GEMCITABINE 200MG AND 1000MG POWDER FOR SOLUTION FOR INFUSION

PL 33410/0019-20

UKPAR

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LAY SUMMARY

The Medicines and Healthcare products Regulatory Agency granted APSLA Limited Marketing Authorisations (licences) for the medicinal products Gemcitabine 200mg and 1000mg Powder for Solution for Infusion (PL 33410/0019-20) on 10th March 2011. These are prescription-only medicines (POM).

Gemcitabine is a group of medicines called cytotoxics. These medicines kill dividing cells, including cancer cells. Gemcitabine may be given alone or in combination with other anti-cancer medicines, depending on the type of cancer.

Gemcitabine is used in the treatment of the following types of cancer:
- non-small cell lung cancer (NSCLC)
- breast cancer
- pancreatic cancer
- ovarian cancer
- bladder cancer

No new or unexpected safety concerns arose from these applications and it was, therefore, judged that the benefits of taking Gemcitabine 200mg and 1000mg Powder for Solution for Infusion outweigh the risks; hence Marketing Authorisations have been granted.
SCIENTIFIC DISCUSSION

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INTRODUCTION

The UK granted Marketing Authorisations for the medicinal products Gemcitabine 200mg and 1000mg Powder for Solution for Infusion (PL 33410/0019-20) to APSLA Limited on 10th March 2011. These products are prescription-only medicines.

These applications were submitted as abridged applications according to Article 10(1) of Directive 2001/83/EC. The applications refer to the innovator products, Gemzar® 200mg (PL 00006/0301) and 1000 mg (PL 00006/0302) Powder for Solution for Infusion, authorised to Eli Lilly UK, on 26th October 1995. The reference products have been authorised in the EEA for over 10 years.

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.

The pharmacovigilance system, as described by the MAH, fulfils the requirements and provides adequate evidence that the MAH has the services of a qualified person responsible for pharmacovigilance and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

The MAH has provided adequate justification for not submitting a Risk Management Plan (RMP). As the application is for a generic version of an already authorised reference product, for which safety concerns requiring additional risk minimisation have not been identified, a risk minimisation system is not considered necessary. The reference product has been in use for many years and the safety profile of the active is well established.

No new pre-clinical or clinical studies were performed, which is acceptable given that the proposed products are generic medicinal products of the reference products that have been licensed for over 10 years.

No new or unexpected safety concerns arose during the review of information provided by the Marketing Authorisation Holder (MAH) and it was, therefore, judged that the benefits of taking product Gemcitabine 200mg and 1000mg Powder for Solution for Infusion outweigh the risks; hence Marketing Authorisations have been granted.
PHARMACEUTICAL ASSESSMENT

DRUG SUBSTANCE

Gemcitabine Hydrochloride

INN: Gemcitabine Hydrochloride
Chemical name: 4-Amino-1-(2-deoxy-2,2-difluoro-β-D-erythro-pentofuranosyl)pyrimidin-2(1H)-one hydrochloride

Structure:

![Structure of Gemcitabine Hydrochloride](image)

Molecular mass: 299.7
Molecular formula: C₉H₁₂ClF₂N₃O₄

General Properties

Description: White or almost white crystalline powder.

Gemcitabine hydrochloride is the subject of a European Pharmacopoeia monograph (Ph Eur).

Manufacture

All aspects of the manufacture and control of the active substance gemcitabine hydrochloride are covered by a European Directorate for the Quality of Medicines (EDQM) Certificate of Suitability.

DRUG PRODUCT

Description and Composition

Gemcitabine 200mg & 1000mg Powder for solution for infusion is presented as a white to off white freeze dried cake. Each vial contains gemcitabine hydrochloride equivalent to 200mg or 1000mg of gemcitabine. After reconstitution the solution contains 40mg/ml of gemcitabine.

Other ingredients consist of pharmaceutical excipients, namely mannitol, sodium acetate trihydrate, hydrochloric acid (for pH adjustment), sodium hydroxide (for pH adjustment). Appropriate justification for the inclusion of each excipient has been provided. All
excipients used comply with their relevant European Pharmacopoeia (Ph. Eur) monographs. Satisfactory Certificates of Analysis have been provided for all excipients.

The applicant has provided a declaration confirming that there are no materials of human or animal origin contained in or used in the manufacturing process of the proposed product. None of the excipients are sourced from genetically modified organisms.

**Pharmaceutical Development**

Suitable pharmaceutical development data have been provided for these applications.

The physico-chemical properties of the drug product have been compared with the originator product. These data demonstrate that the proposed product can be considered a generic medicinal product to Gemzar® 200mg (PL 00006/0301) and 1000mg (PL 00006/0302) Powder for Solution for Infusion, (Eli Lilly UK).

Compatibility studies have been carried with sterile sodium chloride 0.9% for injection in line with the innovator. The studies show that the product is chemically stable.

**Manufacture**

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

In-process controls were considered appropriate considering the nature of the product and the method of manufacture. Process validation studies have been conducted and are accepted.

**Finished Product Specification**

The finished product specification is satisfactory. Acceptance limits have been justified with respect to conventional pharmaceutical requirements and, where appropriate, safety. Test methods have been described and have been adequately validated, as appropriate. Satisfactory batch analysis data are provided and comply with the release specification. Certificates of Analysis have been provided for any reference standards used.

**Container Closure System**

The finished product is presented in 10ml (200mg powder) and 50ml (1000mg powder) Type I moulded glass vials sealed with bromobutyl rubber stoppers with flip-off tear-off aluminium seals. Each vial contains gemcitabine hydrochloride equivalent to 200mg or 1000mg gemcitabine.

Each vial is packaged with the patient information leaflet into outer cardboard cartons.

Satisfactory specifications and Certificates of Analysis for all packaging components used have been provided. All primary product packaging complies with EU legislation, Directive 2002/72/EC (as amended), and is suitable for parenteral preparations.

**Stability**

Finished product stability studies have been conducted in accordance with current guidelines and results were within the proposed specification limits. Based on the results, a shelf-life of 2 years has been set for the unopened vial which is satisfactory. Storage conditions are ‘‘Store in original package’’. 
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. Chemical and physical in-use stability has been demonstrated for 24 hours at 30°C following reconstitution. Solutions should not be refrigerated, as crystallisation may occur. For full details of shelf-life and storage conditions for the reconstituted, diluted medicinal products, refer to Section 6.3 of the SmPC. Please also refer to Section 6.6 of the SmPC for information on proper handling and disposal of the products and contaminated materials.

**Bioequivalence Study**
Bioequivalence studies are not necessary to support these applications for parenteral products.

**Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL), Labels**
The approved SmPCs, PILs and labelling are pharmaceutically acceptable. Mock-ups of the package leaflet and labelling have been provided.

**Expert Report**
The pharmaceutical expert report has been written by an appropriately qualified person and is a suitable summary of the pharmaceutical dossier. The CV of the expert has been provided.

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

This application was submitted as an abridged, application, according to Article 10.1 of Directive 2001/83/EC, as amended.

The pharmacodynamic, pharmacokinetic and toxicological properties of gemcitabine hydrochloride are well-known. Therefore, no further studies are required and the applicant has provided none.

The pre-clinical overview was written by a suitably qualified person and is satisfactory. The *curriculum vitae* of the expert has been provided.

A suitable justification has been provided for the non-submission of an environmental risk assessment.
CLINICAL ASSESSMENT

Pharmacokinetics
No new data have been submitted and none are required for an application of this type.

Gemcitabine 200mg/1000mg Powder for Solution for Infusion are generic versions of the originator products Gemzar 200 mg/1 g powder for solution for infusion,(Eli Lilly and Company Limited). The use of the reference product is well-established in the UK. Both products contain the same quantitative and qualitative composition of the active ingredient, gemcitabine. Thus, in accordance with the “Guideline on the Investigation of Bioequivalence”, the applicant is not required to submit a bioequivalence study, if the product is to be administered as an aqueous intravenous solution containing the same active substance, in the same concentration as the currently authorised product.

Pharmacodynamics
No new data have been submitted and none are required for an application of this type.

Clinical efficacy
No new data have been submitted and none are required for an application of this type.

Clinical safety
No new safety data have been submitted or required for this generic application. As gemcitabine is a well-known product with an acceptable adverse event profile, this is satisfactory.

Expert Report
A satisfactory clinical overview is provided, and has been prepared by an appropriately qualified physician. The curriculum vitae of the expert has been provided.

Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL), Labels
The SmPC and PIL are medically acceptable, and consistent with those for the reference product. The labelling is medically acceptable and in-line with current requirements.

MAA form
The MAA form is medically satisfactory.

Conclusion
There are no objections to approval of Gemcitabine 200mg and 1000mg Powder for Solution for Infusion from a clinical point of view.
OVERALL CONCLUSION AND RISK BENEFIT ASSESSMENT

QUALITY
The important quality characteristics of Gemcitabine 200mg and 1000mg Powder for Solution for Infusion are well-defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

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

EFFICACY
The applicant’s Gemcitabine 200mg and 1000mg Powder for Solution for Infusion has been demonstrated to be generic versions of the reference product, Gemzar® 200mg (PL 00006/0301) and 1000 mg (PL 00006/0302) Powder for Solution for Infusion, authorised to Eli Lilly UK, dated 26 October 1995.

No new or unexpected safety concerns arise from these applications.

PRODUCT LITERATURE
The SmPCs and PILs are acceptable, and consistent with those for the reference products. The labelling is acceptable and in-line with current requirements.

The package leaflet has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The results show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

BENEFIT/RISK ASSESSMENT
The quality of the product is acceptable, and no new preclinical or clinical safety concerns have been identified. The qualitative and quantitative assessment supports the claim that the applicant’s Gemcitabine 200mg and 1000mg Powder for Solution for Infusion and the reference products Gemzar 200mg & 1000mg Powder for Solution for Infusion (Eli Lilly UK) are interchangeable. Extensive clinical experience with gemcitabine hydrochloride is considered to have demonstrated the therapeutic value of the active substance. The benefit:risk is, therefore, considered to be positive.
## STEPS TAKEN FOR ASSESMENT

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<tr>
<td>1</td>
<td>The MHRA received the marketing authorisation application on 9th November 2009.</td>
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<td>2</td>
<td>Following standard checks and communication with the applicant the MHRA considered the application valid on 14th December 2009.</td>
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<td>3</td>
<td>Following assessment of the applications the MHRA requested further information relating to the quality dossiers on 26th February 2010, 23rd July 2010, 4th November 2010 and 14th December 2010.</td>
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<tr>
<td>4</td>
<td>The applicant responded to the MHRA’s requests, providing further information on the quality dossier on 1st July 2010, 24th September 2010, 1st December 2010 and 23rd December 2010.</td>
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<td>5</td>
<td>The application was determined on 10th March 2011.</td>
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GEMCITABINE 200MG AND 1000MG POWDER FOR SOLUTION FOR INFUSION

PL 33410/0019-20

**STEPS TAKEN AFTER AUTHORISATION - SUMMARY**

<table>
<thead>
<tr>
<th>Date submitted</th>
<th>Application type</th>
<th>Scope</th>
<th>Outcome</th>
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The UK Summary of Product Characteristics (SmPC) for Gemcitabine 200mg Powder for Solution for Infusion (PL 33410/0019) is as follows:

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

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each vial contains 227.60 mg gemcitabine hydrochloride equivalent to 200 mg gemcitabine.

After reconstitution, the solution contains 40 mg/ml of gemcitabine.

Also contains mannitol, sodium acetate trihydrate, hydrochloric acid and sodium hydroxide acid (for pH adjustment).

Each 200 mg vial contains 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 freeze dried cake.

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 Days 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 &gt;100,000</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>500 - 1,000 or 50,000-100,000</td>
<td>75</td>
<td></td>
</tr>
<tr>
<td>&lt;500 or &lt;50,000</td>
<td>Omit dose*</td>
<td></td>
</tr>
</tbody>
</table>

*Treatment omitted will not be reinstated within a cycle before the absolute granulocyte count reaches at least 500 (x10⁶/l) and the platelet count reaches 50,000 (x10⁶/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>&gt;1,200 and &gt;75,000</td>
<td>100</td>
<td></td>
</tr>
<tr>
<td>1,000 - &lt;1,200 or 50,000-75,000</td>
<td>75</td>
<td></td>
</tr>
<tr>
<td>700 - &lt;1,000 and ≥50,000</td>
<td>50</td>
<td></td>
</tr>
<tr>
<td>&lt;700 or &lt;50,000</td>
<td>Omit dose*</td>
<td></td>
</tr>
</tbody>
</table>

*Treatment omitted will not be reinstated within a cycle. Treatment will start on Day 1 of the next cycle once the absolute granulocyte count reaches at least 1,500 (x10⁶/l) and the platelet count reaches 100,000 (x10⁶/l).

**Dose modification of gemcitabine within a cycle 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>
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<td></td>
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<tr>
<td>1,000 - &lt;1,500 or 75,000-100,000</td>
<td>50</td>
<td></td>
</tr>
<tr>
<td>&lt;1000 or &lt;75,000</td>
<td>Omit dose*</td>
<td></td>
</tr>
</tbody>
</table>

*Treatment omitted will not be reinstated within a cycle. Treatment will start on Day 1 of the next cycle once the absolute granulocyte count reaches at least 1,500 (x10⁶/l) and the platelet count reaches 100,000 (x10⁶/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 neutropenia
- 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 recommendations 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 any of the excipients.

Breast-feeding (see section 4.6).

4.4 Special warnings and precautions for use

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

Haematological toxicity

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

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

Peripheral blood counts may continue to deteriorate after gemcitabine administration has been stopped. In patients with impaired bone marrow function, the treatment should be started with caution.

As with other cytotoxic treatments, the risk of cumulative bone-marrow suppression must be considered when gemcitabine treatment is given together with other chemotherapy.

Hepatic 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 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 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. Preclinical 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% of patients; dyspnoea reported in 10 to 40% of patients (highest incidence in lung cancer patients); allergic skin rashes occur in approximately 25% of patients and are associated with itching in 10% of patients.

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

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

The following table of undesirable effects and frequencies is based on data from clinical trials.

<table>
<thead>
<tr>
<th>Organ System</th>
<th>Frequency</th>
<th>Very Common (≥1/10)</th>
<th>Common (≥1/100 to &lt;1/10)</th>
<th>Uncommon (≥1/1,000 to &lt;1/100)</th>
<th>Rare (≥1/10,000 to &lt;1/1,000)</th>
<th>Very rare (&lt;1/10,000), not known (cannot be estimated from the available data)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood and Lymphatic System Disorders</td>
<td>leucopenia (Neutropenia Grade 3 = 19.3 %, Grade 4 = 6 %), bone-marrow suppression is usually mild to moderate and mostly affects the granulocyte</td>
<td>febrile neutropenia.</td>
<td></td>
<td></td>
<td></td>
<td>thrombocytosis.</td>
</tr>
<tr>
<td>Disorder Type</td>
<td>Symptoms</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>-------------------------------------</td>
<td>--------------------------------------------------------------------------</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Immune System Disorders</td>
<td>anaplasticity, thrombocytopenia, anaemia</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td>anorexia</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>somnolence, headache, insomnia</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiac disorders</td>
<td>myocardial infarct</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vascular Disorders</td>
<td>hypotension</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| Respiratory, thoracic, and mediastinal disorders | dyspnoea - usually mild and passes rapidly without treatment. 
|                                     | cough, rhinitis 
|                                     | interstitial pneumonitis (see section 4.4), bronchospasmism - usually mild and transient but may require parenteral treatment. |
| Gastro-intestinal disorders        | nausea, vomiting, stomatitis and ulceration of mouth, diarrhoea, constipation. |
| Hepatobiliary disorders            | elevation of liver transaminases (AST and ALT) and alkaline phosphate. 
|                                     | increased bilirubin. 
|                                     | Increased gamma-glutamyl transferase (GGT). |
| Skin and subcutaneous tissue disorders | allergic skin rash frequently associated with pruritus, alopecia 
|                                     | itching, sweating. 
|                                     | vesicle and sore formation, ulceration, scaling. |
| Musculo-skeletal and connective tissue disorders | back pain, myalgia |
| Renal and urinary disorders        | haematuria, mild proteinuria                                             |
| General disorders and administration | Influenza-like symptoms - the most common 
|                                     | fever, asthenia, chills 
|                                     | Injection site reactions - mainly mild in |
site conditions

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.

Post-marketing experience (spontaneous reports): frequency not known (cannot be estimated from the available data)

Injury, poisoning and procedural complications

Radiation toxicity (see section 4.5).

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)
Gastro-intestinal disorders:
Ischaemic colitis

Hepato-biliary 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, Stevens-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>Number (%) of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Paclitaxel Arm (N = 259)</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>Neutropenia</td>
<td>11 (4.2)</td>
</tr>
<tr>
<td>Non-laboratory</td>
<td></td>
</tr>
<tr>
<td>Febrile neutropenia</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 neutropenia lasting for more than 7 days occurred in 12.6% of patients in the combination arm and 5.0% of patients in the paclitaxel arm.

### Combination use in bladder cancer

<table>
<thead>
<tr>
<th>Grade 3 and 4 Adverse Events MVAC versus Gemcitabine plus cisplatin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number (%) of Patients</td>
</tr>
<tr>
<td>MVAC (methotrexate, vinblastine, doxorubicin and cisplatin) arm (N=196)</td>
</tr>
<tr>
<td>Grade 3</td>
</tr>
<tr>
<td>Laboratory</td>
</tr>
<tr>
<td>Anaemia</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
</tr>
<tr>
<td>Non-laboratory</td>
</tr>
<tr>
<td>Nausea and vomiting</td>
</tr>
<tr>
<td>Diarrhoea</td>
</tr>
<tr>
<td>Infection</td>
</tr>
<tr>
<td>Stomatitis</td>
</tr>
</tbody>
</table>

### Combination use in ovarian cancer

<table>
<thead>
<tr>
<th>Grade 3 and 4 Adverse Events Carboplatin versus Gemcitabine plus carboplatin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number (%) of Patients</td>
</tr>
</tbody>
</table>
Carboplatin arm (N=174) | Gemcitabine plus carboplatin arm (N=175)
---|---
**Laboratory** |  |  |  |  |
Anaemia | 10(5.7) | 4(2.3) | 39(22.3) | 9(5.1) |
Neutropenia | 19(10.9) | 2(1.1) | 73(41.7) | 50(28.6) |
Thrombocytopenia | 18(10.3) | 2(1.1) | 53(30.3) | 8(4.6) |
Leucopenia | 11(6.3) | 1(0.6) | 84(48.0) | 9(5.1) |
**Non-laboratory** |  |  |  |  |
Haemorrhage | 0(0.0) | 0(0.0) | 3(1.8) | (0.0) |
Febrile neutropenia | 0(0.0) | 0(0.0) | 2(1.1) | (0.0) |
Infection without neutropenia | 0(0.0) | 0(0.0) | 0(0.0) | 1(0.6) |

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.

**Antitumoral activity in preclinical models**
In animal tumour models, anti-tumoural activity of gemcitabine is schedule-dependent. When gemcitabine is administered daily, high mortality among the animals, but minimal anti-tumoural activity, is observed. If, however, gemcitabine is given every third or fourth day, it can be administered in non-lethal doses with substantial anti-tumoural 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.
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 IIIB or IV NSCLC, a combination of gemcitabine and cisplatin showed a statistically significant higher response rate than a combination of cisplatin and etoposide (40.6% and 21.2%, respectively, \( p=0.025 \)). A statistically significant prolongation of the time to progression, from 4.3 to 6.9 months (p=0.014) was observed in patients treated with gemcitabine/cisplatin compared to patients treated with etoposide/cisplatin. In both studies it was found that tolerability was similar in the two treatment arms.

**Ovarian carcinoma**

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

**Breast cancer**

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

### 5.2 Pharmacokinetic properties

The pharmacokinetics of gemcitabine have been examined in 353 patients in seven studies. The 121 women and 232 men ranged in age from 29 to 79 years. Of these patients, approximately 45% had non-small cell lung cancer and 35% were diagnosed with pancreatic cancer. The following pharmacokinetic parameters were obtained for doses ranging from 500 to 2,592 mg/m² that were infused from 0.4 to 1.2 hours.
Peak plasma concentrations (obtained within 5 minutes of the end of the infusion) were 3.2 to 45.5 µg/ml. Plasma concentrations of the parent compound following a dose of 1,000 mg/m²/30-minutes are greater than 5 µg/ml for approximately 30-minutes after the end of the infusion and greater than 0.4 µg/ml for an additional hour.

**Distribution**

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

The plasma protein binding was considered to be negligible.

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

**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 5µg/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 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 -288 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 perinatal and postnatal development.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

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

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal 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 30°C. From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at room temperature, unless reconstitution (and further dilution, if applicable) has taken place in controlled and validated aseptic conditions. Solutions 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.

6.4 Special precautions for storage

Vial before opening:

Store in the original package.

For storage conditions of the reconstituted medicinal product see section 6.3

6.5 Nature and contents of container

10 ml Type I moulded glass vial with bromobutyl rubber stopper and with 20 mm neck and flip off tear off aluminium seal.

Carton containing a single vial containing 200 mg gemcitabine.

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 5ml of sterile sodium chloride 9mg/ml (0.9%) solution for injection, without preservative, to the 200 mg vial. The total volume after reconstitution is 5.26 ml (200 mg vial). This yields a gemcitabine concentration of 38mg/ml, which includes accounting for the displacement volume of the lyophilised powder. Shake to dissolve. Further dilution with sterile sodium chloride 90
mg/ml (0.9%) solution for injection, without preservative, can be done. Reconstituted solution is clear, colourless to light straw-coloured solution.

3. Parenteral medicinal products 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
APSLA Limited,
Bayview House,
49 North Strand Road,
Dublin 3, Ireland

8 MARKETING AUTHORISATION NUMBER(S)
PL 33410/0019

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
10/03/2011

10 DATE OF REVISION OF THE TEXT
10/03/2011
The UK Summary of Product Characteristics (SmPC) for Gemcitabine 1000mg Powder for Solution for Infusion (PL 33410/0020) is as follows:

1 **NAME OF THE MEDICINAL PRODUCT**
   Gemcitabine 1000 mg Powder for solution for infusion

2 **QUALITATIVE AND QUANTITATIVE COMPOSITION**
   Each vial contains 1138 mg gemcitabine hydrochloride equivalent to 1000 mg gemcitabine.

   After reconstitution, the solution contains 40 mg/ml of gemcitabine.

   Also contains mannitol, sodium acetate trihydrate, hydrochloric acid and sodium hydroxide acid (for pH adjustment).

   Each 1,000 mg vial contains 22.985 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 freeze dried cake.

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 Days 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
Absolute granulocyte count
(x 10^6 /l)Platelet count
(x 10^6 /l)Percentage of standard dose of gemcitabine (%)
>1,000 and >100,000  100
500 - 1,000 or 50,000-100,000  75
<500 or <50,000  Omit dose*
*Treatment omitted will not be reinstated within a cycle before the absolute granulocyte count reaches at least 500 (x10^6/l) and the platelet count reaches 50,000 (x10^6/l).

Dose modification of gemcitabine within a cycle for breast cancer, given in combination with paclitaxel
Absolute granulocyte count
(x 10^6 /l)Platelet count
(x 10^6 /l)Percentage of standard dose of gemcitabine (%)
>1,200 and >75,000  100
1,000 - <1,200 or 50,000-75,000  75
700 - <1,000 and ≥ 50,000  50
<700 or <50,000  Omit dose*
*Treatment omitted will not be reinstated within a cycle. Treatment will start on Day 1 of the next cycle once the absolute granulocyte count reaches at least 1,500 (x10^6/l) and the platelet count reaches 100,000 (x10^6/l).

Dose modification of gemcitabine within a cycle ovarian cancer, given in combination with carboplatin
Absolute granulocyte count
(x 10^6 /l)Platelet count
(x 10^6 /l)Percentage of standard dose of gemcitabine (%)
>1,500 and ≥100,000  100
1,000 - <1,500 or 75,000-100,000  50
<1000 or <75,000  Omit dose*
*Treatment omitted will not be reinstated within a cycle. Treatment will start on Day 1 of the next cycle once the absolute granulocyte count reaches at least 1,500 (x10^6/l) and the platelet count reaches 100,000 (x10^6/l).

Dose modifications due to haematological toxicity in subsequent cycles, for all indications:
The gemcitabine dose should be reduced to 75% of the original cycle initiation dose, in the case of the following haematological toxicities:
- Absolute granulocyte count < 500 x 10^6/l for more than 5 days
- Absolute granulocyte count < 100 x 10^6/l for more than 3 days
- Febrile neutropenia
- Platelets < 25,000 x 10^6/l
- Cycle delay of more than 1 week due to toxicity

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

Gemcitabine is contra-indicated in those patients with a known hypersensitivity to the drug.

Breast-feeding (see section 4.6).

### 4.4 Special warnings and precautions for use

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

**Haematological toxicity**

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

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

Peripheral blood counts may continue to deteriorate after gemcitabine administration has been stopped. In patients with impaired bone marrow function, the treatment should be started with caution.

As with other cytotoxic treatments, the risk of cumulative bone-marrow suppression must be considered when gemcitabine treatment is given together with other chemotherapy.

**Hepatic 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 measure 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 1000 mg contains 22.985 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% of patients; dyspnoea reported in 10 to 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>Frequency</th>
<th>Organ System</th>
<th>System Disorders</th>
<th>Metabolism and nutrition disorders</th>
<th>Nervous system disorders</th>
<th>Cardiac</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very Common (≥1/10)</td>
<td>Blood and Lymphatic System Disorders</td>
<td>leucopenia (Neutropenia Grade 3 = 19.3% Grade 4 = 6%). bone-marrow suppression is usually mild to moderate and mostly affects the granulocyte count (see section 4.2). thrombocytopenia, anaemia</td>
<td>anorexia</td>
<td>somnolence, headache, insomnia</td>
<td>myocardial</td>
</tr>
<tr>
<td>Common (≥1/100 to &lt;1/10)</td>
<td></td>
<td>febrile neutropenia.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Uncommon (≥1/1,000 to &lt;1/100)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rare (≥1/10,000 to &lt;1/1,000)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Very rare (&lt;1/10,000), not known (cannot be estimated from the available data)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Immune System Disorders</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Metabolism</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>and nutrition disorders</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>disorders</td>
<td></td>
<td>infarct</td>
<td></td>
<td></td>
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<tr>
<td>-----------</td>
<td>------------------</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vascular Disorders</td>
<td>hypotension</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Respiratory, thoracic, and mediastinal disorders</td>
<td>dyspnoea - usually mild and passes rapidly without treatment.</td>
<td>cough, rhinitis</td>
<td>interstitial pneumonitis (see section 4.4). bronchospasm - usually mild and transient but may require parenteral treatment.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gastro-intestinal disorders</td>
<td>nausea, vomiting.</td>
<td>stomatitis and ulceration of mouth, diarrhoea, constipation.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hepatobiliary disorders</td>
<td>elevation of liver transaminases (AST and ALT) and alkaline phosphate.</td>
<td>increased bilirubin.</td>
<td>Increased gamma-glutamyl transferase (GGT).</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>allergic skin rash frequently associated with pruritus, alopecia</td>
<td>itching, sweating</td>
<td>vesicle and sore formation, ulceration, scaling.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Musculo skeletal and connective tissue disorders</td>
<td>back pain, myalgia</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Renal and urinary disorders</td>
<td>haematuria, mild proteinuria</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>General disorders and administration site 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. Oedema/peripheral oedema - including facial</td>
<td>fever, asthenia, chills</td>
<td>Injection site reactions - mainly mild in nature.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
oedema. oedema is usually reversible after stopping treatment.

| Injury poisoning and procedural complications |  |  | radiation toxicity (see section 4.5). |

Post-marketing experience (spontaneous reports): frequency not known (cannot be estimated from the available data)

Nervous system disorders:
Cerebrovascular accident.

Cardiac disorders:
Arrythmias, 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)
Gastro-intestinal disorders:
Ischaemic colitis

Hepato-biliary 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, Stevens-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.

<table>
<thead>
<tr>
<th>Grade 3 and 4 Adverse Events</th>
<th>Paclitaxel versus Gemcitabine plus Paclitaxel</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number (%) of Patients</td>
<td>Paclitaxel Arm (N = 259)</td>
</tr>
<tr>
<td>Laboratory</td>
<td>Grade 3</td>
</tr>
<tr>
<td>Anaemia</td>
<td>5 (1.9)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>0</td>
</tr>
</tbody>
</table>
Neutropenia  11 (4.2)  17 (6.6)*  82 (31.3)  45 (17.2)*
Non-laboratory
Febrile neutropenia  3 (1.2)  0  12 (4.6)  1 (0.4)
Fatigue  3 (1.2)  1 (0.4)  15 (5.7)  2 (0.8)
Diarrhoea  5 (1.9)  0  8 (3.1)  0
Motor neuropathy  2(0.8)  0  6(2.3)  1(0.4)
Sensory neuropathy  9(3.5)  0  14(5.3)  1(0.4)
*Grade 4 neutropenia lasting for more than 7 days occurred in 12.6% of patients in the combination arm and 5.0% of patients in the paclitaxel arm.

**Combination use in bladder cancer**

<table>
<thead>
<tr>
<th>Grade 3 and 4 Adverse Events</th>
<th>MVAC versus Gemcitabine plus cisplatin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number (% of Patients)</td>
<td>MVAC (methotrexate, vinblastine, doxorubicin and cisplatin) arm (N=196)</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>Number (% of Patients)</td>
<td>Carboplatin arm (N=174)</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>Neutropenia</td>
<td>19(10.9)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>18(10.3)</td>
</tr>
<tr>
<td>Leucopenia</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 neutropenia</td>
<td>0(0.0)</td>
</tr>
</tbody>
</table>
Infection without neutropenia | 0(0) | 0(0.0) | 0(0.0) | 1(0.6) |

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

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.

Anti-tumoural activity in preclinical models
In animal tumour models, anti-tumoural activity of gemcitabine is schedule-dependent. When gemcitabine is administered daily, high mortality among the animals, but minimal anti-tumoural activity, is observed. If, however, gemcitabine is given every third or fourth day, it can be administered in non-lethal doses with substantial anti-tumoural 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 IIIB or IV NSCLC, a combination of gemcitabine and cisplatin showed a statistically significant higher response rate than a combination of cisplatin and etoposide (40.6% and 21.2%, respectively, p=0.025). A statistically significant prolongation of the time to progression, from 4.3 to 6.9 months (p=0.014) was observed in patients treated with gemcitabine/cisplatin compared to patients treated with etoposide/cisplatin. In both studies it was found that tolerability was similar in the two treatment arms.

**Ovarian carcinoma**

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

**Breast cancer**

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

5.2 Pharmacokinetic properties

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

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

**Distribution**

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

Half-life: This ranged from 42 to 94 minutes depending on age and gender. For the recommended dosing schedule, gemcitabine elimination should be virtually complete within 5 to 11 hours of the start of the infusion. Gemcitabine does not accumulate when administered once weekly.
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 (interindividual 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 5µg/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 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 -288 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 perinatal and postnatal development.
6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Mannitol
Sodium acetate trihydrate
Hydrochloric acid (for pH adjustment)
Sodium hydroxide (for pH adjustment)

6.2 Incompatibilities
This medicinal product must not be mixed with other medicinal 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 30°C.
From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at room temperature, unless reconstitution (and further dilution, if applicable) has taken place in controlled and validated aseptic conditions.
Solutions 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.

6.4 Special precautions for storage
Vial before opening:
Store in the original package.
For storage conditions of the reconstituted medicinal product see section 6.3

6.5 Nature and contents of container
50 ml type I moulded glass vial with bromobutyl rubber stopper and with 20 mm neck and flip off tear off aluminium seal.
Carton containing a single vial containing 1000 mg gemcitabine.

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 25 ml sterile sodium chloride 9 ml/ml (0.9%) solution for injection, without preservative, to the 1000 mg vial. The total volume after reconstitution is 26.3 ml (1000 mg vial). 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 90 mg/ml (0.9%) solution for injection, without preservative, can be done. Reconstituted solution is clear, colourless to light straw-coloured solution.
3. Parenteral medicinal products should be inspected visually for particulate matter and
discoulouration prior to administration. If particulate matter is observed, do not administer.

Disposal
All items used for preparation, administration or otherwise coming into contact with gemcitabine
should undergo disposal according to hospital standard procedures applicable to cytotoxic agents
with due regard to current laws related to the disposal of hazardous waste.
PATIENT INFORMATION LEAFLET

PACKAGE LEAFLET: INFORMATION FOR THE USER

GEMCITABINE 200 mg & 1000 mg
POWDER FOR SOLUTION FOR INFUSION

Read all of this leaflet carefully before you start using this medicine.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if they are the same age as you.
- If any of the side effects listed above occur, or if you notice any side effects not listed in this leaflet, tell your doctor or pharmacist.

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

1. WHAT GEMCITABINE IS AND WHAT IT IS USED FOR

The name of your medicine is Gemcitabine 200 mg or 1000 mg Powder for solution for infusion. In the rest of this leaflet your medicine is called Gemcitabine.

Gemcitabine 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

Do not use Gemcitabine:
- if you are allergic (hypersensitive) to gemcitabine hydrochloride or any other ingredient of gemcitabine
- if you are breast-feeding

Take special care with Gemcitabine:
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 your blood cells are sensitive to gemcitabine. You 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.
- if you have recently had, or are going to have radiotherapy.
- if you have been vaccinated recently.
- if you develop breathing difficulties or feel very weak and are very pale (may be a sign of liver failure).

You must be advised not to father a child during or up to 6 months following treatment with Gemcitabine. If you would like to father a child during the treatment or in the 6 months following treatment, ask 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 vitamins 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 should be avoided during pregnancy.

If you are breast-feeding, tell your doctor.

You must avoid breast-feeding during Gemcitabine treatment.

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

Driving and using machines:
Gemcitabine may make you feel sleepy. If you get drowsy, particular if you have consumed any alcohol, do not drive a car or use machinery until you are sure that Gemcitabine treatment has not made you feel sleepy.

Important information about some of the ingredients of Gemcitabine
Gemcitabine contains 5 mg (c. 1 milliliter) of sodium in each 200 mg vial and 22,566 mg (c. 1 milliliter) sodium in each 1000 mg vial. To be taken into consideration by patients and in controlled sodium diet.

3. HOW GEMCITABINE WILL BE GIVEN TO YOU

Gemcitabine will be given to you by a healthcare professional, who will have dissolved the Gemcitabine powder beforehand.

The usual dose of Gemcitabine is 1000-2500 mg for every square meter of your body 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 dose may be adjusted, or treatment may be delayed depending on your blood cell counts and your general condition.

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

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

If you are given too much Gemcitabine:
Your doctor will ensure that the correct dose for your condition is given. In cases of suspected overdose, your blood count should be monitored. Appropriate treatment should be started if required.

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

4. POSSIBLE SIDE EFFECTS

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

Frequency 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
- occasional: affects 1 to 10 users in 1,000
- rare: affects less than 1 user in 10,000
- very rare: affects less than 1 user in 100,000
- not known: frequency cannot be estimated from the available data

You must see your doctor IMMEDIATELY if you notice any of the following:
- fever or infection (commonly): if you have a temperature of 37.5°C or greater, or any other sign of infection (frequent pain you might feel cold white blood cells than normal which is very common)
- painful bladder (rarely done known)
- pain, redness, swelling or urching as you might have less bladder (very common)
- allergic reaction: you develop skin rash (very common)/rash (common), or fever (very common)/fever (common), or tiredness, breathing difficulty (may be very common)
- bleeding from the gums, nose or mouth (unusual)
- unexpected bleeding (may be very common to have bleeding difficulty worse than normal which is very common)
- difficulty breathing (it is very common to have feeling difficulty breathing even after the Gemcitabine infusion which may persist, however uncommonly or rarely these may be more severe lung problems).

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MHRA-UKPAR – Gemcitabine 200mg & 1000mg Powder for Solution for Infusion

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THE FOLLOWING INFORMATION IS INTENDED FOR HEALTHCARE PROFESSIONALS ONLY

Below is a summary of information to assist in the administration of GEMCITABINE. You should be experienced in the handling and use of cytotoxic agents and be familiar with the SPC for GEMCITABINE.

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 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 1000 mg vial. Shake to dissolve. The total volume after reconstitution is 5.26 ml (200 mg vial) or 26.3 ml (1000 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 30°C. From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 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 cytotoxic 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

All items used for preparation, administration or otherwise coming into contact with gemcitabine should undergo disposal according to local guidelines for the handling of cytotoxic compounds.
Side effects of gemcitabine 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
- Headache
- 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 neutropenia)
- Anorexia (poor appetite)
- Headache
- Nausea
- Sleepiness
- Cough
- Ruddy skin
- Constipation
- Diarrhoea
- Pain, redness, swelling or oedema in the mouth
- Itching
- Exfoliating
- Muscle pain
- Back pain
- Fever
- Oedema
- Chills

**Uncommon side effects**
- Urinary tract symptoms (including the urethra of the penis)
- A rise in the serum glucose (diabetes)
- A rise in the liver enzymes (liver function)
- Some injection site reactions

**Rare side effects**
- Heart attack (myocardial infarction)
- Low blood pressure
- Skin reactions, allergic reaction
- Injection site reactions

**Very rare side effects**
- Increased platelet count
- Exacerbation of skin rash (severe cutaneous adverse reaction)

**Side effects with frequency not known**
- Angina/heart attack, arthritis
- Autoimmune disorder (severe lung inflammation causing respiratory failure)
- Radiation recall – skin rash like severe sunburn which can occur on skin that has previously been exposed to radiotherapy
- Fluid in the lungs
- Radiation therapy – swelling of the skin associated with radiation therapy
- Haemorrhage in the lungs
- Life-threatening injury
- Gangrene of fingers or toes
- Severe 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.

**5. HOW TO STORE GEMCITABINE**

Keep out of the reach and sight of children.

Do not use Gemcitabine after the expiry date which is stated on the label and carton after EXP. The expiry date refers to the last day of that month.

Unopened vials: Store in the original package.

Reconstituted solution:

Chemical and physical in-use stability has been demonstrated for 24 hours at 30°C.

From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage must and conditions prior to use are the responsibility of the user and should 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.

The reconstituted solution should not be refrigerated, as crystallisation may occur.

Do not use Gemcitabine if you notice a cloudy solution or an insoluble precipitate.

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

**6. FURTHER INFORMATION**

**What Gemcitabine contains**

The active substance is gemcitabine hydrochloride. Each vial contains 200 mg or 1000 mg of the active ingredient gemcitabine hydrochloride.

The other ingredients are mannitol, sodium acetate trihydrate, sodium hydroxide and hydrochloric acid.

**What Gemcitabine looks like and comes as the pack**

Gemcitabine powder is white to off white mass dried cake presented in Type I flavoured glass vial.

The 200 mg and 1000 mg vials are available separately in single packs.

**Marketing Authorisation Holder**

APC Limited, Brayview House, 49 North Strand Road, Dublin 3, Ireland.

**Manufacturer**

APC Pharmaceuticals & Chemicals (Europe) Limited, 9th floor, CP House, 97-107 Uxbridge Road, Ealing, London W5 5ST.

**Distributor**

APC Pharmaceuticals & Chemicals (Europe) Limited, 9th floor, CP House, 97-107 Uxbridge Road, Ealing, London W5 5ST.

This leaflet was last revised in July 2010.
GEMCITABINE 200MG AND 1000MG POWDER FOR SOLUTION FOR INFUSION

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CARTON