropaenia</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>2 (1.1)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Infection without neutropaenia</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>1 (0.6)</td>
</tr>
</tbody>
</table>

Sensory neuropathy was also more frequent in the combination arm than with single agent carboplatin.
**Non-small cell lung cancer**

In a randomised phase III study of 522 patients with inoperable, locally advanced or metastatic NSCLC, gemcitabine in combination with cisplatin showed a statistically significant higher response rate than cisplatin alone (31.0% and 12.0%, respectively, p< 0.0001). A statistically significant prolongation of the time to progression, from 3.7 to 5.6 months (log-rank p< 0.0012) and a statistically significant prolongation of median survival from 7.6 months to 9.1 months (log-rank p< 0.004) was observed in patients treated with gemcitabine/cisplatin compared to patients treated with cisplatin.

In another randomised phase III study of 135 patients with stage IIIIB or IV NSCLC, a combination of gemcitabine and cisplatin showed a statistically significant higher response rate than a combination of cisplatin and etoposide (40.6% and 21.2%, respectively, p=0.025). A statistically significant prolongation of the time to progression, from 4.3 to 6.9 months (p=0.014) was observed in patients treated with gemcitabine/cisplatin compared to patients treated with etoposide/cisplatin.

In both studies it was found that tolerability was similar in the two treatment arms.

**Ovarian carcinoma**

In a randomised phase III study, 356 patients with advanced epithelial ovarian carcinoma who had relapsed at least 6 months after completing platinum based therapy were randomised to therapy with gemcitabine and carboplatin (GCb), or carboplatin (Cb). A statistically significant prolongation of the time to progression of disease, from 5.8 to 8.6 months (log-rank p=0.0038) was observed in the patients treated with GCb compared to patients treated with Cb. Differences in response rate of 47.2% in the GCb arm versus 30.9% in the Cb arm (p=0.0016) and median survival 18 months (GCb) versus 17.3 (Cb) (p=0.73) favoured the GCb arm.

**Breast cancer**

In a randomised phase III study of 529 patients with inoperable, locally recurrent or metastatic breast cancer with relapse after adjuvant/neoadjuvant chemotherapy, gemcitabine in combination with paclitaxel showed a statistically significant prolongation of time to documented disease progression from 3.98 to 6.14 months (log-rank p=0.0002) in patients treated with gemcitabine/paclitaxel compared to patients treated with paclitaxel. After 377 deaths, the overall survival was 18.6 months versus 15.8 months (log rank p=0.0489, HR 0.82) in patients treated with gemcitabine/paclitaxel compared to patients treated with paclitaxel and the overall response rate was 41.4% and 26.2% respectively (p= 0.0002).

### 5.2 Pharmacokinetic properties

The pharmacokinetics of gemcitabine have been examined in 353 patients in seven studies. The 121 women and 232 men ranged in age from 29 to 79 years. Of these patients, approximately 45% had non-small cell lung cancer and 35% were diagnosed with pancreatic cancer. The following pharmacokinetic parameters were obtained for doses ranging from 500 to 2,592 mg/m² that were infused from 0.4 to 1.2 hours.

Peak plasma concentrations (obtained within 5 minutes of the end of the infusion) were 3.2 to 45.5 µg/ml. Plasma concentrations of the parent compound following a dose of 1,000 mg/m²/30-minutes are greater than 5 µg/ml for approximately 30 minutes after the end of the infusion and greater than 0.4 µg/ml for an additional hour.

**Distribution**

The volume of distribution of the central compartment was 12.4 l/m² for women and 17.5 l/m² for men (inter-individual variability was 91.9%). The volume of distribution of the peripheral compartment: 47.4 l/m². The volume of the peripheral compartment was not sensitive to gender. The plasma protein binding was considered to be negligible.

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

**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.

**Excretion**

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 was 2 to 7 l/hr/m².

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

**dFdCTP kinetics**

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

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

**dFdU kinetics**

Peak plasma concentrations (3-15 minutes after end of 30-minute infusion, 1,000 mg/m²): 28-52 µg/ml.

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

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

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

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

Mean steady-state volume of distribution (Vss): 150 l/m² (range 96-228 l/m²).

Tissue distribution: extensive.

Mean apparent clearance: 2.5 l/hr/m² (range 1.4-4 l/hr/m²).

Urinary excretion: all.

Gemcitabine and paclitaxel combination therapy:

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

Gemcitabine and carboplatin combination therapy

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

Renal impairment

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

5.3 Preclinical safety data

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

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

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

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

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Gemcitabine 200 mg contains:

- Mannitol (E421)
- Sodium acetate (E262)
- Hydrochloric acid (E507) (for pH adjustment)
- Sodium hydroxide (E524) (for pH adjustment)

6.2 Incompatibilities

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

6.3 Shelf life

Unopened vials: 2 years.

Reconstituted solution:

Chemical and physical in-use stability has been demonstrated for 24 hours at 20-25°C. From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be
longer than 24 hours at room temperature, unless reconstitution (and further dilution, if applicable) has taken place in controlled and validated aseptic conditions. Solutions of reconstituted gemcitabine should not be refrigerated, as crystallisation may occur.

6.4 Special precautions for storage
Unopened vials: this medicinal product does not require any special storage conditions. For storage conditions of the reconstituted medicinal product see section 6.3.

6.5 Nature and contents of container
Type I clear glass vials, stoppered with a grey bromobutyl rubber stopper and sealed with an aluminium flip-off cap, combined with a polypropylene disk.
Each pack contains 1 vial.

6.6 Special precautions for disposal

Handling
The normal safety precautions for cytostatic agents must be observed when preparing and disposing of the infusion solution. Handling of the solution for infusion should be done in a safety box and protective coats and gloves should be used. If no safety box is available, the equipment should be supplemented with a mask and protective glasses.

If the preparation comes into contact with the eyes, this may cause serious irritation. The eyes should be rinsed immediately and thoroughly with water. If there is lasting irritation, a doctor should be consulted. If the solution is spilled on the skin, rinse thoroughly with water.

Instructions for reconstitution (and further dilution, if performed)
The only approved diluent for reconstitution of gemcitabine sterile powder is sodium chloride 9 mg/ml (0.9%) solution for injection (without preservative). Due to solubility considerations, the maximum concentration for gemcitabine upon reconstitution is 40 mg/ml. Reconstitution at concentrations greater than 40 mg/ml may result in incomplete dissolution and should be avoided.

7. Use aseptic technique during the reconstitution and any further dilution of gemcitabine for intravenous infusion administration.

8. To reconstitute, add 5 ml of sterile sodium chloride 9 mg/ml (0.9%) solution for injection, without preservative, to the 200 mg vial or 25 ml of sterile sodium chloride 9 mg/ml (0.9%) solution for injection, without preservative, to the 1,000 mg vial. The total volume after reconstitution is 5.26 ml (200 mg vial) or 26.3 ml (1,000 mg vial) respectively. This yields a gemcitabine concentration of 38 mg/ml, which includes accounting for the displacement volume of the lyophilised powder. Shake to dissolve. Further dilution with sterile sodium chloride 9 mg/ml (0.9 %) solution for injection, without preservative can be done. Reconstituted solution is a clear colourless to light straw-coloured solution.

9. Parenteral medicinal drugs should be inspected visually for particulate matter and discolouration prior to administration. If particulate matter is observed, do not administer.

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

1 NAME OF THE MEDICINAL PRODUCT
Gemcitabine 1 g powder for solution for infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
One vial contains gemcitabine hydrochloride equivalent to 1,000 mg gemcitabine.
After reconstitution, the solution contains 38 mg/ml of gemcitabine.
Excipients
Each 1,000 mg vial contains 17.5 mg (< 1 mmol) sodium.
For a full list of excipients see section 6.1.

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

4 CLINICAL PARTICULARS
4.1 Therapeutic indications
Gemcitabine is indicated for the treatment of locally advanced or metastatic bladder cancer in combination with cisplatin.
Gemcitabine is indicated for treatment of patients with locally advanced or metastatic adenocarcinoma of the pancreas.
Gemcitabine, in combination with cisplatin is indicated as first line treatment of patients with locally advanced or metastatic non-small cell lung cancer (NSCLC). Gemcitabine monotherapy can be considered in elderly patients or those with performance status 2.
Gemcitabine is indicated for the treatment of patients with locally advanced or metastatic epithelial ovarian carcinoma, in combination with carboplatin, in patients with relapsed disease following a recurrence-free interval of at least 6 months after platinum-based, first-line therapy.
Gemcitabine, in combination with paclitaxel, is indicated for the treatment of patients with unresectable, locally recurrent or metastatic breast cancer who have relapsed following adjuvant/neoadjuvant chemotherapy. Prior chemotherapy should have included an anthracycline unless clinically contraindicated.

4.2 Posology and method of administration
Gemcitabine should only be prescribed by a physician qualified in the use of anti-cancer chemotherapy.
Recommended posology

Bladder Cancer
Combination use
The recommended dose for gemcitabine is 1,000 mg/m², given by 30-minute infusion. The dose should be given on Days 1, 8, and 15 of each 28-day cycle in combination with cisplatin. Cisplatin is given at a recommended dose of 70 mg/m² on Day 1 following gemcitabine or Day 2 of each 28-day cycle. This 4-week cycle is then repeated. Dosage reduction with each cycle or within a cycle may be applied based upon the grade of toxicity experienced by the patient.

Pancreatic cancer
The recommended dose of gemcitabine is 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 with each cycle or within a cycle may be applied based upon the grade of toxicity experienced by the patient.

Non-small cell lung cancer
Monotherapy
The recommended dose of gemcitabine is 1,000 mg/m², given by 30-minute intravenous infusion. This should be repeated once weekly for 3 weeks, followed by a 1-week rest period. This 4-week cycle is then repeated. Dosage reduction with each cycle or within a cycle may be applied based upon the grade of toxicity experienced by the patient.
Combination use
The recommended dose for gemcitabine is 1,250 mg/m² body surface area given as a 30-minute intravenous infusion on Day 1 and 8 of the treatment cycle (21 days). Dosage reduction with each cycle or within a cycle may be applied based upon the grade of toxicity experienced by the patient. Cisplatin has been used at doses between 75-100 mg/m² once every 3 weeks.
**Breast Cancer**

**Combination use**

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

**Ovarian cancer**

**Combination use**

Gemcitabine in combination with carboplatin is recommended using gemcitabine 1,000 mg/m² administered on Days 1 and 8 of each 21-day cycle as a 30-minute intravenous infusion. After gemcitabine, carboplatin will be given on Day 1 consistent with a target Area under Curve (AUC) of 4.0 mg/ml·min. Dosage reduction with each cycle or within a cycle may be applied based upon the grade of toxicity experienced by the patient.

**Monitoring for toxicity and dose modification due to toxicity**

**Dose modification due to non-haematological toxicity**

Periodic physical examination and checks of renal and hepatic function should be made to detect non-haematological toxicity. Dosage reduction with each cycle or within a cycle may be applied based upon the grade of toxicity experienced by the patient. In general, for severe (Grade 3 or 4) non-haematological toxicity, except nausea/vomiting, therapy with gemcitabine should be withheld or decreased depending on the judgement of the treating physician. Doses should be withheld until toxicity has resolved in the opinion of the physician.

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

**Dose modification due to haematological toxicity**

**Initiation of a cycle**

For all indications, the patient must be monitored before each dose for platelet and granulocyte counts. Patients should have an absolute granulocyte count of at least 1,500 (x 10⁶/l) and platelet count of 100,000 (x 10⁶/l) prior to the initiation of a cycle.

**Within a cycle**

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

### Dose modification of gemcitabine within a cycle for bladder cancer, NSCLC and pancreatic cancer, given in monotherapy or in combination with cisplatin

<table>
<thead>
<tr>
<th>Absolute granulocyte count (x 10⁶/l)</th>
<th>Platelet count (x 10⁶/l)</th>
<th>Percentage of standard dose of gemcitabine (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 1,000 and 500-1,000 or &lt; 500</td>
<td>&gt; 100,000 or 50,000-100,000 or &lt; 50,000</td>
<td>100 or 75 or Omit dose*</td>
</tr>
</tbody>
</table>

*Treatment omitted will not be re-instated within a cycle before the absolute granulocyte count reaches at least 500 (x 10⁶/l) and the platelet count reaches 50,000 (x 10⁶/l).

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

<table>
<thead>
<tr>
<th>Absolute granulocyte count (x 10⁶/l)</th>
<th>Platelet count (x 10⁶/l)</th>
<th>Percentage of standard dose of gemcitabine (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 1,200 and 1,000-&lt; 1,200 or 700-&lt; 1,000</td>
<td>&gt; 75,000 or 50,000-75,000 or ≥ 50,000</td>
<td>100 or 75 or 50</td>
</tr>
</tbody>
</table>

*Treatment omitted will not be re-instated within a cycle. Treatment will start on Day 1 of the next cycle once the absolute granulocyte count reaches at least 1,500 (x 10⁶/l) and the platelet count reaches 100,000 (x 10⁶/l).
**Dose modification of gemcitabine within a cycle for ovarian cancer, given in combination with carboplatin**

<table>
<thead>
<tr>
<th>Absolute granulocyte count (x 10⁶/l)</th>
<th>Platelet count (x 10⁶/l)</th>
<th>Percentage of standard dose of gemcitabine (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 1,500 and ≥ 100,000</td>
<td></td>
<td>100</td>
</tr>
<tr>
<td>1,000-1,500 or 75,000-100,000</td>
<td></td>
<td>50</td>
</tr>
<tr>
<td>&lt; 1,000 or &lt; 75,000</td>
<td></td>
<td>Omit dose*</td>
</tr>
</tbody>
</table>

*Treatment omitted will not be re-instated within a cycle. Treatment will start on Day 1 of the next cycle once the absolute granulocyte count reaches at least 1,500 (x 10⁶/l) and the platelet count reaches 100,000 (x 10⁶/l).

**Dose modifications due to haematological toxicity in subsequent cycles, for all indications**

The gemcitabine dose should be reduced to 75% of the original cycle initiation dose, in the case of the following haematological toxicities:
- Absolute granulocyte count < 500 x 10⁶/l for more than 5 days
- Absolute granulocyte count < 100 x 10⁶/l for more than 3 days
- Febrile neutropaenia
- Platelets < 25,000 x 10⁶/l
- Cycle delay of more than 1 week due to toxicity

**Method of administration**

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

For instructions on reconstitution, see section 6.6.

**Special populations**

**Patients with renal or hepatic impairment**

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

**Elderly population (> 65 years)**

Gemcitabine has been well tolerated in patients over the age of 65. There is no evidence to suggest that dose adjustments, other than those already recommended for all patients, are necessary in the elderly (see section 5.2).

**Paediatric population (< 18 years)**

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

### 4.3 Contraindications

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

Breast-feeding (see section 4.6).

### 4.4 Special warnings and precautions for use

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

**Haematological toxicity**

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

Patients receiving gemcitabine should be monitored prior to each dose for platelet, leucocyte and granulocyte counts. Suspension or modification of therapy should be considered when drug-induced bone marrow depression is detected (see section 4.2). However, myelosuppression is short lived and usually does not result in dose reduction and rarely in discontinuation.

Peripheral blood counts may continue to deteriorate after gemcitabine administration has been stopped.

In patients with impaired bone marrow function, the treatment should be started with caution. As with other cytotoxic treatments, the risk of cumulative bone-marrow suppression must be considered when gemcitabine treatment is given together with other chemotherapy.

**Hepatic insufficiency**

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

Laboratory evaluation of renal and hepatic function (including virological tests) should be performed periodically.
Gemcitabine should be used with caution in patients with hepatic insufficiency or with impaired renal function as there is insufficient information from clinical studies to allow clear dose recommendation for this patient population (see section 4.2).

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

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

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

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

**Renal**
Clinical findings consistent with the haemolytic uraemic syndrome (HUS) were rarely reported in patients receiving gemcitabine (see section 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. Renal failure may not be reversible with discontinuation of therapy and dialysis may be required.

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

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

### 4.5 Interaction with other medicinal products and other forms of interaction

No specific interaction studies have been performed (see section 5.2).

**Radiotherapy**
Concurrent (given together or ≤ 7 days apart) - toxicity associated with this multimodality therapy is dependent on many different factors, including dose of gemcitabine, frequency of gemcitabine administration, dose of radiation, radiotherapy planning technique, the target tissue, and target volume. Pre-clinical and clinical studies have shown that gemcitabine has radiosensitising activity. In a single trial, where gemcitabine at a dose of 1,000 mg/m² was administered concurrently for up to 6 consecutive weeks with therapeutic thoracic radiation to patients with non-small cell lung cancer, significant toxicity in the form of severe, and potentially life threatening mucositis, especially oesophagitis, and pneumonitis was observed, particularly in patients receiving large volumes of radiotherapy [median treatment volumes 4,795 cm³]. Studies done subsequently have suggested that it is feasible to administer gemcitabine at lower doses with concurrent radiotherapy with predictable toxicity, such as a phase II study in non-small cell lung cancer, where thoracic radiation doses of 66 Gy were applied concomitantly with an administration with gemcitabine (600 mg/m², four times) and cisplatin (80 mg/m² twice) during 6 weeks. The optimum regimen for safe administration of gemcitabine with therapeutic doses of radiation has not yet been determined in all tumour types.

Non-concurrent (given > 7 days apart) - analysis of the data does not indicate any enhanced toxicity when gemcitabine is administered more than 7 days before or after radiation, other than radiation recall. Data suggest that gemcitabine can be started after the acute effects of radiation have resolved or at least one week after radiation.

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

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

Pregnancy

There are no adequate data from the use of gemcitabine in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3). Based on results from animal studies and the mechanism of action of gemcitabine, this substance should not be used during pregnancy unless clearly necessary. Women should be advised not to become pregnant during treatment with gemcitabine and to warn their attending physician immediately, should this occur after all.

Breast-feeding

It is not known whether gemcitabine is excreted in human milk and adverse effects on the suckling child cannot be excluded. Breast-feeding must be discontinued during gemcitabine therapy.

Fertility

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

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

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

Clinical trial data

Frequencies are defined as: Very common (≥ 1/10), Common (≥ 1/100 to < 1/10), Uncommon (≥ 1/1,000 to < 1/100), Rare (≥ 1/10,000 to < 1/1,000), Very Rare (< 1/10,000).

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

<table>
<thead>
<tr>
<th>System Organ Class</th>
<th>Frequency Grouping</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood and lymphatic system disorders</td>
<td>Very common</td>
</tr>
<tr>
<td></td>
<td>• Leucopaenia (Neutropaenia Grade 3 = 19.3%; Grade 4 = 6%).</td>
</tr>
<tr>
<td></td>
<td>Bone-marrow suppression is usually mild to moderate and mostly affects the granulocyte count (see section 4.2).</td>
</tr>
<tr>
<td></td>
<td>• Thrombocytopenia</td>
</tr>
<tr>
<td></td>
<td>• Anaemia</td>
</tr>
<tr>
<td>Common</td>
<td>Common</td>
</tr>
<tr>
<td></td>
<td>• Febrile neutropaenia</td>
</tr>
<tr>
<td></td>
<td>Very rare</td>
</tr>
<tr>
<td></td>
<td>• Thrombocytosis</td>
</tr>
<tr>
<td>Immune system disorders</td>
<td>Very rare</td>
</tr>
<tr>
<td></td>
<td>• Anaphylactoid reaction</td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td>Common</td>
</tr>
<tr>
<td></td>
<td>• Anorexia</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>Common</td>
</tr>
<tr>
<td>System Organ Class</td>
<td>Frequency Grouping</td>
</tr>
<tr>
<td>--------------------------------------------------</td>
<td>-----------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Headache</td>
<td>•</td>
</tr>
<tr>
<td>Insomnia</td>
<td>•</td>
</tr>
<tr>
<td>Somnolence</td>
<td>•</td>
</tr>
<tr>
<td>Cardiac disorders</td>
<td>Rare</td>
</tr>
<tr>
<td>Myocardial infarct</td>
<td>•</td>
</tr>
<tr>
<td>Vascular disorders</td>
<td>Rare</td>
</tr>
<tr>
<td>Hypotension</td>
<td>•</td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td>Very common</td>
</tr>
<tr>
<td>Dyspnoea - usually mild and passes rapidly without treatment</td>
<td>•</td>
</tr>
<tr>
<td>Common</td>
<td>Cough</td>
</tr>
<tr>
<td>Rhinitis</td>
<td>•</td>
</tr>
<tr>
<td>Uncommon</td>
<td>Interstitial pneumonitis (see section 4.4)</td>
</tr>
<tr>
<td>Bronchospasm - usually mild and transient but may require parenteral treatment</td>
<td>•</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>Very common</td>
</tr>
<tr>
<td>Vomiting</td>
<td>•</td>
</tr>
<tr>
<td>Nausea</td>
<td>•</td>
</tr>
<tr>
<td>Common</td>
<td>Diarrhoea</td>
</tr>
<tr>
<td>Stomatitis and ulceration of the mouth</td>
<td>•</td>
</tr>
<tr>
<td>Constipation</td>
<td>•</td>
</tr>
<tr>
<td>Hepatobiliary disorders</td>
<td>Very common</td>
</tr>
<tr>
<td>Elevation of liver transaminases (AST and ALT) and alkaline phosphatase</td>
<td>•</td>
</tr>
<tr>
<td>Common</td>
<td>Increased bilirubin</td>
</tr>
<tr>
<td>Rare</td>
<td>Increased gamma-glutamyl transferase (GGT)</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>Very common</td>
</tr>
<tr>
<td>Allergic skin rash frequently associated with pruritus</td>
<td>•</td>
</tr>
<tr>
<td>Alopecia</td>
<td>•</td>
</tr>
<tr>
<td>Common</td>
<td>Itching</td>
</tr>
<tr>
<td>Sweating</td>
<td>•</td>
</tr>
<tr>
<td>Rare</td>
<td>Ulceration</td>
</tr>
<tr>
<td>Ulceration</td>
<td>•</td>
</tr>
<tr>
<td>Vesicle and sore formation</td>
<td>•</td>
</tr>
<tr>
<td>System Organ Class</td>
<td>Frequency Grouping</td>
</tr>
<tr>
<td>------------------------------------------------</td>
<td>--------------------------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>System Organ Class</td>
<td>Frequency Grouping</td>
</tr>
<tr>
<td>• Scaling</td>
<td>Very rare</td>
</tr>
<tr>
<td>• Severe skin reactions, including desquamation</td>
<td>Very rare</td>
</tr>
<tr>
<td>Renal and urinary disorders</td>
<td>Very common</td>
</tr>
<tr>
<td>• Back pain</td>
<td>Very common</td>
</tr>
<tr>
<td>• Myalgia</td>
<td>Very common</td>
</tr>
<tr>
<td>Renal and urinary disorders</td>
<td>Very common</td>
</tr>
<tr>
<td>• Haematuria</td>
<td>Very common</td>
</tr>
<tr>
<td>• Mild proteinuria</td>
<td>Very common</td>
</tr>
<tr>
<td>General disorders and administration site</td>
<td>Very common</td>
</tr>
<tr>
<td>conditions</td>
<td>Influenza-like symptoms - the most common symptoms are fever, headache, chills, myalgia, asthenia and anorexia. Cough, rhinitis, malaise, perspiration, and sleeping difficulties have also been reported.</td>
</tr>
<tr>
<td>Injury, poisoning and procedural complications</td>
<td>Rare</td>
</tr>
<tr>
<td>• Injection site reactions - mainly mild in</td>
<td>Rare</td>
</tr>
<tr>
<td>nature</td>
<td>Radiation toxicity (see section 4.5).</td>
</tr>
</tbody>
</table>

**System Organ Class**

<table>
<thead>
<tr>
<th>System Organ Class</th>
<th>Frequency Grouping</th>
</tr>
</thead>
<tbody>
<tr>
<td>System Organ Class</td>
<td>Frequency Grouping</td>
</tr>
<tr>
<td>• Scaling</td>
<td>Very rare</td>
</tr>
<tr>
<td>• Severe skin reactions, including desquamation</td>
<td>Very rare</td>
</tr>
</tbody>
</table>

**System Organ Class**

<table>
<thead>
<tr>
<th>System Organ Class</th>
<th>Frequency Grouping</th>
</tr>
</thead>
<tbody>
<tr>
<td>System Organ Class</td>
<td>Frequency Grouping</td>
</tr>
<tr>
<td>• Scaling</td>
<td>Very rare</td>
</tr>
<tr>
<td>• Severe skin reactions, including desquamation</td>
<td>Very rare</td>
</tr>
</tbody>
</table>

**Postmarketing experience (spontaneous reports) frequency not known (can’t be estimated from the available data)**

**Nervous system disorders**

Cerebrovascular accident

**Cardiac disorders**

Arrhythmias, predominantly supraventricular in nature

Heart failure

**Vascular disorders**

Clinical signs of peripheral vasculitis and gangrene

**Respiratory, thoracic and mediastinal disorders**

Pulmonary oedema

Adult respiratory distress syndrome (see section 4.4)

**Gastrointestinal disorders**

Ischaemic colitis

**Hepatobiliary disorders**

Serious hepatotoxicity, including liver failure and death

**Skin and subcutaneous tissue disorders**

Severe skin reactions, including desquamation and bullous skin eruptions, Lyell’s Syndrome, Steven-
**Johnson Syndrome**

*Renal and urinary disorders*
Renal failure (see section 4.4)
Haemolytic uraemic syndrome (see section 4.4)

*Injury, poisoning and procedural complications*
Radiation recall

**Combination Use in Breast Cancer**
The frequency of Grade 3 and 4 haematological toxicities, particularly neutropaenia, 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 neutropaenia 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**

<table>
<thead>
<tr>
<th>Grade 3</th>
<th>Grade 4</th>
<th>Grade 3</th>
<th>Grade 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Laboratory</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anaemia</td>
<td>5 (1.9)</td>
<td>1 (0.4)</td>
<td>15 (5.7)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>0</td>
<td>0</td>
<td>14 (5.3)</td>
</tr>
<tr>
<td>Neutropaenia</td>
<td>11 (4.2)</td>
<td>17 (6.6)*</td>
<td>82 (31.3)</td>
</tr>
<tr>
<td>Non-laboratory</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Febrile neutropaenia</td>
<td>3 (1.2)</td>
<td>0</td>
<td>12 (4.6)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>3 (1.2)</td>
<td>1 (0.4)</td>
<td>15 (5.7)</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>5 (1.9)</td>
<td>0</td>
<td>8 (3.1)</td>
</tr>
<tr>
<td>Motor neuropathy</td>
<td>2 (0.8)</td>
<td>0</td>
<td>6 (2.3)</td>
</tr>
<tr>
<td>Sensory neuropathy</td>
<td>9 (3.5)</td>
<td>0</td>
<td>14 (5.3)</td>
</tr>
</tbody>
</table>

* Grade 4 neutropaenia lasting for more than 7 days occurred in 12.6% of patients in the combination arm and 5.0% of patients in the paclitaxel arm.

**Combination use in bladder cancer**

### Grade 3 and 4 Adverse Events
**MVAC versus Gemcitabine plus cisplatin**

<table>
<thead>
<tr>
<th>Grade 3</th>
<th>Grade 4</th>
<th>Grade 3</th>
<th>Grade 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Laboratory</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anaemia</td>
<td>30 (16)</td>
<td>4 (2)</td>
<td>47 (24)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>15 (8)</td>
<td>25 (13)</td>
<td>57 (29)</td>
</tr>
<tr>
<td>Non-laboratory</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea and vomiting</td>
<td>37 (19)</td>
<td>3 (2)</td>
<td>44 (22)</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>15 (8)</td>
<td>1 (1)</td>
<td>6 (3)</td>
</tr>
<tr>
<td>Infection</td>
<td>19 (10)</td>
<td>10 (5)</td>
<td>4 (2)</td>
</tr>
<tr>
<td>Stomatitis</td>
<td>34 (18)</td>
<td>8 (4)</td>
<td>2 (1)</td>
</tr>
</tbody>
</table>

**Combination use in ovarian cancer**

### Grade 3 and 4 Adverse Events
**Carboplatin versus Gemcitabine plus carboplatin**

<table>
<thead>
<tr>
<th>Grade 3</th>
<th>Grade 4</th>
<th>Grade 3</th>
<th>Grade 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Laboratory</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anaemia</td>
<td>10 (5.7)</td>
<td>4 (2.3)</td>
<td>39 (22.3)</td>
</tr>
<tr>
<td>Neutropaenia</td>
<td>19 (10.9)</td>
<td>2 (1.1)</td>
<td>73 (41.7)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>18 (10.3)</td>
<td>2 (1.1)</td>
<td>53 (30.3)</td>
</tr>
<tr>
<td>Sensory neuropathy was also more frequent in the combination arm than with single agent carboplatin.</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

4.9 Overdose
There is no known antidote for overdose of gemcitabine. Doses as high as 5,700 mg/m² have been administered by intravenous infusion over 30 minutes every 2 weeks with clinically acceptable toxicity. In the event of suspected overdose, the patient should be monitored with appropriate blood counts and receive supportive therapy, as necessary.

5 PHARMACOLOGICAL PROPERTIES

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

Cytotoxic activity in cell cultures
Gemcitabine shows significant cytotoxic effects against a variety of cultured murine and human tumour cells. Its action is phase-specific such that gemcitabine primarily kills cells that are undergoing DNA synthesis (S-phase) and, under certain circumstances, blocks the progression of cells at the junction of the G₁/S-phase boundary. In vitro, the cytotoxic effect of gemcitabine is dependent on both concentration and time.

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

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

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

Clinical data

Bladder cancer
A randomised phase III study of 405 patients with advanced or metastatic urothelial transitional cell carcinoma showed no difference between the two treatment arms, gemcitabine/cisplatin versus methotrexate/vinblastine/adriamycin/cisplatin (MVAC), in terms of median survival (12.8 and 14.8 months respectively, p=0.547), time to disease progression (7.4 and 7.6 months respectively, p=0.842) and response rate (49.4% and 45.7% respectively, p=0.512). However, the combination of gemcitabine and cisplatin had a better toxicity profile than MVAC.

Pancreatic cancer
In a randomised phase III study of 126 patients with advanced or metastatic pancreatic cancer, gemcitabine showed a statistically significant higher clinical benefit response rate than 5-fluorouracil (23.8% and 4.8% respectively, p=0.0022). Also, a statistically significant prolongation of the time to progression from 0.9 to 2.3 months (log-rank p< 0.0002) and a statistically significant prolongation of median survival from 4.4 to 5.7 months (log-rank p< 0.0024) was observed in patients treated with gemcitabine compared to patients treated with 5-fluorouracil.
Non-small cell lung cancer

In a randomised phase III study of 522 patients with inoperable, locally advanced or metastatic NSCLC, gemcitabine in combination with cisplatin showed a statistically significant higher response rate than cisplatin alone (31.0% and 12.0%, respectively, p< 0.0001). A statistically significant prolongation of the time to progression, from 3.7 to 5.6 months (log-rank p< 0.0012) and a statistically significant prolongation of median survival from 7.6 months to 9.1 months (log-rank p< 0.004) was observed in patients treated with gemcitabine/cisplatin compared to patients treated with cisplatin.

In another randomised phase III study of 135 patients with stage IIIIB or IV NSCLC, a combination of gemcitabine and cisplatin showed a statistically significant higher response rate than a combination of cisplatin and etoposide (40.6% and 21.2%, respectively, p=0.025). A statistically significant prolongation of the time to progression, from 4.3 to 6.9 months (p=0.014) was observed in patients treated with gemcitabine/cisplatin compared to patients treated with etoposide/cisplatin.

In both studies it was found that tolerability was similar in the two treatment arms.

Ovarian carcinoma

In a randomised phase III study, 356 patients with advanced epithelial ovarian carcinoma who had relapsed at least 6 months after completing platinum based therapy were randomised to therapy with gemcitabine and carboplatin (GCb), or carboplatin (Cb). A statistically significant prolongation of the time to progression of disease, from 5.8 to 8.6 months (log-rank p=0.0038) was observed in the patients treated with GCb compared to patients treated with Cb. Differences in response rate of 47.2% in the GCb arm versus 30.9% in the Cb arm (p=0.0016) and median survival 18 months (GCb) versus 17.3 (Cb) (p=0.73) favoured the GCb arm.

5.2 Pharmacokinetic properties

The pharmacokinetics of gemcitabine have been examined in 353 patients in seven studies. The 121 women and 232 men ranged in age from 29 to 79 years. Of these patients, approximately 45% had non-small cell lung cancer and 35% were diagnosed with pancreatic cancer. The following pharmacokinetic parameters were obtained for doses ranging from 500 to 2,592 mg/m² that were infused from 0.4 to 1.2 hours.

Peak plasma concentrations (obtained within 5 minutes of the end of the infusion) were 3.2 to 45.5 µg/ml. Plasma concentrations of the parent compound following a dose of 1,000 mg/m²/30-minutes are greater than 5 µg/ml for approximately 30 minutes after the end of the infusion and greater than 0.4 µg/ml for an additional hour.

Distribution

The volume of distribution of the central compartment was 12.4 l/m² for women and 17.5 l/m² for men (inter-individual variability was 91.9%). The volume of distribution of the peripheral compartment: 47.4 l/m². The volume of the peripheral compartment was not sensitive to gender.

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

Metabolism

Gemcitabine is rapidly 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. Excretion

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 was 2 to 7 l/hr/m². During the week following administration, 92 to 98% of the dose of gemcitabine administered is recovered, 99% in the urine, mainly in the form of dFdU and 1% of the dose is excreted in faeces.

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

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

dFdU kinetics
Peak plasma concentrations (3-15 minutes after end of 30-minute infusion, 1,000 mg/m²): 28-52 µg/ml.

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

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

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

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

Mean steady-state volume of distribution (Vss): 150 l/m² (range 96-228 l/m²).

Tissue distribution: extensive.

Mean apparent clearance: 2.5 l/hr/m² (range 1.4-4 l/hr/m²).

Urinary excretion: all.

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

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

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

5.3 Preclinical safety data
In repeat-dose studies of up to 6 months in duration in mice and dogs, the principal finding was schedule and dose-dependent haematopoietic suppression which was reversible. Gemcitabine is mutagenic in an in vitro mutation test and an in vivo bone marrow micronucleus test. Long term animal studies evaluating the carcinogenic potential have not been performed.

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

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

6 PHARMACEUTICAL PARTICULARS
6.1 List of excipients
Gemcitabine 1 g contains:
Mannitol (E421)
Sodium acetate (E262)
Hydrochloric acid (E507) (for pH adjustment)
Sodium hydroxide (E524) (for pH adjustment)

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

6.3 Shelf life
Unopened vials: 2 years.
Reconstituted solution:
Chemical and physical in-use stability has been demonstrated for 24 hours at 20-25°C. From a microbiological point of view, the product should be used immediately. If not used immediately, in-use
storage times and conditions prior to use are the responsibility of the user and would normally not be
longer than 24 hours at room temperature, unless reconstitution (and further dilution, if applicable) has
taken place in controlled and validated aseptic conditions.
Solutions of reconstituted gemcitabine should not be refrigerated, as crystallisation may occur.

6.4 Special precautions for storage
Unopened vials: this medicinal product does not require any special storage conditions.
For storage of the reconstituted medicinal product see section 6.3.

6.5 Nature and contents of container
Type I clear glass vials, stoppered with a grey bromobutyl rubber stopper and sealed with an
aluminium flip-off cap, combined with a polypropylene disk.
Each pack contains 1 vial.

6.6 Special precautions for disposal
Handling
The normal safety precautions for cytostatic agents must be observed when preparing and disposing of
the infusion solution. Handling of the solution for infusion should be done in a safety box and
protective coats and gloves should be used. If no safety box is available, the equipment should be
supplemented with a mask and protective glasses.
If the preparation comes into contact with the eyes, this may cause serious irritation. The eyes should
be rinsed immediately and thoroughly with water. If there is lasting irritation, a doctor should be
consulted. If the solution is spilled on the skin, rinse thoroughly with water.
Instructions for reconstitution (and further dilution, if performed)
The only approved diluent for reconstitution of gemcitabine sterile powder is sodium chloride 9 mg/ml
(0.9%) solution for injection (without preservative). Due to solubility considerations, the maximum
concentration for gemcitabine upon reconstitution is 40 mg/ml. Reconstitution at concentrations greater
than 40 mg/ml may result in incomplete dissolution and should be avoided.
10. Use aseptic technique during the reconstitution and any further dilution of gemcitabine for
intravenous infusion administration.
11. To reconstitute, add 5 ml of sterile sodium chloride 9 mg/ml (0.9%) solution for injection, without
preservative, to the 200 mg vial or 25 ml of sterile sodium chloride 9 mg/ml (0.9%) solution for
injection, without preservative, to the 1,000 mg vial. The total volume after reconstitution is
5.26 ml (200 mg vial) or 26.3 ml (1,000 mg vial) respectively. This yields a gemcitabine
concentration of 38 mg/ml, which includes accounting for the displacement volume of the
lyophilised powder. Shake to dissolve. Further dilution with sterile sodium chloride 9 mg/ml (0.9
%) solution for injection, without preservative can be done. Reconstituted solution is a clear
colourless to light straw-coloured solution.
12. Parenteral medicinal drugs should be inspected visually for particulate matter and discolouration
prior to administration. If particulate matter is observed, do not administer.

Any unused product or waste material should be disposed of in accordance with local requirements.
Module 3
PATIENT INFORMATION LEAFLET

1. What Gemcitabine Solution is and what it is used for

Gemcitabine Solution is used in the treatment of the following types of cancers:
- non-small cell lung cancer (NSCLC), alone or in combination with platinum
- pancreatic cancer
- breast cancer, together with paclitaxel
- ovarian cancer, together with carboplatin
- bladder cancer, together with cisplatin.

2. Before you are given Gemcitabine Solution

You should not be given Gemcitabine Solution:
- if you are allergic to any of the ingredients of Gemcitabine Solution;
- if you are breast feeding.

3. Take special care with Gemcitabine Solution

During the first infusion you will have samples of your blood taken to evaluate your reaction to the medicine before the infusion starts. After each infusion, you will have samples of your blood taken to evaluate your reaction to the medicine.

4. Pregnancy and breast-feeding

Gemcitabine Solution should be avoided during pregnancy. Your doctor will discuss with you the potential risks of taking Gemcitabine Solution during pregnancy.

5. Possible side effects

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

6. How Gemcitabine Solution is given

The usual dose of Gemcitabine Solution is 2,000 – 2,250 mg for 1 dose. If you need more doses of Gemcitabine Solution in 29 days, the dose will be no more than 8,000 mg in 4 weeks. The dose is repeated every 4 weeks.
PAR Gemcitabine 200mg & 1g Powder for Solution for Infusion   UK/H/1574/01-02/DC
UK/H/2439/01-02/DC

PACKAGE LEAFLET: INFORMATION FOR THE USER

Gemcitabine 200 mg powder for solution for infusion
Gemcitabine 1 g powder for solution for infusion
gemcitabine

The name of the product is Gemcitabine 200 mg powder for solution for infusion or Gemcitabine 1 g powder for solution for infusion and will be referred to as Gemcitabine Solution throughout this document.

Read all of this leaflet carefully before you start receiving this medicine.

• Keep this leaflet. You may need to read it again.
• If you have any further questions, ask your doctor, nurse 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, nurse or pharmacist.

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

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

Gemcitabine Solution belongs to a group of medicines called “cytotoxics”. These medicines kill dividing cells, including cancer cells.

Gemcitabine Solution may be given alone or in combination with other anti-cancer medicines, depending on the type of cancer.

Gemcitabine Solution is used in the treatment of the following types of cancer:
• non-small cell lung cancer (NSCLC), alone or together with cisplatin
• pancreatic cancer
• breast cancer, together with paclitaxel
• ovarian cancer, together with carboplatin
• bladder cancer, together with cisplatin.

2. BEFORE YOU ARE GIVEN GEMCITABINE SOLUTION

You should not be given Gemcitabine Solution:
• if you are allergic (hypersensitive) to gemcitabine or any of the other ingredients of Gemcitabine Solution;
• if you are breast-feeding.

Take special care with Gemcitabine Solution:
Before the first infusion you will have samples of your blood taken to evaluate if you have sufficient kidney and liver function. Before each infusion you will have samples of your blood taken to evaluate if you have enough blood cells to receive Gemcitabine Solution. Your
doctor may decide to change the dose or delay treating you depending on your general condition and if your blood cell counts are too low. Periodically you will have samples of your blood taken to evaluate your kidney and liver function.

Please tell your doctor if:
- you have, or have previously had liver disease, heart disease or vascular disease;
- you have recently had, or are going to have radiotherapy;
- you have been vaccinated recently;
- you develop breathing difficulties or feel very weak and are very pale (may be a sign of kidney failure).

Men are advised not to father a child during and up to 6 months following treatment with Gemcitabine Solution. If you would like to father a child during the treatment or in the 6 months following treatment, seek advice from your doctor or pharmacist. You may want to seek counselling on sperm storage before starting your therapy.

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

Pregnancy and breast-feeding
If you are pregnant, or thinking about becoming pregnant, tell your doctor. The use of Gemcitabine Solution should be avoided during pregnancy. Your doctor will discuss with you the potential risk of taking Gemcitabine Solution during pregnancy.

If you are breast-feeding, tell your doctor.
You must discontinue breast-feeding during Gemcitabine Solution treatment.

Driving and using machines
Gemcitabine Solution may make you feel sleepy, particularly if you have consumed any alcohol. Do not drive a car or use machinery until you are sure that Gemcitabine Solution treatment has not made you feel sleepy.

Important information about some of the ingredients of Gemcitabine Solution
Gemcitabine Solution contains 3.5 mg (< 1 mmol) of sodium in each 200 mg vial and 17.5 mg (< 1 mmol) sodium in each 1 g vial. To be taken into consideration by patients on a controlled sodium diet.

3. HOW GEMCITABINE SOLUTION IS GIVEN

The usual dose of Gemcitabine Solution is 1,000-1,250 mg for every square metre of your body's surface area. Your height and weight are measured to work out the surface area of your body. Your doctor will use this body surface area to work out the right dose for you. This dosage may be adjusted, or treatment may be delayed depending on your blood cell counts and on your general condition.

How frequently you receive your Gemcitabine Solution infusion depends on the type of cancer that you are being treated for.

A hospital pharmacist or doctor will have dissolved the Gemcitabine Solution powder before it is given to you.

You will always receive Gemcitabine Solution by infusion into one of your veins.
The infusion will last approximately 30 minutes.

If you have further questions on the use of this product ask your doctor or pharmacist.

4. POSSIBLE SIDE EFFECTS

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

Frequencies of the observed side effects are defined as:

- very common: affects more than 1 user in 10
- common: affects 1 to 10 users in 100
- uncommon: affects 1 to 10 users in 1,000
- rare: affects 1 to 10 users in 10,000
- very rare: affects less than 1 user in 10,000
- not known: frequency can’t be estimated from the available data.

You must contact your doctor immediately if you notice any of the following:

- fever or infection (common): if you have a temperature of 38°C or greater, sweating or other signs of infection (since you might have less white blood cells than normal which is very common),
- irregular heart rate (arrhythmia) (frequency not known),
- pain, redness, swelling or sores in your mouth (common),
- allergic reactions: if you develop skin rash (very common) / itching (common), or fever (very common),
- tiredness, feeling faint, becoming easily breathless or if you look pale (since you might have less haemoglobin than normal which is very common),
- bleeding from the gums, nose or mouth or any bleeding that would not stop, reddish or pinkish urine, unexpected bruising (since you might have less platelets than normal which is very common),
- difficulty breathing (it is very common to have mild breathing difficulty soon after the Gemcitabine Solution infusion which soon passes, however uncommonly or rarely there can be more severe lung problems).

Side effects with Gemcitabine Solution may include:

Very common side effects:

- low haemoglobin level (anaemia)
- low white blood cells
- low platelet count
- difficulty breathing
- vomiting
- nausea
- skin rash - allergic skin rash, frequently itchy
- hair loss
- liver problems: found through abnormal blood test results
- blood in urine
- abnormal urine tests: protein in urine
- flu like symptoms including fever
- oedema (swelling of ankles, fingers, feet, face).
Common side effects:
- fever accompanied by low white blood cell count (febrile neutropaenia)
- anorexia (poor appetite)
- headache
- insomnia
- sleepiness
- cough
- runny nose
- constipation
- diarrhoea
- pain, redness, swelling or sores in the mouth
- itching
- sweating
- muscle pain
- back pain
- fever
- weakness
- chills.

Uncommon side effects:
- interstitial pneumonitis (scarring of the air sacs of the lung)
- spasm of the airways (wheeze)
- abnormal chest X ray/scan (scarring of the lungs).

Rare side effects:
- heart attack (myocardial infarction)
- low blood pressure
- skin scaling, ulceration or blister formation
- injection site reactions.

Very rare side effects:
- increased platelet count
- anaphylactic reaction (severe hypersensitivity/ allergic reaction)
- sloughing of skin and severe skin blistering.

Side effects with frequency not known:
- irregular heart beat (arrhythmia)
- Adult Respiratory Distress Syndrome (severe lung inflammation causing respiratory failure)
- radiation recall (a skin rash like severe sunburn) which can occur on skin that has previously been exposed to radiotherapy
- fluid in the lungs
- radiation toxicity- scarring of the air sacs of the lung associated with radiation therapy
- ischaemic colitis (inflammation of the lining of the large bowel, caused by reduced blood supply)
- heart failure
- kidney failure
- gangrene of fingers or toes
- serious liver damage, including liver failure
- stroke.

You might have any of these symptoms and/or conditions. You must tell your doctor as
soon as possible when you start experiencing any of these side effects.

If you are concerned about any side effects, talk to your doctor.

If any of the side effects get serious or if you notice any side effects not mentioned in this leaflet, please tell your doctor.

5. **HOW TO STORE GEMCITABINE SOLUTION**

Keep out of the reach and sight of children.
Do not use after the expiry date which is stated on the carton.

Unopened vials: this medicinal product does not require any special storage conditions.

Reconstituted solution: the product should be used immediately. When prepared as directed, chemical and physical in-use stability of reconstituted solutions of gemcitabine were demonstrated for 24 hours at 20-25°C. Further dilution by a healthcare provider may be done. Solutions of reconstituted gemcitabine should not be refrigerated, as crystallisation may occur.

This medicine is for single use only; any unused solution should be discarded under the local requirements.

6. **FURTHER INFORMATION**

**What Gemcitabine Solution contains**
- The active substance is gemcitabine. Each vial contains 200 mg or 1 gram (g) of gemcitabine (as gemcitabine hydrochloride).
- The other ingredients are mannitol (E421), sodium acetate, hydrochloric acid and sodium hydroxide.

**What Gemcitabine Solution looks like and contents of the pack**
Gemcitabine Solution is a white to off-white powder, for solution for infusion in a vial. Each vial contains 200 mg or 1 gram (g) of gemcitabine. Each pack of Gemcitabine Solution contains 1 vial.

**Marketing Authorisation Holder and Manufacturer**

**Marketing Authorisation Holder:**
Flynn Pharma Ltd
Alton House
4 Herbert Street
Dublin 2
Ireland

**Manufacturer:**
Cancernova GmbH
Onkologische Arzneimittel
Hirtweg 2 – 4
79276 Reute
Germany
This medicinal product is authorised in the Member States of the EEA under the following names:

<table>
<thead>
<tr>
<th>Name of the Member State</th>
<th>Name of the medicinal product</th>
</tr>
</thead>
<tbody>
<tr>
<td>Austria</td>
<td>Gemcitabin Xellex 200 mg &amp; 1000 mg Pulver zur Herstellung einer Infusionslösung</td>
</tr>
<tr>
<td>Spain</td>
<td>Gemcitabina IPS 200 mg &amp; 1000 mg polvo para solución para perfusión</td>
</tr>
<tr>
<td>Germany</td>
<td>Gemcitabin Xellex 200 mg &amp; 1000 mg Pulver zur Herstellung einer Infusionslösung</td>
</tr>
</tbody>
</table>

This leaflet was last approved in MM/YYYY
INFORMATION FOR THE HEALTHCARE PROFESSIONAL

Gemcitabine 200 mg powder for solution for infusion
Gemcitabine 1 g powder for solution for infusion
gemcitabine

The following information is intended for medical or healthcare professionals only:

Instructions for use, handling and disposal

1. Use aseptic techniques during the reconstitution and any further dilution of Gemcitabine for intravenous infusion administration.

2. Calculate the dose and the number of Gemcitabine vials needed.

3. Reconstitute 200 mg vials with 5 ml of 9 mg/ml (0.9%) sterile sodium chloride solution for injection, without preservative, or 25 ml sterile sodium chloride solution for injection, without preservative to the 1,000 mg vial. Shake to dissolve. The total volume after reconstitution is 5.26 ml (200 mg vial) or 26.3 ml (1,000 mg vial) respectively. This dilution yields a gemcitabine concentration of 38 mg/ml, which includes accounting for the displacement volume of the lyophilised powder. Further dilution with sterile sodium chloride 9 mg/ml (0.9%) solution for injection, without preservative may be done. The resulting solution is clear and ranges in colour from colourless to light straw-coloured.

4. Parenteral medicinal products should be inspected visually for particulate matter and discoloration prior to administration. If particulate matter is observed, do not administer.

5. Solutions of reconstituted gemcitabine should not be refrigerated, as crystallisation may occur. Chemical and physical in-use stability has been demonstrated for 24 hours at 20-25°C. From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at room temperature, unless reconstitution/dilution has taken place in controlled and validated aseptic conditions.

6. Gemcitabine solutions are for single use only. Any unused product or waste material should be disposed of in accordance with local requirements.

Preparation and administration precautions

The normal safety precautions for cytostatic agents must be observed when preparing and disposing of the infusion solution. Handling of the solution for infusion should be done in a safety box and protective coats and gloves should be used. If no safety box is available, the equipment should be supplemented with a mask and protective glasses.

If the preparation comes into contact with the eyes, this may cause serious irritation. The eyes should be rinsed immediately and thoroughly with water. If there is lasting irritation, a doctor should be consulted. If the solution is spilled on the skin, rinse thoroughly with water.

Disposal

Any unused product should be disposed of in accordance with local requirements.
Module 4
Labelling

Carton

Vial label
Scientific discussion during initial procedure

I  INTRODUCTION
Based on the review of the data on quality, safety and efficacy, the RMS considers that the applications for Gemcitabine 200mg and 1g Powder for Solution for Infusion, in the treatment of the following indications:

- for the treatment of locally advanced or metastatic bladder cancer in combination with cisplatin.

- for treatment of patients with locally advanced or metastatic adenocarcinoma of the pancreas.

- in combination with cisplatin is indicated as first line treatment of patients with locally advanced or metastatic non-small cell lung cancer (NSCLC).

- monotherapy can be considered in elderly patients or those with performance status 2.

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

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

These abridged decentralised applications concern generic versions of gemcitabine submitted under Article 10(1) of Directive 2001/83/EC as amended. The originator product is Gemzar 200mg Powder for Solution for Infusion (PL 000062/0301) and Gemzar 1g Powder for Solution for Infusion (PL 000062/0302), authorised to Eli Lilly UK, dated 26 October 1995. The legal basis is satisfactory.

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

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

No new preclinical or clinical studies were conducted and none are required for an application of this type.

The RMS has been assured that acceptable standards of GMP are in place for these product types at all sites responsible for the manufacture, batch release and assembly of this product.
For manufacturing sites within the Community, the RMS has accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.

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

A package leaflet has been submitted to the MHRA along with results of consultations with target patient groups ("user testing"), in accordance with Article 59 of Council Directive 2001/83/EC. The results indicate that the package leaflet is well-structured and organised, easy to understand and written in a comprehensive manner. The test shows that the patients/users are able to act upon the information that it contains.

II. ABOUT THE PRODUCT

| Name of the product in the Reference Member State | Gemcitabine 200mg and 1g Powder for solution for infusion |
| Name(s) of the active substance(s) (INN) | Gemcitabine hydrochloride |
| Pharmacotherapeutic classification (ATC code) | L01BC05 |
| Pharmaceutical form and strength(s) | Powder for solution for infusion |
| Reference numbers for the Mutual Recognition Procedure | UK/H/1574/01-02/DC, UK/H/2439/01-02/DC |
| Reference Member State | United Kingdom |
| Member States concerned | UK/H/1574/01-02/DC - Ireland, UK/H/2439/01-02/DC - Austria, Germany and Spain |
| Marketing Authorisation Number(s) | PL 13621/0038-39, PL 13621/0050-51 |
| Name and address of the authorisation holder | Flynn Pharma Ltd, Alton House, 4 Herbert Street, Dublin 2, Republic of Ireland |

III. SCIENTIFIC OVERVIEW AND DISCUSSION

III.1 QUALITY ASPECTS

S. Active substance

General Information
Nomenclature
INN: Gemcitabine hydrochloride

Structure

\[ \text{Molecular formula: } C_{9}H_{11}F_{2}N_{3}O_{4}.HCl \]

Molecular Mass: 299.66

Description: White or almost white crystalline powder
Manufacture
All aspects of the manufacture and control of gemcitabine hydrochloride are supported by a European Directorate for the Quality of Medicines and Healthcare (EDQM) Certificate of Suitability. This certificate is accepted as confirmation of the suitability of gemcitabine hydrochloride for inclusion in the medicinal product.

The specification is in compliance with the pharmacopoeia monograph and Certificate of Suitability and is satisfactory.

Gemcitabine hydrochloride is stored in appropriate packaging that has been evaluated in relation to the grant of the EDQM Certificate of Suitability.

Batch analysis data are provided and comply with the proposed specification.

Appropriate stability data have been generated showing the active substance to be a physically and chemically stable drug. The data support a re-test period of 12 months when stored in the appropriate packaging at 25°C.

Medicinal Product
Other ingredients consist of pharmaceutical excipients mannitol, sodium acetate, hydrochloride and sodium hydroxide

All excipients are subject of European Pharmacopoeia monographs. Satisfactory certificates of analysis have been provided for all excipients showing compliance with their respective monograph/specifications. None of the excipients contain material from animal or human origin.

The development of the product has been described, the choice of excipients is justified and their functions explained.

Impurity profiles
Impurity profiles of drug product were found to be similar to those for the reference product.

Manufacture
A description and flow-chart of the manufacturing method has been provided.

Manufacturing Process
In-process controls are appropriate considering the nature of the product and the method of manufacture. Validations of the analytical methods have been presented. Process validation has been carried out on three commercial-scale batches with satisfactory results.

Finished Product Specification
The finished product specifications proposed for the products are acceptable. Test methods have been described and have been adequately validated, as appropriate. The batch analysis results show that the finished products meet the specifications proposed. Certificates of analysis have been provided for any working standards used.

Container Closure System
The product is packaged in Type I clear glass vials, stoppered with a grey bromobutyl rubber stopper and sealed with an aluminium flip-off cap, combined with a polypropylene disk. Each pack contains 1 vial.

Specifications and a certificate of analysis for the packaging type used have been provided.
Stability
Finished product stability studies have been conducted in accordance with current guidelines. Based on the results, a shelf-life of 2 years (unopened) has been set, which is satisfactory with no specific storage conditions. Please refer to Section 6.3 of the Summary of Product Characteristics for storage details concerning the reconstituted solution.

Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and Labelling
The text of the SmPCs, PILs and labelling is satisfactory and consistent with that for the reference products.

The approved labelling artwork complies with statutory requirements for PL 13621/0038 & PL 13621/0039.

For PLs 13621/0050 & 13621/0051, the Marketing Authorisation Holder (MAH) has committed to submitting mock-ups for all packaging and PILs for assessment before those packs are commercially marketed.

Conclusion
It is recommended that Marketing Authorisations are granted for these applications.

The proposed product has met the requirements of a generic medicinal product with respect to qualitative and quantitative content of the active substance and pharmaceutical form.

III.2 Non clinical aspects
The pharmacodynamic, pharmacokinetic and toxicological properties of gemcitabine are well known. As gemcitabine is a well known active substance, the applicant has not provided additional studies and further studies are not required. An overview based on the literature review is therefore appropriate.

The non-clinical overview has been written by a physician by training and who is a consultant to the pharmaceutical industry. The overview, dated August 2007, refers to 45 references from the published literature dated 1990 to 2006. The overview is acceptable.

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

III.3 Clinical aspects
Pharmacokinetics
Gemcitabine 200 mg and 1g powder for solution for intravenous infusion is an aqueous solution for intravenous infusion containing the same active substance in the same concentration as the innovator product (Gemzar) that is marketed in most European countries. Therefore, no bioequivalence study is required and all data available for the original product also apply for Gemcitabine 200 mg and 1g powder for solution for infusion.

Pharmacodynamics, Clinical efficacy and Clinical safety
The application contains an adequate review of published clinical data. The Clinical Overview has been written by a suitably qualified person. No new pharmacodynamic or clinical data were submitted for this application and none were required. Regarding safety, no
serious or unexpected adverse events were identified in the expert report.

The SPC of Gemcitabine 200 mg and 1g powder for solution for infusion is in accordance with the innovator’s SPC.

It is acceptable from a clinical point of view.

**BENEFIT RISK ASSESSMENT**

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

With regard to clinical aspects the application contains an adequate review of published clinical data. The reference medicinal product Gemzar powder for solution for infusion 200 mg and 1g contains the widely used and well-known active substance gemcitabine hydrochloride with an established favourable benefit-risk profile for the proposed indications in the updated SPC.

The proposed SPC & PIL are in line with recently published harmonized SPC for the innovator product Gemzar (EMEA/CHMP/327265/2008).

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

**IV OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT**

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

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

No new or unexpected safety concerns arise from this application.

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

The quality of the product is acceptable and no new preclinical or clinical safety concerns have been identified. Extensive clinical experience with gemcitabine hydrochloride is considered to have demonstrated the therapeutic value of the compound. The risk benefit is, therefore, considered to be positive.
## Module 6

**STEPS TAKEN AFTER INITIAL PROCEDURE - SUMMARY**

<table>
<thead>
<tr>
<th>Date submitted</th>
<th>Application type</th>
<th>Scope</th>
</tr>
</thead>
<tbody>
<tr>
<td>14/09/2009</td>
<td>PL-ADD/AMEND</td>
<td>Revisions made to the joint UK/IE outer and inner product labelling mock-ups. Assessor has agreed to the removal of the volume of the vial given on the packaging affecting PL 13621/0038 (UK/H/1574/01/DC) only.</td>
</tr>
</tbody>
</table>