Public Assessment Report

Decentralised Procedure

Gemcitabine 38 mg/ml powder for solution for infusion

(Gemcitabine hydrochloride)

UK/H/1437/01/DC
UK/H/2568/01/DC
UK/H/2569/01/DC

UK licence numbers: PL 11587/0045, 0055 & 0056

MEDAC Gesellschaft für klinische Spezialpräparate mbH
On 23rd March 2009, the MHRA granted MEDAC Gesellschaft für klinische Spezialpräparate mbH Marketing Authorisations (licences) for the medicinal product, Gemcitabine 38 mg/ml powder for solution for infusion (PL 11587/0055 & 0056, UK/H/2568-9/01/DC). On 30th March 2009, the MHRA granted MEDAC Gesellschaft für klinische Spezialpräparate mbH a licence for the medicinal product Gemcitabine medac 38 mg/ml powder for solution for infusion (PL 11587/0045, UK/H/1437/01/DC). These are prescription-only medicines (POM) used in the treatment of different types of cancer.

Gemcitabine 38 mg/ml powder for solution for infusion contains the active ingredient gemcitabine, which belongs to a group of medicines called ‘cytotoxics’. These medicines kill dividing cells, including cancer cells.

Gemcitabine 38 mg/ml powder for solution for infusion can be used alone or in combination with other anti-cancer medicines, depending on the type of cancer. Gemcitabine 38 mg/ml powder for solution for infusion 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

These applications are based on reference products with valid UK licences. No new or unexpected safety concerns arose from these applications and it was, therefore, judged that the benefits of taking Gemcitabine 38 mg/ml powder for solution for infusion outweigh the risks; hence Marketing Authorisations have been granted.

The UK licence for Gemcitabine 38 mg/ml powder for solution for infusion (PL 11587/0056) was cancelled on 30/03/2009.
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</table>
## Module 1

### Information about Initial Procedure

<table>
<thead>
<tr>
<th>Product Name</th>
<th>Gemcitabine medac 38 mg/ml powder for solution for infusion Gemcitabine 38 mg/ml powder for solution for infusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type of Application</td>
<td>Generic, Article 10.1</td>
</tr>
<tr>
<td>Active Substance</td>
<td>Gemcitabine hydrochloride</td>
</tr>
<tr>
<td>Form</td>
<td>Powder for solution for infusion</td>
</tr>
<tr>
<td>Strength</td>
<td>38mg / ml</td>
</tr>
<tr>
<td>MA Holder</td>
<td>medac \n Gesellschaft für klinische Spezialpräparate mbH \n Fehlandtstr. 3 \n 20354 Hamburg \n Germany</td>
</tr>
<tr>
<td>Reference Member State (RMS)</td>
<td>UK</td>
</tr>
<tr>
<td>Concerned Member State / s (CMS)</td>
<td>UK/H/1437/01/DC – AT, BE, BG, CZ, DE, DK, EE, EL, ES, FI, FR, HU, IE, LT, LV, NL, NO, PL, PT, RO, SE, SI, SK \n UK/H/2568/01/DC – AT \n UK/H/2569/01/DC – AT, BG, CZ, DE, DK, EE, EL, FR, LT, LV, NL, NO, PL, PT, RO, SK</td>
</tr>
<tr>
<td>Procedure Number</td>
<td>UK/H/1437/01/DC \n UK/H/2568/01/DC \n UK/H/2569/01/DC</td>
</tr>
<tr>
<td>Timetable</td>
<td>Day 210 – 6(^{th}) January 2009</td>
</tr>
</tbody>
</table>
Module 2

Summary of Product Characteristics

Gemcitabine medac 38 mg/ml powder for solution for infusion (PL 11587/0045)

1 NAME OF THE MEDICINAL PRODUCT
Gemcitabine medac 38 mg/ml powder for solution for infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
One vial contains gemcitabine hydrochloride equivalent to 200 mg gemcitabine.
One vial contains gemcitabine hydrochloride equivalent to 1,000 mg gemcitabine.
One vial contains gemcitabine hydrochloride equivalent to 1,500 mg gemcitabine.

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

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

For a full list of excipients see section 6.1.

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

4 CLINICAL PARTICULARS

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

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

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

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

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

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

Recommended posology

Bladder cancer
Combination use
The recommended dose for gemcitabine is 1000 mg/m², given by 30-minute intravenous 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 1000 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 1000 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 1250 mg/m² body surface area given as a 30-minute intravenous infusion on Day 1 and 8 of the treatment cycle (21 days). Dosage reduction with each cycle or within a cycle may be applied based upon the grade of toxicity experienced by the patient. Cisplatin has been used at doses between 75-100 mg/m² once every 3 weeks.

Breast cancer
Combination use
Gemcitabine in combination with paclitaxel is recommended using paclitaxel (175 mg/m²) administered on Day 1 over approximately 3-hours as an intravenous infusion, followed by gemcitabine (1250 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 1000 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 account of 100,000 (x 10⁹/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</td>
<td>&gt; 100,000</td>
<td>100</td>
</tr>
<tr>
<td>500-1,000</td>
<td>50,000-100,000</td>
<td>75</td>
</tr>
<tr>
<td>&lt;500</td>
<td>&lt; 50,000</td>
<td>Omit dose *</td>
</tr>
</tbody>
</table>

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

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

### Dose modification of gemcitabine within a cycle for ovarian cancer, given in combination with carboplatin

<table>
<thead>
<tr>
<th>Absolute granulocyte count (x 10⁶/l)</th>
<th>Platelet count (x 10⁶/l)</th>
<th>Percentage of standard dose of gemcitabine (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 1,500</td>
<td>≥ 100,000</td>
<td>100</td>
</tr>
<tr>
<td>1000-1,500</td>
<td>75,000-100,000</td>
<td>50</td>
</tr>
<tr>
<td>&lt;1000</td>
<td>&lt;75,000</td>
<td>Omit dose*</td>
</tr>
</tbody>
</table>

*Treatment omitted will not be re-instated within a cycle. Treatment will start on day 1 of the next cycle once the absolute granulocyte count reaches at least 1,500 (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).

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

4.3 Contraindications
Hypersensitivity to the active substance gemcitabine or to any of the excipients.

Breast-feeding during treatment with gemcitabine.

4.4 Special warnings and precautions for use
Prolongation of the infusion time and increased dosing frequency have been shown to increase toxicity.

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

Hepatic 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 recommendations for this patient population (see section 4.2).

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

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

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

Pulmonary
Pulmonary effects, sometimes severe (such as pulmonary oedema, interstitial pneumonitis or adult respiratory distress syndrome (ARDS)) have been reported in association with gemcitabine therapy. The aetiology of these effects is unknown. If such effects develop, consideration should be made to discontinuing gemcitabine therapy. Early use of supportive care measures may help ameliorate the condition.
Renal
Clinical findings consistent with the haemolytic uraemic syndrome (HUS) were rarely reported in patients receiving gemcitabine (see section 4.8). Gemcitabine should be discontinued at the first signs of any evidence of microangiopathic haemolytic anaemia, such as rapidly falling haemoglobin with concomitant thrombocytopenia, elevation of serum bilirubin, serum creatinine, blood urea nitrogen, or LDH. Renal failure may not be reversible with discontinuation of therapy and dialysis may be required.

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

Sodium
The 200 mg vial of Gemcitabine medac contains 3.5 mg (< 1 mmol) sodium per vial.
The 1,000 mg vial of Gemcitabine medac contains 17.5 mg (< 1 mmol) sodium per vial.
The 1,500 mg vial of Gemcitabine medac contains 26.3 mg (< 1 mmol) sodium per vial.
This should be taken into consideration by patients on a controlled sodium diet.

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

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

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

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

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

4.6 Pregnancy and lactation

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

Breast-feeding
It is not known whether gemcitabine is excreted in human milk and adverse effects on the suckling child cannot be excluded. Breast-feeding must be discontinued during gemcitabine therapy.
Fertility
In fertility studies gemcitabine caused hypospermatogenesis in male mice (see section 5.3). Therefore, men being treated with gemcitabine are advised not to father a child during and up to 6 months after treatment and to seek further advice regarding cryoconservation of sperm prior to treatment because of the possibility of infertility due to therapy with gemcitabine.

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

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

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

Clinical trial data
Frequencies are defined as: Very common (≥1/10), Common (≥1/100 to <1/10), Uncommon (≥1/1000 to <1/100), Rare (≥1/10,000 to <1/1000), Very Rare (<1/10,000).

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

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

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

**Nervous system disorders**
- Cerebrovascular accident

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

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

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

**Gastrointestinal disorders**
- Ischaemic colitis

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

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

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

**Injury, poisoning and procedural complications**
- 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>
<th>Paclitaxel arm (N=259)</th>
<th>Gemcitabine plus Paclitaxel arm (N=262)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Grade 3</td>
<td>Grade 4</td>
</tr>
<tr>
<td><strong>Laboratory</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anaemia</td>
<td></td>
<td>5 (1.9)</td>
<td>1 (0.4)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td></td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Neutropenia</td>
<td></td>
<td>11 (4.2)</td>
<td>17 (6.6)*</td>
</tr>
<tr>
<td><strong>Non-laboratory</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Febrile neutropenia</td>
<td></td>
<td>3 (1.2)</td>
<td>0</td>
</tr>
<tr>
<td>Fatigue</td>
<td></td>
<td>3 (1.2)</td>
<td>1 (0.4)</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td></td>
<td>5 (1.9)</td>
<td>0</td>
</tr>
<tr>
<td>Motor neuropathy</td>
<td></td>
<td>2 (0.8)</td>
<td>0</td>
</tr>
<tr>
<td>Sensory neuropathy</td>
<td></td>
<td>9 (3.5)</td>
<td>0</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**

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

<table>
<thead>
<tr>
<th></th>
<th>Number (%) of Patients</th>
<th>MVAC (methotrexate, vinblastine, doxorubicin and cisplatin) arm (N=196)</th>
<th>Gemcitabine plus cisplatin arm (N=200)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Grade 3</td>
<td>Grade 4</td>
</tr>
<tr>
<td><strong>Laboratory</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anaemia</td>
<td></td>
<td>30 (16)</td>
<td>4 (2)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td></td>
<td>15 (8)</td>
<td>25 (13)</td>
</tr>
<tr>
<td><strong>Non-laboratory</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea and vomiting</td>
<td></td>
<td>37 (19)</td>
<td>3 (2)</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td></td>
<td>15 (8)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Infection</td>
<td></td>
<td>19 (10)</td>
<td>10 (5)</td>
</tr>
<tr>
<td>Stomatitis</td>
<td></td>
<td>34 (18)</td>
<td>8 (4)</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>
<tr>
<td>Infection without neutropenia</td>
<td>0(0.0)</td>
</tr>
</tbody>
</table>

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

4.9 Overdose

There is no known antidote for overdose of gemcitabine. Doses as high as 5700 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, antitumoural activity of gemcitabine is schedule-dependent. When gemcitabine is administered daily, high mortality among the animals but minimal antitumoural activity is observed. If, however, gemcitabine is given every third or fourth day, it can be administered in non-lethal doses with substantial antitumoural activity against a broad spectrum of mouse tumours.

Mechanism of action

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

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

Clinical data

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

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

Non small cell lung cancer
In a randomised phase III study of 522 patients with inoperable, locally advanced or metastatic NSCLC, gemcitabine in combination with cisplatin showed a statistically significant higher response rate than cisplatin alone (31.0% and 12.0%, respectively, \( p<0.0001 \)). A statistically significant prolongation of the time to progression, from 3.7 to 5.6 months (log-rank \( p=0.012 \)) 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 /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 1000 mg/m² given as a 30-minute infusion, lower clearance values for women and men should not necessitate a decrease in the gemcitabine dose.

Urinary excretion: Less than 10% is excreted as unchanged drug. Renal clearance was 2 to 7 l/hr/m².

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

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

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

dFdU kinetics
Peak plasma concentrations (3-15 minutes after end of 30-minute infusion, 1000 mg/m²): 28-52 µg/ml. Trough concentration following once weekly dosing: 0.07-1.12 µg/ml, with no apparent accumulation. Triphasic plasma concentration versus time curve, mean half-life of terminal phase - 65 hours (range 33-84 hr).

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

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

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

Tissue distribution: Extensive.

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

Urinary excretion: All.

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

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

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

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

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

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

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

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Gemcitabine medac 38 mg/ml contains:
Mannitol (E421)
Sodium acetate trihydrate (E262)
Hydrochloric acid (E507) (for pH-adjustment)
Sodium hydroxide (E524) (for pH-adjustment)

6.2 Incompatibilities

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

6.3 Shelf life

2 years

*After reconstitution:*
Chemical and physical in-use stability has been demonstrated for 35 days at 25 °C. From a microbiological point of view, the product should be used immediately.

If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 25 °C, unless reconstitution / dilution has taken place in controlled and validated aseptic conditions.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

*Reconstituted solution:*
Do not refrigerate (crystallisation may occur).
For storage condition of the reconstituted medicinal product, see section 6.3.

6.5 Nature and contents of container

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

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

6.6 Special precautions for disposal

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

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

The appropriate amount of medicinal product may be further diluted with sodium chloride 9 mg/ml (0.9 %) solution for injection.

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

Any unused solution should be discarded as described below.

**Guidelines for the Safe Handling of Cytotoxic Medicinal Products:**

Local guidelines on safe preparation and handling of cytotoxic medicinal products must be adhered to. Cytotoxic preparations should not be handled by pregnant staff. The preparation of injectable solutions of cytotoxic agents must be carried out by trained specialist personnel with knowledge of the medicines used. This should be performed in a designated area. The work surface should be covered with disposable plastic-backed absorbent paper.

Suitable eye protection, disposable gloves, face mask and disposable apron should be worn.

Precautions should be taken to avoid the medicinal product accidentally coming into contact with the eyes. If accidental contamination occurs, the eye should be washed with water thoroughly and immediately.

Syringes and infusion sets should be assembled carefully to avoid leakage (use of Luer lock fittings is recommended). Large bore needles are recommended to minimise pressure and the possible formation of aerosols. The latter may also be reduced by the use of a venting needle.

Actual spillage or leakage should be mopped up wearing protective gloves. Excreta and vomit must be handled with care.

**Disposal:**

Adequate care and precaution should be taken in the disposal of items used to reconstitute this medicinal product. Any unused dry product or contaminated materials should be placed in a high-risk waste bag. Sharp objects (needles, syringes, vials, etc) should be placed in a suitable rigid container. Personnel concerned with the collection and disposal of this waste should be aware of the hazard involved. Waste material should be destroyed by incineration. Any unused product or waste material should be disposed of in accordance with local requirements.
Gemcitabine 38 mg/ml powder for solution for infusion (PL 11587/0055 & 0056)

NAME OF THE MEDICINAL PRODUCT

Gemcitabine 38 mg/ml powder for solution for infusion

QUALITATIVE AND QUANTITATIVE COMPOSITION

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

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

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

For a full list of excipients see section 6.1.

PHARMACEUTICAL FORM

Powder for solution for infusion
White to off-white powder.

CLINICAL PARTICULARS

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.

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 1000 mg/m², given by 30-minute intravenous 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 1000 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 1000 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 1250 mg/m² body surface area given as a 30-minute intravenous infusion on Day 1 and 8 of the treatment cycle (21 days). Dosage reduction with each cycle or within a cycle may be applied based upon the grade of toxicity experienced by the patient. Cisplatin has been used at doses between 75-100 mg/m² once every 3 weeks.

Breast cancer
Combination use
Gemcitabine in combination with paclitaxel is recommended using paclitaxel (175 mg/m²) administered on Day 1 over approximately 3-hours as an intravenous infusion, followed by gemcitabine (1250 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 1000 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 account of 100,000 (x 10⁶/l) prior to the initiation of a cycle.

Within a cycle
Dose modifications of gemcitabine within a cycle should be performed according to the following tables:
Dose modification of gemcitabine within a cycle for bladder cancer, NSCLC and pancreatic cancer, given in monotherapy or in combination with cisplatin

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

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

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

Dose modification of gemcitabine within a cycle for ovarian cancer, given in combination with carboplatin

<table>
<thead>
<tr>
<th>Absolute granulocyte count (x 10⁶/l)</th>
<th>Platelet count (x 10⁶/l)</th>
<th>Percentage of standard dose of gemcitabine (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 1,500 and</td>
<td>≥ 100,000</td>
<td>100</td>
</tr>
<tr>
<td>1000-1,500 or</td>
<td>75,000-100,000</td>
<td>50</td>
</tr>
<tr>
<td>&lt;1000 or</td>
<td>&lt; 75,000</td>
<td>Omit dose *</td>
</tr>
</tbody>
</table>

*Treatment omitted will not be re-instated within a cycle. Treatment will start on day 1 of the next cycle once the absolute granulocyte count reaches at least 1,500 (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).

**Children**

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

### 4.3 Contraindications

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

Breast-feeding during treatment with gemcitabine.

### 4.4 Special warnings and precautions for use

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

**Haematological toxicity**

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

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

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

**Hepatic 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 recommendations for this patient population (see section 4.2).

**Concomitant radiotherapy**

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

**Live vaccinations**

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

**Cardiovascular**

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

**Pulmonary**

Pulmonary effects, sometimes severe (such as pulmonary oedema, interstitial pneumonitis or adult respiratory distress syndrome (ARDS)) have been reported in association with gemcitabine therapy. The aetiology of these effects is unknown. If such effects develop, consideration should be made to discontinuing gemcitabine therapy. Early use of supportive care measures may help ameliorate the condition.
Renal
Clinical findings consistent with the haemolytic uraemic syndrome (HUS) were rarely reported in patients receiving gemcitabine (see section 4.8). Gemcitabine should be discontinued at the first signs of any evidence of microangiopathic haemolytic anaemia, such as rapidly falling haemoglobin with concomitant thrombocytopenia, elevation of serum bilirubin, serum creatinine, blood urea nitrogen, or LDH. Renal failure may not be reversible with discontinuation of therapy and dialysis may be required.

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

Sodium
The 200 mg vial of Gemcitabine contains 3.5 mg (< 1 mmol) sodium per vial.
The 1,000 mg vial of Gemcitabine contains 17.5 mg (< 1 mmol) sodium per vial.
The 1,500 mg vial of Gemcitabine contains 26.3 mg (< 1 mmol) sodium per vial.
This should be taken into consideration by patients on a controlled sodium diet.

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

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

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

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

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

4.6 Pregnancy and lactation

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

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

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

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

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

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

Clinical trial data

Frequencies are defined as: Very common (≥1/10), Common (≥1/100 to <1/10), Uncommon (≥1/1000 to <1/100), Rare (≥1/10,000 to <1/1000), Very Rare (<1/10,000).

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

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

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

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

**Nervous system disorders**
Cerebrovascular accident

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

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

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

**Gastrointestinal disorders**
Ischaemic colitis

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

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

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

**Injury, poisoning and procedural complications**
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>Laboratory</th>
<th>Paclitaxel arm (N=259)</th>
<th>Gemcitabine plus Paclitaxel arm (N=262)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anaemia</td>
<td>Grade 3 5 (1.9)</td>
<td>Grade 3 15 (5.7)</td>
</tr>
<tr>
<td></td>
<td>Grade 4 1 (0.4)</td>
<td>Grade 4 3 (1.1)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>Grade 3 0</td>
<td>Grade 3 14 (5.3)</td>
</tr>
<tr>
<td></td>
<td>Grade 4 0</td>
<td>Grade 4 1 (0.4)</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>Grade 3 11 (4.2)</td>
<td>Grade 3 82 (31.3)</td>
</tr>
<tr>
<td></td>
<td>Grade 4 17 (6.6)*</td>
<td>Grade 4 45 (17.2)*</td>
</tr>
</tbody>
</table>

*Non-laboratory:

<table>
<thead>
<tr>
<th></th>
<th>Paclitaxel arm (N=259)</th>
<th>Gemcitabine plus Paclitaxel arm (N=262)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Laboratory</td>
<td>Grade 3 3 (1.2)</td>
<td>Grade 3 12 (4.6)</td>
</tr>
<tr>
<td>Anaemia</td>
<td>Grade 4 0</td>
<td>Grade 4 1 (0.4)</td>
</tr>
<tr>
<td>Nausea and vomiting</td>
<td>37(19)</td>
<td>44(22) (22)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>Grade 3 3 (1.2)</td>
<td>Grade 3 15 (5.7)</td>
</tr>
<tr>
<td></td>
<td>Grade 4 1 (0.4)</td>
<td>Grade 4 2 (0.8)</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>Grade 3 5 (1.9)</td>
<td>Grade 3 8 (3.1)</td>
</tr>
<tr>
<td></td>
<td>Grade 4 0</td>
<td>Grade 4 0</td>
</tr>
<tr>
<td>Motor neuropathy</td>
<td>2(0.8)</td>
<td>6(2.3)</td>
</tr>
<tr>
<td></td>
<td>0</td>
<td>1(0.4)</td>
</tr>
<tr>
<td>Sensory neuropathy</td>
<td>9(3.5)</td>
<td>14(5.3)</td>
</tr>
<tr>
<td></td>
<td>0</td>
<td>1(0.4)</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>Laboratory</th>
<th>MVAC (methotrexate, vinblastine, doxorubicin and cisplatin) arm (N=196)</th>
<th>Gemcitabine plus cisplatin arm (N=200)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anaemia</td>
<td>Grade 3 30(16)</td>
<td>Grade 3 47(24)</td>
</tr>
<tr>
<td></td>
<td>Grade 4 4(2)</td>
<td>Grade 4 7(4)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>Grade 3 15(8)</td>
<td>Grade 3 57(29)</td>
</tr>
<tr>
<td></td>
<td>Grade 4 25(13)</td>
<td>Grade 4 57(29)</td>
</tr>
<tr>
<td>Nausea and vomiting</td>
<td>37(19)</td>
<td>44(22) (22)</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>Grade 3 15(8)</td>
<td>Grade 3 6(3)</td>
</tr>
<tr>
<td></td>
<td>Grade 4 1(1)</td>
<td>Grade 4 0(0)</td>
</tr>
<tr>
<td>Infection</td>
<td>Grade 3 19(10)</td>
<td>Grade 3 4(2)</td>
</tr>
<tr>
<td></td>
<td>Grade 4 10(5)</td>
<td>Grade 4 1(1)</td>
</tr>
<tr>
<td>Stomatitis</td>
<td>Grade 3 34(18)</td>
<td>Grade 3 2(1)</td>
</tr>
<tr>
<td></td>
<td>Grade 4 8(4)</td>
<td>Grade 4 0(0)</td>
</tr>
</tbody>
</table>
Combination use in ovarian cancer

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

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

4.9 Overdose

There is no known antidote for overdose of gemcitabine. Doses as high as 5700 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, antitumoural activity of gemcitabine is schedule-dependent. When gemcitabine is administered daily, high mortality among the animals but minimal antitumoural activity is observed. If, however, gemcitabine is given every third or fourth day, it can be administered in non-lethal doses with substantial antitumoural activity against a broad spectrum of mouse tumours.

Mechanism of action

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

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

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

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

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

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

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

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

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

5.2 Pharmacokinetic properties

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

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 1000 mg/m² given as a 30-minute infusion, lower clearance values for women and men should not necessitate a decrease in the gemcitabine dose.

Renal excretion: Less than 10% is excreted as unchanged drug. Renal clearance was 2 to 7 l/hr/m².

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

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

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

dFdU kinetics
Peak plasma concentrations (3-15 minutes after end of 30-minute infusion, 1000 mg/m²): 28-52 µg/ml. Trough concentration following once weekly dosing: 0.07-1.12 µg/ml, with no apparent accumulation. Triphasic plasma concentration versus time curve, mean half-life of terminal phase - 65 hours (range 33-84 hr).

Formation of dFdU from parent compound: 91%-98%.
Mean volume of distribution of central compartment: 18 l/m² (range 11-22 l/m²).
Mean steady state volume of distribution (Vss): 150 l/m² (range 96-228 l/m²).
Tissue distribution: Extensive.
Mean apparent clearance: 2.5 l/hr/m² (range 1-4 l/hr/m²).
Urinary excretion: All.

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

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

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

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

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

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

### 6 PHARMACEUTICAL PARTICULARS

#### 6.1 List of excipients

Gemcitabine 38 mg/ml contains:
- Mannitol (E421)
- Sodium acetate trihydrate (E262)
- Hydrochloric acid (E507) (for pH-adjustment)
- Sodium hydroxide (E524) (for pH-adjustment)

#### 6.2 Incompatibilities

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

#### 6.3 Shelf life

2 years

*After reconstitution:*

Chemical and physical in-use stability has been demonstrated for 35 days at 25 °C. From a microbiological point of view, the product should be used immediately.

If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 25 °C, unless reconstitution / dilution has taken place in controlled and validated aseptic conditions.

#### 6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

*Reconstituted solution:*

Do not refrigerate (crystallisation may occur).

For storage condition of the reconstituted medicinal product, see section 6.3.

#### 6.5 Nature and contents of container

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

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

#### 6.6 Special precautions for disposal

*Reconstitution:*

For single use only.

This medicinal product has only been shown to be compatible with sodium chloride 9 mg/ml (0.9 %) solution for injection. Accordingly, only this diluent should be used for reconstitution. Compatibility with other active substances has not been studied. Therefore, it is not recommended to mix this medicinal product with other active substances when reconstituted.

Reconstitution at concentrations greater than 38 mg/ml may result in incomplete dissolution, and should be avoided.

To reconstitute, slowly add the appropriate volume of sodium chloride 9 mg/ml (0.9 %) solution for injection (as stated in the table below) and shake to dissolve.
Presentation | Presentation volume of sodium chloride 9 mg/ml (0.9 %) solution for injection to be added | Reconstituted volume | Final concentration
---|---|---|---
200 mg | 5 ml | 5.26 ml | 38 mg/ml
1,000 mg | 25 ml | 26.3 ml | 38 mg/ml
1,500 mg | 37.5 ml | 39.5 ml | 38 mg/ml

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

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

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

7 MARKETING AUTHORISATION HOLDER
Medac Gesellschaft für klinische Spezialpräparate mbH Fehlandstr. 3 20354 Hamburg Germany Phone: +49 4103 8006-0 Fax: +49 4103 8006-100

8 MARKETING AUTHORISATION NUMBER(S)
PL 11587/0055
PL 11587/0056

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
24/03/2009

10 DATE OF REVISION OF THE TEXT
24/03/2009
Module 3

Product Information Leaflets

Gemcitabine medac 38 mg/ml powder for solution for infusion (PL 11587/0045)

PACKAGE LEAFLET: INFORMATION FOR THE USER

Gemcitabine medac
38 mg/ml powder for solution for infusion
Gemcitabine

Read all of this leaflet carefully before you start receiving this medicine.
• Keep this leaflet. You may need to read it again.
• If you have further questions, please ask your doctor, nurse or pharmacist.
• This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
• If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor, nurse or pharmacist.

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

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

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

Gemcitabine medac may be given alone or in combination with other anti-cancer medicines, depending on the type of cancer. No sufficient data are available about the safety and efficacy of gemcitabine in children.

Gemcitabine medac 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 MEDAC

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

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

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

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

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

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

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

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

Important information about some of the
ingredients of Gemcitabine medac

Gemcitabine medac contains 3.5 mg (< 1 mmol) of
sodium in each 200 mg vial, 17.5 mg (< 1 mmol)
sodium in each 1000 mg vial and 26.3 mg (< 1 mmol)
sodium in each 1500 mg vial. To be taken into
consideration by patients on a controlled sodium diet.

3. HOW GEMCITABINE MEDAC IS GIVEN

The usual dose of Gemcitabine medac is 1000 –
1250 mg for every square metre of your body’s surface
area. Your height and weight are measured to work out
the surface area of your body. Your doctor will use this
body surface area to work out the right dose for you.
This dosage may be adjusted, or treatment may be
delayed depending on your blood cell counts and on
your general condition.

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

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

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

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

4. POSSIBLE SIDE EFFECTS

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

Frequencies of the observed side effects are defined as:
• very common: affects more than 1 user in 10
• common: affects 1 to 10 users in 100
• uncommon: affects 1 to 10 users in 1,000
• rare: affects 1 to 10 users in 10,000
• very rare: affects less than 1 user in 10,000
• not known: frequency can’t be estimated from the
available data
You must contact your doctor immediately if you notice any of the following:

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

Side effects with Gemcitabine medac may include:

**Very common side effects**

- Low haemoglobin level (anaemia)
- Low white blood cells
- Low platelet count
- Difficulty breathing
- Vomiting
- Nausea
- Skin rash – allergic skin rash, frequently itchy
- Hair loss
- Liver problems: found through abnormal blood test results
- Blood in urine
- Abnormal urine tests: protein in urine

- Flu-like symptoms including fever
- Oedema (swelling of ankles, fingers, feet, face)

**Common side effects**

- Fever accompanied by low white blood cell count (febrile neutropenia)
- Anorexia (poor appetite)
- Headache
- Insomnia
- Sleepiness
- Cough
- Runny nose
- Constipation
- Diarrhoea
- Pain, redness, swelling or sores in the mouth
- Itching
- Sweating
- Muscle pain
- Back pain
- Fever
- Weakness
- Chills

**Uncommon side effects**

- Interstitial pneumonitis (scarring of the air sacs of the lung)
- Spasm of the airways (wheeze)
- Abnormal chest X ray/scan (scarring of the lungs)

**Rare side effects**

- Heart attack (myocardial infarction)
- Low blood pressure
- Skin scaling, ulceration or blister formation
- Injection site reactions

**Very rare side effects**

- Increased platelet count
- Anaphylactic reaction (severe hypersensitivity/allergic reaction)
- Sloughing of skin and severe skin blistering
**Side effects with frequency not known**
- Irregular heart beat (arrhythmia)
- Adult Respiratory Distress Syndrome (severe lung inflammation causing respiratory failure)
- Radiation recall (a skin rash like severe sunburn) which can occur on skin that has previously been exposed to radiotherapy.
- Fluid in the lungs
- Radiation toxicity – scarring of the air sacs of the lung associated with radiation therapy
- Ischaemic colitis (inflammation of the lining of the large bowel, caused by reduced blood supply)
- Heart failure
- Kidney failure
- Gangrene of fingers or toes
- Serious liver damage, including liver failure
- Stroke

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

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

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

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5. HOW TO STORE GEMCITABINE MEDAC

Keep out of the reach and sight of children.

Do not use after the expiry date which is stated on the carton after EXP.

This medicinal product does not require any special storage conditions.

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6. FURTHER INFORMATION

**What Gemcitabine medac contains**

The active substance is gemcitabine. Each vial contains 200, 1000 or 1500 mg of gemcitabine (as gemcitabine hydrochloride).

The other ingredients are mannitol (E421), sodium acetate, hydrochloric acid and sodium hydroxide.

**What Gemcitabine medac looks like and contents of the pack**

Gemcitabine medac is a white to off-white powder, for solution for infusion in a vial. Each vial contains 200, 1000 or 1500 mg of gemcitabine. Each pack of Gemcitabine medac contains 1 vial.

**Marketing Authorisation Holder and Manufacturer**

Gemcitabine medac is a white to off-white powder, for solution for infusion in a vial. Each vial contains 200, 1000 or 1500 mg of gemcitabine. Each pack of Gemcitabine medac contains 1 vial.

**Marketing Authorisation Holder and Manufacturer**

Gesellschaft für klinische Spezialpräparate mbH
Fehlandtstr. 3
20354 Hamburg
Germany
Phone: +49 4103 8006-0
Fax: +49 4103 8006-100
This medicinal product is authorised in the Member States of the EEA under the following names:

- Austria: Gemcitabin mediac 38 mg/ml Pulver zur Herstellung einer infusionslösung
- Belgium: Gemcitabine medac 38 mg/ml Pulver zur Herstellung einer infusionslösung
- Belgium, France: Gemcitabine medac 38 mg/ml poudre pour solution pour perfusion
- Belgium: Gemcitabine medac 38 mg/ml
- Netherlands: Gemcitabine medac 38 mg/ml Prah za infuzionen razvr
- Czech Republic: Gemcitabine medac 38 mg/ml prášek pro přípravu infuzního roztoku
- Denmark: Gemcitabine "medac"
- Estonia: Gemcitabine medac
- Finland: Gemcitabine medac
- Germany: Gemcitabine medac 38 mg/ml Pulver zur Herstellung einer Infusionslösung
- Greece: Gemcitabine medac 38 mg/ml κόνις για διάλυμα προς εγχύση
- Hungary: Gemcitabine medac 38 mg/ml poroldatos infúzóhoz
- Ireland: Gemcitabine medac 200 mg / 1000 mg / 1500 mg powder for solution for infusion
- Latvia: Gemcitabine medac 38 mg/ml pulvers infuzijai šķīduma pagatavošanai
- Lithuania: Gemcitabine medac 38 mg/ml milteliai infuziniam tirpaliui
- Norway: Gemcitabine medac 38 mg/ml pulver til infusionsvæske, opplosning
- Poland: Gemcitabine medac
- Portugal: Gemcitabine medac 38 mg/ml pó para solução para perfusão
- Romania: Gemcitabine medac 38 mg/ml pulbere pentru soluție perfuzabilă
- Slovak Republic: Gemcitabine medac 38 mg/ml prášok na infúzny roztok
- Slovenia: Gemcitabine medac 38 mg/ml prašek za raztopino za infundiranje
- Spain: Gemcitabina medac 200 mg / 1000 mg / 1500 mg polvo para solución para perfusión
- Sweden: Gemcitabine medac 38 mg/ml pulver till infusionsvåtska, lösning
- United Kingdom: Gemcitabine medac 38 mg/ml powder for solution for infusion

This leaflet was last approved in 01/2009.

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

Special precautions for disposal and other handling

Reconstitution:

For single use only.

This medicinal product has only been shown to be compatible with sodium chloride 9 mg/ml (0.9 %) solution for injection. Accordingly, only this diluent should be used for reconstitution. Compatibility with other active substances has not been studied.

Therefore, it is not recommended to mix this medicinal product with other active substances when reconstituted.

Reconstitution at concentrations greater than 38 mg/ml may result in incomplete dissolution, and should be avoided.

To reconstitute, slowly add the appropriate volume of sodium chloride 9 mg/ml (0.9 %) solution for injection (as stated in the table below) and shake to dissolve.
**Presentation** | **Presentation volume of sodium chloride 9 mg/ml (0.9%) solution for injection to be added** | **Reconstituted volume** | **Final concentration**
---|---|---|---
200 mg | 5 ml | 5.25 ml | 38 mg/ml
1,000 mg | 25 ml | 26.3 ml | 38 mg/ml
1,500 mg | 37.5 ml | 39.5 ml | 36 mg/ml

carefully to avoid leakage (use of Luer lock fittings is recommended). Large bore needles are recommended to minimise pressure and the possible formation of aerosols. The latter may also be reduced by the use of a venting needle. Actual spillage or leakage should be mopped up wearing protective gloves. Excreta and vomit must be handled with care.

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

**Guidelines for the Safe Handling of Cytotoxic Medicinal Products:**
Local guidelines on safe preparation and handling of cytotoxic medicinal products must be adhered to. Cytotoxic preparations should not be handled by pregnant staff. The preparation of injectable solutions of cytotoxic agents must be carried out by trained specialist personnel with knowledge of the medicines used. This should be performed in a designated area. The work surface should be covered with disposable plastic-backed absorbent paper. Suitable eye protection, disposable gloves, face mask and disposable apron should be worn. Precautions should be taken to avoid the medicinal product accidentally coming into contact with the eyes. If accidental contamination occurs, the eye should be washed with water thoroughly and immediately.

Syringes and infusion sets should be assembled
Gemcitabine 38 mg/ml powder for solution for infusion (PL 11587/0055)

PACKAGE LEAFLET: INFORMATION FOR THE USER

Gemcitabine 38 mg/ml powder for solution for infusion
Gemcitabine

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

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

1. WHAT GEMCITABINE IS AND WHAT IT IS USED FOR

Gemcitabine belongs to 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. No sufficient data are available about the safety and efficacy of gemcitabine in children.

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

You should not be given Gemcitabine
- if you are allergic (hypersensitive) to gemcitabine or any of the other ingredients 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 you have enough blood cells to receive Gemcitabine. Your doctor may decide to change the dose or delay treating you depending on your general condition and if your blood cell counts are too low. Periodically you will have samples of your blood taken to evaluate your kidney and liver function. Please tell your doctor if:
• you have, or have previously had liver disease, heart disease or vascular disease.
• you have recently had, or are going to have radiotherapy.
• you have been vaccinated recently.
• you develop breathing difficulties or feel very weak and are very pale (may be a sign of kidney failure).

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

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

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

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

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

Important information about some of the ingredients of Gemcitabine
Gemcitabine contains 3.5 mg (< 1 mmol) of sodium in each 200 mg vial, 17.5 mg (< 1 mmol) sodium in each 1000 mg vial and 26.3 mg (< 1 mmol) sodium in each 1500 mg vial. To be taken into consideration by patients on a controlled sodium diet.

3. HOW GEMCITABINE IS GIVEN

The usual dose of Gemcitabine is 1000 – 1250 mg for every square metre of your body’s surface area. Your height and weight are measured to work out the surface area of your body. Your doctor will use this body surface area to work out the right dose for you. This dosage may be adjusted, or treatment may be delayed depending on your blood cell counts and on your general condition.

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

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

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

If you have further questions on the use of this product ask your doctor or pharmacist.
4. **POSSIBLE SIDE EFFECTS**

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

Frequencies of the observed side effects are defined as:
- Very common: affects more than 1 user in 10
- Common: affects 1 to 10 users in 100
- Uncommon: affects 1 to 10 users in 1,000
- Rare: affects 1 to 10 users in 10,000
- Very rare: affects less than 1 user in 10,000
- Not known: frequency can’t be estimated from the available data

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

Side effects with 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
- Hair loss
- Liver problems: found through abnormal blood test results
- Blood in urine
- Abnormal urine tests: protein in urine
- Flu-like symptoms including fever
- Oedema (swelling of ankles, fingers, feet, face)

**Common side effects**
- Fever accompanied by low white blood cell count (febrile neutropaenia)
- Anaemia (poor appetite)
- Headache
- Insomnia
- Sleeplessness
- Cough
- Runny nose
- Constipation
- Diarrhoea
- Pain, redness, swelling or sores in the mouth
- Itching
- Sweating
- Muscle pain
- Back pain
- Fever
- Weakness
- Chills

Uncommon side effects
- Interstitial pneumonitis (scarring of the air sacs of the lung)
- Spasm of the airways (wheeze)
- Abnormal chest X-ray/scan (scarring of the lungs)

Rare side effects
- Heart attack (myocardial infarction)
- Low blood pressure
- Skin scaling, ulceration or blister formation
- Injection site reactions

Very rare side effects
- Increased platelet count
- Anaphylactic reaction (severe hypersensitivity/allergic reaction)
- Sloughing of skin and severe skin blistering

Side effects with frequency not known
- Irregular heart beat (arrhythmia)
- Adult Respiratory Distress Syndrome (severe lung inflammation causing respiratory failure)
- Radiation recall (a skin rash like severe sunburn) which can occur on skin that has previously been exposed to radiotherapy.
- Fluid in the lungs
- Radiation toxicity – scarring of the air sacs of the lung associated with radiation therapy
- Ischaemic colitis (inflammation of the lining of the large bowel, caused by reduced blood supply)
- Heart failure
- Kidney failure
- Gangrene of fingers or toes
- Serious liver damage, including liver failure
- Stroke

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

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

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor.
5. HOW TO STORE GEMCITABINE

Keep out of the reach and sight of children.

Do not use after the expiry date which is stated on the carton after EXP

This medicinal product does not require any special storage conditions.

Reconstituted solution:
The product should be used immediately. When prepared as directed, chemical and physical in-use stability of reconstituted solutions of gemcitabine were demonstrated for 35 days at 25 °C. Further dilution by a healthcare provider may be done. Solutions of reconstituted gemcitabine should not be refrigerated, as crystallisation may occur.

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

6. FURTHER INFORMATION

What Gemcitabine contains:
The active substance is gemcitabine. Each vial contains 200, 1000 or 1500 mg of gemcitabine (as gemcitabine hydrochloride).
The other ingredients are mannitol (E421), sodium acetate, hydrochloric acid and sodium hydroxide.

What Gemcitabine looks like and contents of the pack
Gemcitabine is a white to off-white powder, for solution for infusion in a vial. Each vial contains 200, 1000 or 1500 mg of gemcitabine. Each pack of Gemcitabine contains 1 vial.

Marketing Authorisation Holder and Manufacturer
medac
Gesellschaft für klinische Spezialpräparate mbH
Fehlaustr. 3
20354 Hamburg
Germany
Phone: +49 4103 8006-0
Fax: +49 4103 8006-100

This medicinal product is authorised in the Member States of the EEA under the following names:
Austria Gemicitana 38 mg/ml Pulver zur Herstellung einer Infusionslösung
United Kingdom Gemcitabine 38 mg/ml powder for solution for infusion

This leaflet was last approved in 01/2009.

---------------------------------------------------------------

The following information is intended for medical or healthcare professionals only:
Special precautions for disposal and other handling

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

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

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

Guidelines for the Safe Handling of Cytotoxic Medicinal Products:
Local guidelines on safe preparation and handling of cytotoxic medicinal products must be adhered to.
Cytotoxic preparations should not be handled by pregnant staff. The preparation of injectable solutions of cytotoxic agents must be carried out by trained specialist personnel with knowledge of the medicines used. This should be performed in a designated area. The work surface should be covered with disposable plastic-backed absorbent paper.
Suitable eye protection, disposable gloves, face mask and disposable apron should be worn. Precautions should be taken to avoid the medicinal product accidentally coming into contact with the eyes. If accidental contamination occurs, the eye should be washed with water thoroughly and immediately.

Syringes and infusion sets should be assembled carefully to avoid leakage (use of Luer lock fittings is recommended). Large bore needles are recommended to minimise pressure and the possible formation of aerosols. The latter may also be reduced by the use of a venting needle.
Actual spillage or leakage should be mopped up wearing protective gloves. Excreta and vomit must be handled with care.

Disposal:
Adequate care and precaution should be taken in the disposal of items used to reconstitute this medicinal product. Any unused dry product or contaminated materials should be placed in a high-risk waste bag. Sharp objects (needles, syringes, vials, etc.) should be placed in a suitable rigid container. Personnel concerned with the collection and disposal of this waste should be aware of the hazard involved. Waste material should be destroyed by incineration. Any unused product or waste material should be disposed of in accordance with local requirements.
Gemcitabine 38 mg/ml powder for solution for infusion (PL 11587/0056)

PACKAGE LEAFLET: INFORMATION FOR THE USER

Gemcitabine 38 mg/ml powder for solution for infusion

Gemcitabine

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

• Keep this leaflet. You may need to read it again.
• If you have further questions, please ask your doctor, nurse or pharmacist.
• This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
• If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor, nurse or pharmacist.

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

1. WHAT GEMCITABINE IS AND WHAT IT IS USED FOR

Gemcitabine belongs to 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. No sufficient data are available about the safety and efficacy of gemcitabine in children.

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

You should not be given Gemcitabine
• if you are allergic (hypersensitive) to gemcitabine or any of the other ingredients 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 you have enough blood cells to receive Gemcitabine. Your doctor may decide to change the dose or delay treating you depending on your general condition and if your blood cell counts are too low. Periodically you will have samples of your blood taken to evaluate your kidney and liver function.
Please tell your doctor if:
• you have, or have previously had liver disease, heart disease or vascular disease.
• you have recently had, or are going to have radiotherapy.
• you have been vaccinated recently.
• you develop breathing difficulties or feel very weak and are very pale (may be a sign of kidney failure).

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

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

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

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

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

Important information about some of the ingredients of Gemcitabine
Gemcitabine contains 3.5 mg (< 1 mmol) of sodium in each 200 mg vial, 17.5 mg (< 1 mmol) sodium in each 1000 mg vial and 26.3 mg (< 1 mmol) sodium in each 1500 mg vial. To be taken into consideration by patients on a controlled sodium diet.

3. HOW GEMCITABINE IS GIVEN

The usual dose of Gemcitabine is 1000 – 1250 mg for every square metre of your body’s surface area. Your height and weight are measured to work out the surface area of your body. Your doctor will use this body surface area to work out the right dose for you. This dosage may be adjusted, or treatment may be delayed depending on your blood cell counts and on your general condition.

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

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

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

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

4. POSSIBLE SIDE EFFECTS
Like all medicines, Gemcitabine can cause side effects, although not everybody gets them.

Frequencies of the observed side effects are defined as:
• very common: affects more than 1 user in 10
• common: affects 1 to 10 users in 100
• uncommon: affects 1 to 10 users in 1,000
• rare: affects 1 to 10 users in 10,000
• very rare: affects less than 1 user in 10,000
• not known: frequency can’t be estimated from the available data

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

Side effects with 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
• Hair loss
• Liver problems: found through abnormal blood test results
• Blood in urine
• Abnormal urine tests: protein in urine
• Flu like symptoms including fever
• Oedema (swelling of ankles, fingers, feet, face)

Common side effects
• Fever accompanied by low white blood cell count (febrile neutropaenia)
• Anorexia (poor appetite)
• Headache
• Insomnia
• Sleepiness
• Cough
• Runny nose
- Constipation
- Diarrhoea
- Pain, redness, swelling or sores in the mouth
- Itching
- Sweating
- Muscle pain
- Back pain
- Fever
- Weakness
- Chills

**Uncommon side effects**
- Interstitial pneumonitis (scarring of the air sacs of the lung)
- Spasm of the airways (wheeze)
- Abnormal chest X-ray/scan (scarring of the lungs)

**Rare side effects**
- Heart attack (myocardial infarction)
- Low blood pressure
- Skin scaling, ulceration or blister formation
- Injection site reactions

**Very rare side effects**
- Increased platelet count
- Anaphylactic reaction (severe hypersensitivity/allergic reaction)
- Sloughing of skin and severe skin blistering

**Side effects with frequency not known**
- Irregular heart beat (arrhythmia)
- Adult Respiratory Distress Syndrome (severe lung inflammation causing respiratory failure)
- Radiation recall—(a skin rash like severe sunburn) which can occur on skin that has previously been exposed to radiotherapy.
- Fluid in the lungs
- Radiation toxicity—scarring of the air sacs of the lung associated with radiation therapy
- Ischaemic colitis (inflammation of the lining of the large bowel, caused by reduced blood supply)
- Heart failure
- Kidney failure
- Gangrene of fingers or toes
- Serious liver damage, including liver failure
- Stroke

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

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

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

5. **HOW TO STORE GEMCITABINE**
Keep out of the reach and sight of children.

Do not use after the expiry date which is stated on the carton after EXP.

This medicinal product does not require any special storage conditions.

Reconstituted solution:
The product should be used immediately. When prepared as directed, chemical and physical in-use stability of reconstituted solutions of gemcitabine were demonstrated for 35 days at 25 °C. Further dilution by a healthcare provider may be done. Solutions of reconstituted gemcitabine should not be refrigerated, as crystallisation may occur.

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

6. FURTHER INFORMATION

What Gemcitabine contains
The active substance is gemcitabine. Each vial contains 200, 1000 or 1500 mg of gemcitabine (as gemcitabine hydrochloride).
The other ingredients are mannitol (E421), sodium acetate, hydrochloric acid and sodium hydroxide.

What Gemcitabine looks like and contents of the pack
Gemcitabine is a white to off-white powder, for solution for infusion in a vial. Each vial contains 200, 1000 or 1500 mg of gemcitabine. Each pack of Gemcitabine contains 1 vial.

Marketing Authorisation Holder and Manufacturer
medac
Gesellschaft für klinische Spezialpräparate mbH
Fehlandtstr. 3
20354 Hamburg
Germany
Tel.: +49 4103 8006-0
Fax: +49 4103 8006-100

This medicinal product is authorised in the Member States of the EEA under the following names:

Austria: Gemcit 38 mg/ml Pulver zur Herstellung einer Infusionslösung
Bulgaria: Gemcit 38 mg/ml Празък за инфузия
Czech Republic: Gemcirena 38 mg/ml prášek pro přípravu infuzního roztoku
Denmark: Gemcit
Estonia: Gemcirena
France: Gemcirena 38 mg/ml poudre pour solution pour perfusion
Germany: Gemcit 38 mg/ml Pulver zur Herstellung einer Infusionslösung
Greece: Gemcirena 38 mg/ml κονις για διάλυμα προς εγγυηση
Latvia: Gemcit 38 mg/ml pulveris infuziju šķiduma pagatavošanai
Lithuania: Gemcit 38 mg/ml milteliai infuziiniams tirpalui
Netherlands: Gemcirena 38 mg/ml poeder voor oplossing voor infusie
Norway: Gemcit 38 mg/ml pulver til infusjonsveske, opplossning
Poland: Gemcit
This leaflet was last approved in

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

Special precautions for disposal and other handling

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

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<td>5 ml</td>
<td>5.26 ml</td>
<td>38 mg/ml</td>
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<td>1,000 mg</td>
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<td>1,500 mg</td>
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The appropriate amount of medicinal product may be further diluted with sodium chloride 9 mg/ml (0.9 %) solution for injection.
Parenteral medicinal products should be inspected visually for particulate matter and discoloration, prior to administration, whenever solution and container permit.
Any unused solution should be discarded as described below.

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

Disposal:
Adequate care and precaution should be taken in the disposal of items used to reconstitute this medicinal product. Any unused dry product or contaminated materials should be placed in a high-risk waste bag. Sharp objects (needles, syringes, vials, etc) should be placed in a suitable rigid container. Personnel concerned with the collection and disposal of this waste should be aware of the hazard involved. Waste material should be destroyed by incineration. Any unused product or waste material should be disposed of in accordance with local requirements.
Module 4

Labelling

Gemcitabine medac 38 mg/ml powder for solution for infusion (PL 11587/0045)

Vial carton – 10ml vial, 200mg gemcitabine

Vial label – 10ml vial, 200mg gemcitabine
Vial carton – 50ml vial, 1000mg gemcitabine

Vial label – 50ml vial, 1000mg gemcitabine

Gemcitabine medac 38 mg/ml powder for solution for infusion

Gemcitabine

For intravenous use after reconstitution.
Read the package leaflet before use.
For single use only.
Do not refrigerate the reconstituted solution.
Read the leaflet for the shelf life of the reconstituted product.
Keep out of the reach and sight of children.
Discard any unused contents according to standard practice for cytotoxic agents.

POM

PL 11587/0045

Gemcitabine medac GmbH
Fehlhardtstr. 3, 20354 Hamburg, Germany

Commissioning Agent

Gemcitabine 38 mg/ml powder for solution for infusion PL 11587/0045, 0055-56; UK/H/1437, 2568-9/01/DC
Vial carton – 100ml vial, 1500mg gemcitabine

Vial label – 100ml vial, 1500mg gemcitabine

Gemcitabine medac 38 mg/ml powder for solution for infusion

Gemcitabine

One ml of the reconstituted solution for infusion contains 38 mg gemcitabine. Each vial contains gemcitabine hydrochloride equivalent to 1500 mg gemcitabine. Excipients: Mannitol (E421), sodium acetate trihydrate, hydrochloric acid and sodium hydroxide. See leaflet for further information. Powder for solution for infusion. For intravenous use after reconstitution. Read the package leaflet before use. For single use only. Keep out of the reach and sight of children. Cytostatic agent. Do not refrigerate the reconstituted solution. Read the leaflet for the shelf life of the reconstituted product. Discard unused contents according to standard practice for cytostatic agents.

PL 11587/0045

medac GmbH
Petlandstr. 3, 20354 Hamburg - Germany

POM

1500 mg
Gemcitabine 38 mg/ml powder for solution for infusion

(PL 11587/0055 & 0056)

Vial carton

PARTICULARS TO APPEAR ON OUTER PACKAGING

CARTON

1. NAME OF THE MEDICINAL PRODUCT

Gemcitabine 38 mg/ml powder for solution for infusion
Gemcitabine

2. STATEMENT OF ACTIVE SUBSTANCE(S)

One ml of the reconstituted solution for infusion contains 38 mg gemcitabine.

Each vial contains gemcitabine hydrochloride equivalent to 200 mg gemcitabine.

Each vial contains gemcitabine hydrochloride equivalent to 1000 mg gemcitabine.

Each vial contains gemcitabine hydrochloride equivalent to 1500 mg gemcitabine.

3. LIST OF EXCIPIENTS

Excipients:
Mannitol (E421), sodium acetate trihydrate, hydrochloric acid and sodium hydroxide. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Powder for solution for infusion
1 vial
200 mg  1000 mg  1500 mg

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For intravenous use after reconstitution.
Read the package leaflet before use.
For single use only.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Cytostatic agent.

Do not refrigerate the reconstituted solution.
8. **EXPIRY DATE**

EXP:

9. **SPECIAL STORAGE CONDITIONS**

Read the leaflet for the shelf life of the reconstituted product.

10. **SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE**

Discard any unused contents according to standard practice for cytotoxic agents.

11. **NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

medac
Gesellschaft für klinische
Spezialpräparate mbH
Fehlandstr. 3
20354 Hamburg
Germany

12. **MARKETING AUTHORISATION NUMBER(S)**

PL 11587/0055 or PL 11587/0056

13. **BATCH NUMBER**

Batch:

14. **GENERAL CLASSIFICATION FOR SUPPLY**

POM

15. **INSTRUCTIONS ON USE**

16. **INFORMATION IN BRAILLE**

Justification for not including Braille accepted.
Vial label – 10ml vial, 200mg gemcitabine

PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

LABEL ON VIAL
Bottle (10 ml) / 200 mg

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Gemcitabine 38 mg/ml powder for solution for infusion

Gemcitabine
For intravenous use after reconstitution.

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP:

4. BATCH NUMBER

Batch:

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

200 mg gemcitabine.

6. OTHER

medac GmbH
Fehlandtsir. 3
D-20354 Hamburg

200 mg

Cytostatic agent.
Vial label – 50ml and 100ml vials; 1000mg and 1500mg gemcitabine

PARTICULARS TO APPEAR ON IMMEDIATE PACKAGING

LABEL ON VIAL

1. **NAME OF THE MEDICINAL PRODUCT**

   Gemcitabine 38 mg/ml powder for solution for infusion
   Gemcitabine

2. **STATEMENT OF ACTIVE SUBSTANCE(S)**

   One ml of the reconstituted solution for infusion contains 38 mg gemcitabine.

   Each vial contains gemcitabine hydrochloride equivalent to 1000 mg gemcitabine.

   Each vial contains gemcitabine hydrochloride equivalent to 1500 mg gemcitabine.

3. **LIST OF EXCIPIENTS**

   Excipients: Mannitol (E421), sodium acetate trihydrate, hydrochloric acid and sodium hydroxide. See leaflet for further information.

4. **PHARMACEUTICAL FORM AND CONTENTS**

   Powder for solution for infusion.
   1000 mg  1500 mg

5. **METHOD AND ROUTE(S) OF ADMINISTRATION**

   For intravenous use after reconstitution.
   Read the package leaflet before use.
   For single use only.

6. **SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN**

   Keep out of the reach and sight of children.

7. **OTHER SPECIAL WARNING(S), IF NECESSARY**

   Cytostatic agent.
   Do not refrigerate the reconstituted solution.

8. **EXPIRY DATE**

   EXP:
9. **SPECIAL STORAGE CONDITIONS**

Read the leaflet for the shelf life of the reconstituted product.

10. **SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE**

Discard unused contents according to standard practice for cytotoxic agents.

11. **NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

medac GmbH
Fehlrandstr. 3
20354 Hamburg
Germany

12. **MARKETING AUTHORISATION NUMBER(S)**

PL 11587/0055

13. **BATCH NUMBER**

Batch:

14. **GENERAL CLASSIFICATION FOR SUPPLY**

POM

15. **INSTRUCTIONS ON USE**

16. **INFORMATION IN BRAILLE**

*Justification for not including Braille accepted.*
Module 5
Scientific discussion during initial procedure

I  INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the MHRA granted MEDAC Gesellschaft für klinische Spezialpräparate mbH Marketing Authorisations for the medicinal product Gemcitabine 38 mg/ml powder for solution for infusion on 23rd March 2009 (PL 11587/0055-0056, UK/H/2568-9/01/DC) and for Gemcitabine medac 38 mg/ml powder for solution for infusion on 30th March 2009 (PL 11587/0045, UK/H/1437/01/DC). The UK licence for Gemcitabine 38 mg/ml powder for solution for infusion (PL 11587/0056) was cancelled on 30/03/2009. The products are prescription-only medicines.

These are abridged applications, submitted under Article 10.1 of 2001/83 EC, as amended. The applications refer to the reference products, Gemzar 200mg and Gemzar 1g (PL 00006/0301 and 0302), authorised to Eli Lilly & Company Limited on 26th October 1995. Gemzar 200mg is the innovator product, which has been authorised in the UK for more than 10 years; the period of data exclusivity has expired.

Gemcitabine (2',2'-difluorodeoxycytidine), a pyrimidine antimetabolite, is a deoxycytidine analogue with two fluorine substitutes for the two hydrogen atoms in the 2' position of the deoxyribose moiety. After entering the cell, gemcitabine is phosphorylated to the active forms such as gemcitabine diphosphate and triphosphate. The triphosphate form of gemcitabine is recognised by DNA polymerases and incorporated into the growing DNA strand. This process is followed by the incorporation of one or more natural nucleotides, resulting in an arrest 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 shows significant cytotoxic effects against a variety of cultured murine and human tumour cells. Its action is phase-specific. 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.

Gemcitabine is indicated in the following:

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

• in combination with paclitaxel, 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.

The drug product is presented as a white to off-white powder for solution for infusion. It has only been shown to be compatible with sodium chloride 9 mg / ml (0.9%) solution for injection. Only this diluent should be used for reconstitution. This medicine is not for self-administration; it will be administered to the patient by a healthcare professional.

No new preclinical or clinical studies were conducted, which is acceptable given that the applications cross-refer to a product that has been licensed for over 10 years. Bioequivalence studies are not necessary to support these applications for a parenteral product.

The RMS has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place for these product types at all sites responsible for the manufacture and assembly of these products. Evidence of compliance with GMP has been provided for the named manufacturing and assembly sites. For manufacturing sites within the Community, the RMS has accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.

For manufacturing sites outside the community, the RMS has accepted copies of current GMP Certificates or satisfactory inspection summary reports, ‘close-out letters’ or ‘exchange of information’ issued by the inspection services of the competent authorities (or those countries with which the EEA has a Mutual Recognition Agreement for their own territories) as certification that acceptable standards of GMP are in place at those non-Community sites.
## II. ABOUT THE PRODUCT

| Name of the product in the Reference Member State | Gemcitabine medac 38 mg/ml powder for solution for infusion  
| Gemcitabine 38 mg/ml powder for solution for infusion |
| Name(s) of the active substance(s) (INN) | Gemcitabine hydrochloride |
| Pharmacotherapeutic classification (ATC code) | Pyrimidine analogues (L01B C05) |
| Pharmaceutical form and strength(s) | Powder for solution for infusion 38mg / ml |
| Reference numbers for the Mutual Recognition Procedure | UK/H/1437/01/DC  
| UK/H/2568/01/DC  
| UK/H/2569/01/DC |
| Reference Member State | United Kingdom |
| Member States concerned | UK/H/1437/01/DC – AT, BE, BG, CZ, DE, DK, EE, EL, ES, FI, FR, HU, IE, LT, LV, NL, NO, PL, PT, RO, SE, SI, SK  
| UK/H/2568/01/DC – AT  
| UK/H/2569/01/DC – AT, BG, CZ, DE, DK, EE, EL, FR, LT, LV, NL, NO, PL, PT, RO, SK |
| Marketing Authorisation Number(s) | PL 11587/0045  
| PL 11587/0055  
| PL 11587/0056 |
| Name and address of the authorisation holder | medac  
| Gesellschaft für klinische Spezialpräparate mbH  
| Fehlandtstr. 3  
| 20354 Hamburg  
| Germany |
III    SCIENTIFIC OVERVIEW AND DISCUSSION

III.1  QUALITY ASPECTS

ACTIVE SUBSTANCE

Gemcitabine hydrochloride

Nomenclature:

INN:   Gemcitabine hydrochloride

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

Structure:

```
O
HO F
F
HO
NH2
O
HCl
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Molecular formula:  C_{9}H_{11}F_{2}N_{3}O_{4}.HCl

Molecular weight: 299.66

CAS No:  122111-03-9

Physical form: A white or almost white crystalline powder

Solubility: Soluble in water, slightly soluble in methanol, practically insoluble in acetone.

The active substance, gemcitabine hydrochloride, is the subject of a European Pharmacopeia (EP) monograph.

Synthesis of the active substance from the designated starting materials has been adequately described and appropriate in-process controls and intermediate specifications are applied. Satisfactory specifications are in place for all starting materials and reagents and these are supported by relevant Certificates of Analysis. Confirmation has been provided that the raw materials, intermediates and auxiliary agents used in synthesis of the active are not of animal, biological or genetically modified origin.

An appropriate specification has been provided for the active substance, as set by the 3 active substance manufacturers (ASMF). Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications. Batch analysis data are provided and comply with the proposed specification. Satisfactory Certificates of Analysis have been provided for any reference standards used by the active substance manufacturer during validation studies.

Active gemcitabine hydrochloride is stored in appropriate packaging. Specifications and Certificates of Analysis have been provided for the packaging materials used. The primary packagings in direct contact with the active substance satisfy Directive 2002/72/EC (as amended), and are suitable for contact with foodstuffs.

Appropriate stability data have been generated for the active substance stored in the proposed commercial packaging. These data demonstrate the stability of the active substance and appropriate retest periods have been set for gemcitabine hydrochloride supplied by the different ASMFs.
DRUG PRODUCT

Composition
The drug product is presented as a white to off-white powder for solution for infusion.

Other ingredients consist of pharmaceutical excipients, namely mannitol (E421), sodium acetate trihydrate (E262), and sodium hydroxide and hydrochloric acid for pH adjustment. Appropriate justification for the inclusion of each excipient has been provided.

All excipients used comply with their respective European Pharmacopoeia 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 for the proposed product.

There were no novel excipients used and no overages.

Impurity profiles
Comparative impurity profiles were provided for test and reference products. The impurity profiles were found to be identical, with all impurities within the specification limits.

Pharmaceutical development
Details of the pharmaceutical development of the drug products have been supplied and are satisfactory.

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

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

Finished product specification
The finished product specifications are provided for both release and shelf life and are satisfactory; they provide an assurance of the quality and consistency of the finished products. 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. Batch data have been provided and comply with the release specifications. Certificates of Analysis have been provided for any reference standards used.

Container Closure System
The drug product is presented in clear, colourless Type I glass vials of 10ml, 50ml or 100ml, closed with chlorobutyl rubber stoppers. The vials contain gemcitabine hydrochloride equivalent to 200mg, 1000mg or 1500mg respectively of gemcitabine (concentration 38 mg/ml).

The vials are packaged individually with the Product Information Leaflet (PIL) into cardboard outer cartons. The vials satisfy Directive 2002/72/EC (as amended), and are suitable for contact with parenteral preparations. Specifications and Certificates of Analysis for all packaging components used have been provided, and are satisfactory.
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, which is satisfactory. There are no special storage instructions. For storage conditions and advice for use of the reconstituted medicinal product, refer to the SmPC. The reconstituted solution must not be refrigerated as crystallisation may occur. Please also refer to the SmPC for information on safe handling and disposal of the product and contaminated materials.

Bioequivalence Study
Bioequivalence studies are not necessary to support these applications for a parenteral product.

Expert Report
A satisfactory quality overview is provided, and has been prepared by an appropriately qualified expert. An appropriate CV for the expert has been supplied.

Product Information
The approved SmPCs, leaflets, and labelling are satisfactory.

Conclusion
The proposed products, Gemcitabine 38 mg/ml powder for solution for infusion and Gemcitabine medac 38 mg/ml powder for solution for infusion, have been shown to be generic versions of the reference product, Gemzar 200mg (PL 00006/0301, Eli Lilly & Company Limited), with respect to qualitative and quantitative content of the active substance, and the pharmaceutical form. The test products are pharmaceutically equivalent to the reference product, which has been licensed in the UK for over 10 years. Given the route of administration and pharmaceutical form, it is not necessary to demonstrate bioequivalence of the proposed products to the reference product.

All pharmaceutical issues have been resolved and the quality grounds for these applications are considered adequate. Marketing Authorisations were, therefore, granted.

III.2  PRE-CLINICAL ASPECTS
Specific non-clinical studies have not been performed, which is acceptable for these applications for generic versions of products that have been licensed for over 10 years. The non-clinical overview provides a satisfactory review of the pharmacological and toxicological properties of gemcitabine hydrochloride, which is a widely used and well-known active substance.

III.3  CLINICAL ASPECTS
INDICATIONS
The indications are consistent with those for the innovator products and are satisfactory.

POSOLOGY AND METHOD OF ADMINISTRATION
Full details concerning the posology are provided in the SmPCs.

The posology is consistent with that for the innovator products and is satisfactory.
TOXICOLOGY
No new data have been submitted and none are required for these types of application.

CLINICAL PHARMACOLOGY
The clinical pharmacology of gemcitabine hydrochloride is well known. No novel pharmacodynamic or pharmacokinetic data are supplied or required for these applications.

Clinical efficacy
No new data are submitted and none are required for this type of application. Efficacy is reviewed in the clinical expert report.

Gemcitabine / Gemcitabine medac 38 mg/ml powder for solution for infusion are to be administered as an aqueous intravenous solution and contain the same active substance, in the same concentration, as the currently authorised reference product Gemzar 200mg. Thus, in accordance with the “Note for Guidance on the Investigation of Bioavailability and Bioequivalence”, (CPMP/EWP/QWP/1401/98), the applicant is not required to submit a bioequivalence study.

Clinical safety
No new data have been submitted and none are required for applications of this type. No new or unexpected safety concerns arose from these applications. Safety is reviewed in the clinical overview. The safety profile of gemcitabine hydrochloride is well-known.

PRODUCT INFORMATION:
Summary of Product Characteristics (SmPC)
The approved SmPCs are consistent with that for the innovator product, and are acceptable.

Product Information Leaflet (PIL)
The final PILs are in line with the approved SmPCs and are satisfactory.

Labelling
The labelling is satisfactory.

Expert report
A satisfactory clinical overview is provided, and has been prepared by an appropriately qualified expert. An appropriate CV for the expert has been supplied.

CONCLUSIONS
The grounds for establishing the proposed products, Gemcitabine 38 mg/ml powder for solution for infusion and Gemcitabine medac 38 mg/ml powder for solution for infusion, as generic versions of the reference product, Gemzar 200mg (also Gemzar 1g), are considered adequate. The product literature is approved.

Sufficient clinical information has been submitted to support these applications. All issues have been adequately addressed by the applicant. When used as indicated, Gemcitabine / Gemcitabine medac 38 mg/ml powder for solution for infusion has a favourable benefit-to-risk ratio. The granting of Marketing Authorisations was, therefore, recommended on medical grounds.
IV OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

QUALITY
The important quality characteristics of Gemcitabine 38 mg/ml 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 / Gemcitabine medac 38 mg/ml powder for solution for infusion have been demonstrated to be generic versions of the reference products Gemzar 200mg and Gemzar 1g (PL 00006/0301 and 0302, Eli Lilly & Company Limited).

No new or unexpected safety concerns arise from these applications.

PRODUCT LITERATURE
The text of the SmPCs, PILs and labelling is satisfactory and consistent with that for the reference products.

For PL 11587/0045, a package leaflet has been submitted to the MHRA along with results of consultations with target patient groups ("user testing"), in accordance with Article 59 of Council Directive 2001/83/EC. The results indicate that the package leaflet is well-structured and organised, easy to understand and written in a comprehensive manner. The testing shows that patients/users are able to act upon the information that the leaflet contains.

The approved labelling artwork complies with statutory requirements for PL 11587/0045. For PLs 11587/0055 and 0056, the Marketing Authorisation Holder (MAH) has committed to submitting mock-ups for all packaging and PILs for assessment before those packs are commercially marketed.

RISK BENEFIT ASSESSMENT
The quality of the products 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 / Gemcitabine medac 38 mg/ml powder for solution for infusion and the innovator product, Gemzar 200mg (Eli Lilly & Company Limited), are interchangeable. Extensive clinical experience with gemcitabine hydrochloride is considered to have demonstrated the therapeutic value of the active substance. The risk: benefit is, therefore, considered to be positive.
Module 6

STEPS TAKEN AFTER INITIAL PROCEDURE - SUMMARY

There have been no variation applications submitted after approval of the initial procedure.

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PL 11587/0056 - Gemcitabine 38 mg/ml powder for solution for infusion:

The above licence was cancelled on 30th March 2009.