ANNEX I

LIST OF THE NAMES, PHARMACEUTICAL FORMS, STRENGTHS OF THE MEDICINAL PRODUCTS, ROUTE OF ADMINISTRATION, MARKETING AUTHORISATION HOLDERS IN THE MEMBER STATES

Member State	Marketing Authorisation Holder	(Invented) Name	Strength	Pharmaceutical form	Route of administration
Austria	Eli Lilly Ges.m.b.H Kölblgasse 8-10 1030 Wien Austria	Gemzar 200 mg - Trockensubstanz zur Infusionsbereitung	200 mg	Powder for solution for infusion	Intravenous use
Austria	Eli Lilly Ges.m.b.H Kölblgasse 8-10 1030 Wien Austria	Gemzar 1 g - Trockensubstanz zur Infusionsbereitung	1000 mg	Powder for solution for infusion	Intravenous use
Belgium	ELI LILLY Benelux s.a. Rue De L'Etuve 52 B-1000 Brussels Belgium	GEMZAR 1000	1000 mg	Powder for solution for infusion	Intravenous use
Belgium	ELI LILLY Benelux s.a. Rue De L'Etuve 52 B-1000 Brussels Belgium	GEMZAR 200	200 mg	Powder for solution for infusion	Intravenous use
Bulgaria	Eli Lilly Nederland B.V., Grootslag 1-5, 3991 RA Houten The Netherlands	Gemzar	200 mg	Powder for solution for infusion	intravenous use
Bulgaria	Eli Lilly Nederland B.V., Grootslag 1-5, 3991 RA Houten The Netherlands	Gemzar	1 g	Powder for solution for infusion	Intravenous use
Czech Republic	Eli Lilly ČR, s.r.o, Pobřežní 1A, 186 00 Praha 8 Czech Republic	Gemzar 1 g	1 g	Powder for solution for infusion	Intravenous use
Czech Republic	Eli Lilly ČR, s.r.o, Pobřežní 1A, , 186 00 Praha 8 Czech Republic	Gemzar 200 mg	200 mg	Powder for solution for infusion	Intravenous use

Cyprus	PHADISCO LTD 185 Giannou Kranidioti Avenue CY-2234 Latsia Cyprus	GEMZAR	200 mg	Powder for solution for infusion	Intravenous use
Cyprus	PHADISCO LTD 185 Giannou Kranidioti Avenue CY-2234 Latsia Cyprus	GEMZAR	1g	Powder for solution for infusion	Intravenous use
Denmark	Eli Lilly Danmark A/S, Nybrovej 110, DK-2800 Kongens Lyngby Denmark	Gemzar	200 mg	Powder for solution for infusion	Intravenous use
Denmark	Eli Lilly Danmark A/S, Nybrovej 110, DK-2800 Kongens Lyngby Denmark	Gemzar	1 g	Powder for solution for infusion	Intravenous use
Estonia	Eli Lilly Holdings Linited, Kingsclere Road, Basingstoke, Hampshire, RG21 6XA United Kingdom	Gemzar 200 mg powder for solution for infusion	200 mg	Powder for solution for infusion	Intravenous use
Estonia	Eli Lilly Holdings Linited, Kingsclere Road, Basingstoke, Hampshire, RG21 6XA United Kingdom	Gemzar 1 g powder for solution for infusion	1g	Powder for solution for infusion	Intravenous use
Finland	Oy Eli Lilly Finland,Ab Rajatorpantie 41 C, PL 16, 01641 Vantaa Finland	Gemzar 200 mg powder for solution for infusion	200 mg	Powder for solution for infusion	Intravenous use
Finland	Oy Eli Lilly Finland,Ab Rajatorpantie 41 C, PL 16, 01641 Vantaa Finland	Gemzar 1 g powder for solution for infusion	1 g	Powder for solution for infusion	Intravenous use

France	LILLY France SAS 13, rue Pagès 92158 Suresnes Cedex France	GEMZAR 1000 mg, poudre pour solution pour perfusion	1000 mg	Powder for solution for infusion	Intravenous use
France	LILLY France SAS 13, rue Pagès 92158 Suresnes Cedex France	GEMZAR 200 mg, poudre pour solution pour perfusion	200 mg	Powder for solution for infusion	Intravenous use
Germany	Lilly Deutschland GmbH Teichweg 3 35396 Gießen Germany	Gemzar 200 mg Pulver zur Herstellung einer Infusionsloesung	200 mg	Powder for solution for infusion	Intravenous use
Germany	Lilly Deutschland GmbH Teichweg 3 35396 Gießen Germany	Gemzar 1g Pulver zur Herstellung einer Infusionsloesung	1000 mg	Powder for solution for infusion	Intravenous use
Greece	FARMASERVE LILLY S.A.Cl 15 Km National Road Athens-Lamia Kifissia, 14564 Greece	ΓΚΕΜΖΑΡ	200 mg	Powder for solution for infusion	Intravenous use
Greece	FARMASERVE LILLY S.A.Cl 15 Km National Road Athens-Lamia Kifissia, 14564 Greece	ΓΚΕΜΖΑΡ	1000 mg	Powder for solution for infusion	Intravenous use
Hungary	Eli Lilly Nederland BV PO Box 379 3990 GD Houten The Netherlands	Gemzar 1g powder for injection	1g	Powder for Injection	Intravenous use
Hungary	Eli Lilly Nederland BV PO Box 379 3990 GD Houten The Netherlands	Gemzar 200 mg powder for injection	200 mg	Powder for Injection	Intravenous use

Ireland	Eli Lilly and Company Limited Lilly House, Priestley Road, Basingstoke, Hampshire RG24 9NL United Kingdom	Gemzar 200 mg powder for solution for infusion	200mg	Powder for solution for infusion	Intravenous use
Ireland	Eli Lilly and Company Limited Lilly House, Priestley Road, Basingstoke, Hampshire RG24 9NL United Kingdom	Gemzar 1 g powder for solution for infusion	1g	Powder for solution for infusion	Intravenous use
Iceland	Eli Lilly Denmark, Nybrovej 110, 2800 Lyngby Denmark	Gemzar	200 mg	Powder for solution for infusion	Intravenous use
Iceland	Eli Lilly Denmark, Nybrovej 110, 2800 Lyngby Denmark	Gemzar	1 g	Powder for solution for infusion	Intravenous use
Italy	ELI LILLY ITALIA S.P.A.. Via Gramsci 731/733 - 50019 Sesto Fiorentino, Florence Italy	GEMZAR 200 mg powder for solution for infusion and intravesical instillation	200 mg	Powder for solution for infusion and intravesical instillation	Intravenous use and intravesical use
Italy	ELI LILLY ITALIA S.P.A.. Via Gramsci 731/733 - 50019 Sesto Fiorentino, Florence Italy	GEMZAR 1 g powder for solution for infusion and intravesical instillation	1 g	Powder for solution for infusion and intravesical instillation	Intravenous use and intravesical use
Latvia	Eli Lilly Holdings Limited, Kingsclere Road, Basingstoke, Hampshire, RG 216XA5 United Kingdom	Gemzar	1 g	Powder for solution for infusion	intravenous use

Latvia	Eli Lilly Holdings Limited, Kingsclere Road, Basingstoke, Hampshire, RG 216XA5 United Kingdom	Gemzar	200 mg	Powder for solution for infusion	intravenous use
Lithuania	Eli Lilly Holdings Limited Kingsclere Road, Basingstoke, Hampshire RG21 6XA United Kingdom	Gemzar	200 mg	Powder for solution for infusion	Intravenous use
Lithuania	Eli Lilly Holdings Limited Kingsclere Road, Basingstoke, Hampshire RG21 6XA United Kingdom	Gemzar	1000 mg	Powder for solution for infusion	Intravenous use
Luxembourg	Eli Lilly Benelux s.a. 52, rue de l'Etuve B-1000 Bruxelles Belgium	GEMZAR	200 mg	Powder for solution for infusion	Intravenous use
Luxembourg	Eli Lilly Benelux s.a. 52, rue de l'Etuve B-1000 Bruxelles Belgium	GEMZAR	1g	Powder for solution for infusion	Intravenous use
Malta	Eli Lilly and Company Limited Lilly House, Priestley Road,, Basingstoke, Hampshire RG24 9NL. United Kingdom	Gemzar	200 mg	Powder for solution for infusion	Intravenous use
Malta	Eli Lilly and Company Limited Lilly House, Priestley Road,, Basingstoke, Hampshire RG24 9NL. United Kingdom	Gemzar	1g	Powder for solution for infusion	Intravenous use

The Netherlands	Eli Lilly Nederland BV Grootslag 1-5 3991 RA Houten The Netherlands	Gemzar	200 mg	Powder for solution for infusion	Intravenous use
The Netherlands	Eli Lilly Netherlands BV Grootslag 1-5 3991 RA Houten The Netherlands	Gemzar	1 g	Powder for solution for infusion	Intravenous use
Norway	Eli Lilly Norge AS, Postboks 6090 Etterstad, N-0601 Oslo Norway	Gemzar	1 g	Powder for solution for infusion	Intravenous use
Norway	Eli Lilly Norge AS, Postboks 6090 Etterstad, N-0601 Oslo Norway	Gemzar	200 mg	Powder for solution for infusion	Intravenous use
Poland	Lilly France S.A. 2 rue du colonel Lilly 67642 Fegersheim France	Gemzar	200 mg	Powder for solution for infusion	Intravenous use
Poland	Lilly France S.A. 2 rue du colonel Lilly 67642 Fegersheim France	Gemzar	1 g	Powder for solution for infusion	Intravenous use
Portugal	Lilly Portugal - Produtos Farmacêuticos, Lda. Rua Dr. António Loureiro Borges, 1 - Piso 1 - Arquiparque - Miraflores 1499-016 Algés Portugal	Gemzar	200 mg	Powder for solution for infusion	Intravenous use

Portugal	Lilly Portugal - Produtos Farmacêuticos, Lda. Rua Dr. António Loureiro Borges, 1 - Piso 1 - Arquiparque - Miraflores 1499-016 Algés Portugal	Gemzar	1000 mg	Powder for solution for infusion	Intravenous use
Romania	Lilly France S.A.S 2 Rue du Colonel Lilly 6740 Fegersheim France	Gemzar 1 g	1000 mg	Powder for solution for infusion	Intravenous use
Romania	Lilly France S.A.S 2 Rue du Colonel Lilly 6740 Fegersheim France	Gemzar 200 mg	200 mg	Powder for solution for infusion	Intravenous use
Slovakia	Eli Lilly ČR, s.r.o., Pobřežní 1a, 186 00 Praha 8 Czech Republic	GEMZAR 1 g	1 g	Powder for solution for infusion	Intravenous use
Slovakia	Eli Lilly ČR, s.r.o., Pobřežní 1a, 186 00 Praha 8 Czech Republic	GEMZAR 200 mg	200 mg	Powder for solution for infusion	Intravenous use
Slovenia	Eli Lilly farmacevtska družba, d.o.o. Dunajska 156 1000 Ljubljana Slovenia	Gemzar 200 mg prašek za raztopino za infundiranje	200 mg	Powder for solution for infusion	Intravenous use
Slovenia	Eli Lilly farmacevtska družba, d.o.o. Dunajska 156 1000 Ljubljana Slovenia	Gemzar 1 g prašek za raztopino za infundiranje	1 g	Powder for solution for infusion	Intravenous use
Spain	Lilly, S.A., Avenida de la Industria, 30 28108 Alcobendas Madrid Spain	GEMZAR 1 g Powder for solution for injection	1g	Powder for solution for injection	Intravenous use
Spain	Lilly, S.A., Avenida de la Industria, 30 28108 Alcobendas Madrid Spain	GEMZAR 200 mg Powder for solution for injection	200 mg	Powder for solution for injection	Intravenous use

Sweden	Eli Lilly Sweden AB Box 721 169 27 Solna Sweden	Gemzar®	200 mg	Powder for solution for infusion	Intravenous use
Sweden	Eli Lilly Sweden AB Box 721 169 27 Solna Sweden	Gemzar®	1 g	Powder for solution for infusion	Intravenous use
United Kingdom	Eli Lilly and Company Limited Lilly House, Priestley Road, Basingstoke, Hampshire RG24 9NL United Kingdom	Gemzar 200 mg Powder for Solution for Infusion	200mg	Powder for solution for infusion	Intravenous use
United Kingdom	Eli Lilly and Company Limited Lilly House, Priestley Road, Basingstoke, Hampshire RG24 9NL United Kingdom	Gemzar 1g Powder for Solution for Infusion	1g	Powder for solution for infusion	Intravenous use

ANNEX II

SCIENTIFIC CONCLUSIONS AND GROUNDS FOR AMENDMENT OF THE SUMMARIES OF PRODUCT CHARACTERISTICS, LABELLING AND PACKAGE LEAFLET PRESENTED BY THE EMEA

SCIENTIFIC CONCLUSIONS

OVERALL SUMMARY OF THE SCIENTIFIC EVALUATION OF GEMZAR

Gemzar was included in the list of products for SPC harmonisation, in accordance with Article 30(2) of Directive 2001/83/EC, as amended because of the divergences existing amongst the nationally authorised SPCs due to the divergent national decisions taken by Member States. Gemzar (gemcitabine) is a pyrimidine antagonist (an antimetabolite) that is metabolised intracellularly to active diphosphate and triphosphate nucleosides which inhibit DNA synthesis. It is primarily active against cells in the S phase and is given in the management of solid tumours. Gemcitabine (difluoro-deoxy-cytidine (dFdC)) is a cytotoxic anti-cancer agent, which exhibits cell phase specificity, primarily killing cells undergoing DNA synthesis (S-phase) and under certain conditions blocking the progression of cells through the G1/S phase boundary. The following indications are currently approved for Gemzar and were assessed by the CHMP: 1) Bladder cancer, 2) Advanced Non- small cell lung cancer, 3) Advanced pancreatic cancer, 4) Breast cancer and 5) Ovarian cancer. The CHMP assessed the SPC wording proposed by the MAH and the submitted rationales for the proposal. Particular attention was given to the therapeutic indications of Gemzar.

Critical Evaluation

For the indication in bladder cancer, the MAH provided data from two Phase 2 studies and from a pivotal Phase 3, showing that gemcitabine chemotherapy is active, tolerable, displays manageable toxicity and superiority to MVAC (methotrexate, vinblastine, adriamycin and cisplatin) chemotherapy in the treatment of patients with advanced or metastatic transitional cell carcinoma of the urothelium. The MAH also defended the use of gemcitabine by intravesical administration, based on the proven activity in advanced bladder cancer, on the pharmacokinetic attributes of gemcitabine and on its high total body clearance.

The CHMP considered the data submitted in support of the bladder cancer indication and noted that all the submitted studies were conducted in patients with locally advanced or metastatic bladder cancer. Promising data in advanced bladder cancer and the need for other treatments for superficial bladder cancer led to the study of gemcitabine by intravesical administration in superficial bladder cancer but although the CHMP acknowledged that gemcitabine has shown activity in non-muscle invasive bladder cancer in intermediate and high risk patients, no actual data from Phase III trials has been submitted. Therefore the CHMP considers that the proposed broad indication "bladder cancer" is not justified, as the data provided was not sufficient to support the indication in superficial bladder cancer. The CHMP required the MAH to reflect the target population (patients with advanced/metastatic bladder cancer) and the combination treatment with cisplatin in the harmonized indication. The MAH agreed to delete the indication in superficial bladder cancer and the CHMP accordingly proposed the following revised wording:

"Gemcitabine is indicated in the treatment of locally advance or metastatic bladder cancer in combination with cisplatin.".

The indication in pancreatic cancer is based on data from the pivotal Phase 3 study JHAY and the supporting study JHAZ. Intravenous gemcitabine has become widely accepted as the standard of chemotherapy care for advanced pancreatic cancer but has yielded disappointing results as combination treatment in patients with locally advanced (nonresectable) or metastatic pancreatic cancer and the MAH considered that gemcitabine monotherapy remains the standard of chemotherapy care for advanced/metastatic, nonresectable pancreatic adenocarcinoma.

Therefore the CHMP agreed with the proposal but asked the MAH to justify the proposed wording regarding 5-FU refractory patients. The MAH agreed that the indication is redundant because the first line treatment of pancreatic treatment with gemcitabine is standard of care and agreed to remove it. The CHMP also deleted the mention of performance status and adopted the following wording:

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

The indication in non-small cell lung cancer is based on data from Phase II and Phase III trials and indicated that gemcitabine has been shown to be active in the treatment of non-small cell lung cancer (NSCLC) and that in addition to gemcitabine single-agent activity, a preponderance of data supports the activity and safety of its combination with cisplatin in the treatment of NSCLC, irrespective of the different doses and schedules. The MAH therefore considered the positive benefit-risk ratio to be established for the use of gemcitabine/cisplatin in the treatment of NSCLC.

The CHMP agreed that gemcitabine used as single agent has shown activity against NSCLC but considered that the combination treatment with gemcitabine + cisplatin is the first line of treatment in patients with advanced/metastatic NSCLC and therefore asked the MAH to further justify the indication of Gemzar as combination treatment and as single agent in NSCLC, bearing in mind that single-agent therapy will usually be restricted to patients with a borderline performance status, elderly patients or pretreated patients.

The MAH agreed that platinum-based combination therapies are the standard of care but defended the use of gemcitabine monotherapy in the treatment of elderly patients and patients with a Performance Status of 2, as these groups are at higher risk for chemotherapy-related morbidities or in cases where platinum-based combinations cannot be tolerated. The MAH supported its position by providing guidelines from major oncology societies and review of the literature and proposed a new wording for the single agent in NSCLC indication. The CHMP reviewed the MAH responses and agreed that as a single agent, gemcitabine has a specific role in patients with a borderline performance status and elderly patients and that gemcitabine is an option between other treatments, although no specific agent has been identified to be better than others. The CHMP adopted the proposed revised wording:

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

Regarding breast cancer, the MAH only proposed combination use for inclusion in the harmonised SPC, although a Phase 3 study showed the activity of single-agent gemcitabine for the treatment of metastatic breast cancer (MBC).The indication was supported by a clinical expert report and efficacy data from Phase 2 and 3 single-agent studies of Gemzar in the treatment of breast cancer, including studies conducted by the MAH and results from the published literature. Overall, the MAH therefore considered gemcitabine plus paclitaxel combination chemotherapy to be an effective regimen in patients with metastatic breast cancer, with an expected and manageable toxicity and a favourable risk-benefit profile.

The CHMP was of the opinion that gemcitabine has shown activity as single agent in MBC but the lack of Phase III trials in this setting makes it difficult to give a specific recommendation about the precise place of gemcitabine in the treatment of advance breast cancer. The CHMP therefore considered that the greatest benefit from gemcitabine is achieved when it is administered in the first and second line setting in combination with taxanes and adopted the following wording:

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."

Regarding ovarian cancer, the MAH proposed a wording for combination use in this indication, although activity is shown by gemcitabine as a single agent, and provided a clinical expert report and supplementary information to support the indication. The MAH focused the discussion on the pivotal randomized Phase 3 Study JHQJ, and the main supportive single-arm Phase 2 Study JHRW. The MAH concluded that the studies demonstrated that gemcitabine plus carboplatin is superior to

carboplatin in terms of time to disease progression (TtDP) and response rate in patients with platinum-sensitive recurrent ovarian cancer. This improvement in PFS and response rate is only associated with some additional, readily manageable toxicity, resulting in a favourable risk benefit profile.

The CHMP noted the pivotal study JHQJ was powered to detect differences in TtDP in overall survival and that the pivotal study for the ovarian cancer had a specific population consisting of platinum sensitive patients with a very poor prognosis and the CHMP was of the opinion that the proposed wording was in accordance with the submitted study for the marketing authorisation in this indication. As no studies were available to support the use of gemcitabine as single agent neither in first or second line, the CHMP requested the MAH to further discuss the indication of Gemzar in ovarian cancer.

The MAH defended the use of gemcitabine for the ovarian cancer indication based on a number of guidelines, considering that based on the demonstrated significant benefits of gemcitabine in combination with carboplatin, the acceptable toxicity profile and the tolerability of the treatment, this combination presents a favourable risk/benefit relationship in the treatment of recurrent ovarian cancer patients. In addition, the use of gemcitabine for the treatment of recurrent ovarian cancer has been widely recognized and the MAH therefore believes that carboplatin plus gemcitabine represents a valuable option for treating patients with recurrent ovarian cancer. The CHMP reviewed the information regarding the use of Gemcitabine in ovarian cancer and was of the opinion that the combination gemcitabine/carboplatin is an option in second line therapy in patients with sensitive platinum disease and an alternative in patients with previous paclitaxel/carboplatin toxicity (Therefore the CHMP retained the indication in ovarian cancer in the harmonised SPC, with the wording:

"Gemcitabine is indicated in 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"

For Section 4.2, the MAH proposed a harmonised wording, addressing in particular the sections about dosage adjustment, about impaired renal function and on precautions in administration. The CHMP requested clarifications on treatment continuation and more details specific to the individual indications, in particular breast cancer and ovarian cancer. The CHMP retained the conservative age of 18 and also noted that information regarding hepatic impairment was included and therefore requested the MAH to further discuss patients with renal or hepatic impairment and whether severe impairment had significant effect on gemcitabine pharmacokinetics.

The MAH provided an updated posology taking into account the CHMP comments. No specific studies were performed in severely renally or hepatically impaired patients but based on published literature, the MAH considered that there was no indication that these patients differ significantly from the mild to moderate renally impaired group, in terms of Cmax or clearance. The MAH also considered that the limited data available does not permit any dose modifications to be suggested in the SPC for patients with renal or hepatic impairment and that the precautions already adequately reflect the information available. Based on the responses, the CHMP revised the text in section 4.2.

For Section 4.3, the MAH proposal retained only two of the existing 8 contraindications (relating to hypersensitivity and breast feeding) and removed 6 (hepatic or renal impairment, cisplatin for patients with severe renal failure, pregnancy and lactation, combination with yellow fever, usage in children and concomitant administration of gemcitabine and radiotherapy). The CHMP was of the opinion that the MAH proposal was acceptable, but considered that interactions and conditions relevant for all cytotoxics are expected for gemcitabine and that adequate warning should therefore be provided in section 4.4 and 4.5. Because no studies have been made in patients with renal or hepatic impaired, the CHMP did not consider there to be a need for an absolute contraindication, nor did it consider radiotherapy to be an absolute contra-indication.

For Section 4.4, the MAH addressed impaired renal and hepatic function, paediatric recommendations and concomitant administration of gemcitabine and radiotherapy. In general, the CHMP considered

the proposed wording to be adequate, but implemented a number of revisions, including sections on impaired bone-marrow function, combination with carboplatin and cisplatin, live attenuated vaccines and Pharmacovigilance reports on cardiovascular events and viral hepatitis reactivation.

Sections 4.5, 4.6, 4.7, 4.8 and 4.9 were also harmonised. For Section 4.8, the CHMP requested the clarification of the presentation of the post-marketing spontaneous report and also proposed a list of revised terms to be used in all the tables of adverse event in combination use in this section. Finally, a number of additional minor comments, including comments to remaining sections of the SPC, were made by the CHMP and implemented directly in the SPC text. Other sections of the SPC: While the full harmonisation of the quality dossier was not part of the scope of the referral, the sections of the SPC (in particular sections 2 and 6) and the corresponding Package Leaflet sections relating to Quality were assessed and harmonised.

The CHMP considers that the divergences identified at the start of the referral have been resolved and that all issues raised in the List of Questions and in the List of Outstanding Issues have been properly addressed and answered satisfactorily. The proposed revisions to the Product Information were fully implemented. In summary the MAH has deleted the indication for intravesical use and for 5-FU-refractory pancreatic cancer while the indication in ovarian cancer has been justified. Also, the use of Gemcitabine as a single agent in NSCLC was justified in specific situations. The CHMP therefore adopted the remaining five indications for Gemzar, as worded in the revised SPC.

GROUNDS FOR AMENDMENT OF THE SUMMARIES OF PRODUCT CHARACTERISTICS, LABELLING AND PACKAGE LEAFLET

Whereas

- the scope of the referral was the harmonisation of the Summaries of Products Characteristics, labelling and package leaflet.

- the Summaries of Products Characteristic, labelling and package leaflet proposed by the Marketing Authorisation Holders have been assessed based on the documentation submitted and the scientific discussion within the Committee,

the CHMP has recommended the amendment of the Marketing Authorisations for which the Summary of Product Characteristics, labelling and package leaflet are set out in Annex III for Gemzar.

ANNEX III

SUMMARY OF PRODUCT CHARACTERISTICS, LABELLING AND PACKAGE LEAFLET

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Gemzar 200 mg powder for solution for infusion

Gemzar 1000 mg 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 1000 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 1000 mg vial contains 17.5 mg (<1 mmol) sodium.

For a full list of excipients see section 6.1.

3. PHARMACEUTICAL FORM

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

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

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

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

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

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

4.2 Posology and method of administration

Gemcitabine should only be prescribed by a physician qualified in the use of anti-cancer chemotherapy.

Recommended posology

Bladder cancer
Combination use
The recommended dose for gemcitabine is 1000 mg/m^2, given by 30-minute infusion. The dose should be given on Days 1, 8 and 15 of each 28-day cycle in combination with cisplatin. Cisplatin is given at a recommended dose of 70 mg/m^2 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/m^2, 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/m^2, 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/m^2 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/m^2 once every 3 weeks.

Breast cancer
Combination use
Gemcitabine in combination with paclitaxel is recommended using paclitaxel (175 mg/m^2) administered on Day 1 over approximately 3-hours as an intravenous infusion, followed by gemcitabine (1250 mg/m^2) 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 10^6/l) prior to initiation of gemcitabine + paclitaxel combination.

Ovarian cancer
Combination use
Gemcitabine in combination with carboplatin is recommended using gemcitabine 1000 mg/m^2 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 10^6/l) and platelet account of 100,000 (x 10^6/l) prior to the initiation of a cycle.

Within a cycle

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

Dose modification of gemcitabine within a cycle for bladder cancer, NSCLC and pancreatic cancer, given in monotherapy or in combination with cisplatin			
Absolute granulocyte count (x 10^6/l)		**Platelet count (x 10^6/l)**	**Percentage of standard dose of Gemzar (%)**
> 1,000	and	> 100,000	100
500-1,000	or	50,000-100,000	75
<500	or	< 50,000	Omit dose *

*Treatment omitted will not be re-instated within a cycle before the absolute granulocyte count reaches at least 500 (x10^6/l) and the platelet count reaches 50,000 (x10^6/l).

Dose modification of gemcitabine within a cycle for breast cancer, given in combination with paclitaxel			
Absolute granulocyte count (x 10^6/l)		**Platelet count (x 10^6/l)**	**Percentage of standard dose of Gemzar (%)**
≥ 1,200	and	>75,000	100
1,000- <1,200	or	50,000-75,000	75
700- <1,000	and	≥ 50,000	50
<700	or	<50,000	Omit dose*

*Treatment omitted will not be 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 (x10^6/l) and the platelet count reaches 100,000 (x10^6/l).

Dose modification of gemcitabine within a cycle for ovarian cancer, given in combination with carboplatin			
Absolute granulocyte count (x 10^6/l)		**Platelet count (x 10^6/l)**	**Percentage of standard dose of Gemzar (%)**
> 1,500	and	≥ 100,000	100
1000-1,500	or	75,000-100,000	50
<1000	or	< 75,000	Omit dose*

*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 (x10^6/l) and the platelet count reaches 100,000 (x10^6/l).

Dose modifications due to haematological toxicity in subsequent cycles, for all indications
The gemcitabine dose should be reduced to 75% of the original cycle initiation dose, in the case of the following haematological toxicities:

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

Method of administration

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

For instructions on reconstitution, see section 6.6

Special populations

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

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

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

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients.
Breast-feeding (see section 4.6).

4.4 Special warnings and precautions for use

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

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

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

Laboratory evaluation of renal and hepatic function (including virological tests) should be performed periodically.

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

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

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

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

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

Renal
Clinical findings consistent with the haemolytic uraemic syndrome (HUS) were rarely reported in patients receiving gemcitabine (see section 4.8). Gemcitabine should be discontinued at the first signs of any evidence of microangiopathic haemolytic anaemia, such as rapidly falling haemoglobin with concomitant thrombocytopaenia, 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
Gemzar 200 mg contains 3.5 mg (<1 mmol) sodium per vial. This should be taken into consideration by patients on a controlled sodium diet.

Gemzar 1000 mg contains 17.5 mg (< 1 mmol) sodium per vial. This should be taken into consideration by patients on a controlled sodium diet.

4.5 Interaction with other medicinal products and other forms of interaction

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

Radiotherapy
Concurrent (given together or ≤ 7 days apart) - Toxicity associated with this multimodality therapy is dependent on many different factors, including dose of gemcitabine, frequency of gemcitabine administration, dose of radiation, radiotherapy planning technique, the target tissue, and target volume. Pre-clinical and clinical studies have shown that gemcitabine has radiosensitising activity. In a single trial, where gemcitabine at a dose of 1,000 mg/m^2 was administered concurrently for up to 6 consecutive weeks with therapeutic thoracic radiation to patients with non-small cell lung cancer, significant toxicity in the form of severe, and potentially life threatening mucositis, especially oesophagitis, and pneumonitis was observed, particularly in patients receiving large volumes of radiotherapy [median treatment volumes 4,795 cm^3]. Studies done subsequently have suggested that it is feasible to administer gemcitabine at lower doses with concurrent radiotherapy with predictable toxicity, such as a phase II study in non-small cell lung cancer, where thoracic radiation doses of 66 Gy were applied concomitantly with an administration with gemcitabine (600 mg/m^2, four times) and cisplatin (80 mg/m^2 twice) during 6 weeks. The optimum regimen for safe administration of gemcitabine with therapeutic doses of radiation has not yet been determined 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 Gemzar 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.

System Organ Class	Frequency grouping
Blood and lymphatic system disorders	Very common • Leucopaenia (Neutropaenia Grade 3 = 19.3 %; Grade 4 = 6 %). Bone-marrow suppression is usually mild to moderate and mostly affects the granulocyte count (see section 4.2) • Thrombocytopaenia • Anaemia Common • Febrile neutropaenia Very rare • Thrombocytosis
Immune system disorders	Very Rare • Anaphylactoid reaction
Metabolism and nutrition disorders	Common • Anorexia
Nervous system disorders	Common • Headache • Insomnia • Somnolence
Cardiac disorders	Rare • Myocardial infarct
Vascular disorders	Rare • Hypotension

System Organ Class	Frequency grouping
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

System Organ Class	Frequency grouping
Renal and urinary disorders	Very Common • Haematuria • Mild proteinuria
General disorders and administration site conditions	Very common • Influenza-like symptoms - the most common symptoms are fever, headache, chills, myalgia, asthenia and anorexia. Cough, rhinitis, malaise, perspiration and sleeping difficulties have also been reported. • Oedema/peripheral oedema- including facial oedema. Oedema is usually reversible after stopping treatment Common • Fever • Asthenia • Chills Rare • Injection site reactions-mainly mild in nature
Injury, poisoning, and procedural Complications	Radiation toxicity (see section 4.5).

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

Nervous system disorders
Cerebrovascular accident

Cardiac disorders
Arrythmias, predominantly supraventricular in nature
Heart failure

Vascular disorders
Clinical signs of peripheral vasculitis and gangrene

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

Gastrointestinal disorders
Ischaemic colitis

Hepatobiliary disorders
Serious hepatotoxicity, including liver failure and death

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

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

Injury, poisoning and procedural complications
Radiation recall

Combination use in breast cancer
The frequency of grade 3 and 4 haematological toxicities, particularly neutropaenia, increases when gemcitabine is used in combination with paclitaxel. However, the increase in these adverse reactions is not associated with an increased incidence of infections or haemorrhagic events. Fatigue and febrile neutropaenia occur more frequently when gemcitabine is used in combination with paclitaxel. Fatigue, which is not associated with anaemia, usually resolves after the first cycle.

Grade 3 and 4 Adverse Events
Paclitaxel versus gemcitabine plus paclitaxel

	Number (%) of Patients			
	Paclitaxel arm (N=259)		Gemcitabine plus Paclitaxel arm (N=262)	
	Grade 3	Grade 4	Grade 3	Grade 4
Laboratory				
Anaemia	5 (1.9)	1 (0.4)	15 (5.7)	3 (1.1)
Thrombocytopaenia	0	0	14 (5.3)	1 (0.4)
Neutropaenia	11 (4.2)	17 (6.6)*	82 (31.3)	45 (17.2)*
Non-laboratory				
Febrile neutropaenia	3 (1.2)	0	12 (4.6)	1(0.4)
Fatigue	3 (1.2)	1 (0.4)	15 (5.7)	2 (0.8)
Diarrhoea	5 (1.9)	0	8 (3.1)	0
Motor neuropathy	2(0.8)	0	6(2.3)	1(0.4)
Sensory neuropathy	9(3.5)	0	14(5.3)	1(0.4)

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

Combination use in bladder cancer

Grade 3 and 4 Adverse Events MVAC versus Gemcitabine plus cisplatin				
	Number (%) of Patients			
	MVAC (methotrexate, vinblastine, doxorubicin and cisplatin) arm (N=196)		Gemcitabine plus cisplatin arm (N=200)	
	Grade 3	Grade 4	Grade 3	Grade 4
Laboratory				
Anaemia	30(16)	4(2)	47(24)	7(4)
Thrombocytopaenia	15(8)	25(13)	57(29)	57(29)
Non-laboratory				
Nausea and vomiting	37(19)	3(2)	44(22)	0(0)
Diarrhoea	15(8)	1(1)	6(3)	0(0)
Infection	19(10)	10(5)	4(2)	1(1)
Stomatitis	34(18)	8(4)	2(1)	0(0)

Combination use in ovarian cancer

Grade 3 and 4 Adverse Events Carboplatin versus Gemcitabine plus carboplatin				
	Number (%) of Patients			
	Carboplatin arm (N=174)		Gemcitabine plus carboplatin arm (N=175)	
	Grade 3	Grade 4	Grade 3	Grade 4
Laboratory				
Anaemia	10(5.7)	4(2.3)	39(22.3)	9(5.1)
Neutropaenia	19(10.9)	2(1.1)	73(41.7)	50(28.6)
Thrombocytopaenia	18(10.3)	2(1.1)	53(30.3)	8(4.6)
Leucopaenia	11(6.3)	1(0.6)	84(48.0)	9(5.1)
Non-laboratory				
Haemorrhage	0(0.0)	0(0.0)	3(1.8)	(0.0)
Febrile neutropaenia	0(0.0)	0(0.0)	2(1.1)	(0.0)
Infection without neutropaenia	0(0)	0(0.0)	(0.0)	1(0.6)

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

4.9 Overdose

There is no known antidote for overdose of gemcitabine. Doses as high as 5700 mg/m^2 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 G_1/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 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/m^2 that were infused from 0.4 to 1.2 hours.

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

Distribution
The volume of distribution of the central compartment was 12.4 l/m^2 for women and 17.5 l/m^2 for men (inter-individual variability was 91.9%). The volume of distribution of the peripheral compartment was 47.4 l/m^2. The volume of the peripheral compartment was not sensitive to gender.
The plasma protein binding was considered to be negligible.
Half-life: This ranged from 42 to 94 minutes depending on age and gender. For the recommended dosing schedule, gemcitabine elimination should be virtually complete within 5 to 11 hours of the start of the infusion. Gemcitabine does not accumulate when administered once weekly.

Metabolism
Gemcitabine is rapidly metabolised by cytidine deaminase in the liver, kidney, blood and other tissues. Intracellular metabolism of gemcitabine produces the gemcitabine mono, di and triphosphates (dFdCMP, dFdCDP and dFdCTP) of which dFdCDP and dFdCTP are considered active. These intracellular metabolites have not been detected in plasma or urine. The primary metabolite, 2'-deoxy-2', 2'-difluorouridine (dFdU), is not active and is found in plasma and urine.

Excretion
Systemic clearance ranged from 29.2 l/hr/m^2 to 92.2 /hr/m^2 depending on gender and age (inter-individual variability was 52.2%). Clearance for women is approximately 25% lower than the values for men. Although rapid, clearance for both men and women appears to decrease with age. For the recommended gemcitabine dose of 1000 mg/m^2 given as a 30-minute infusion, lower clearance values for women and men should not necessitate a decrease in the gemcitabine dose.
Urinary excretion: Less than 10% is excreted as unchanged drug.
Renal clearance was 2 to 7 l/hr/m^2.

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/m^2/30-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/m^2): 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/m^2 (range 11-22 l/m^2).
Mean steady state volume of distribution (Vss): 150 l/m^2 (range 96-228 l/m^2).
Tissue distribution: Extensive.
Mean apparent clearance: 2.5 l/hr/m^2 (range 1-4 l/hr/m^2).
Urinary excretion: All.

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

Gemzar 200 mg contains:
Mannitol (E421)
Sodium acetate (E262)
Hydrochloric acid (E507) (for pH adjustment)
Sodium hydroxide (E524) (for pH adjustment)

Gemzar 1000 mg contains:
Mannitol (E421)
Sodium acetate (E262)
Hydrochloric acid (E507) (for pH adjustment)
Sodium hydroxide (E524) (for pH adjustment)

6.2 Incompatibilities

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

6.3 Shelf life

Unopened vials: 3 years.

Reconstituted solution:
Chemical and physical in-use stability has been demonstrated for 24 hours at 30°C. From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at room temperature, unless reconstitution(and further dilution, if applicable) has taken place in controlled and validated aseptic conditions.

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

6.4 Special precautions for storage

Unopened vial: Store below 30°C

For storage conditions of the reconstituted medicinal product see section 6.3

6.5 Nature and contents of container

Type I flint glass vials, stoppered with a grey bromobutyl rubber stopper and sealed with an aluminium seal, combined with a polypropylene cap.

Each pack contains 1 vial

6.6 Special precautions for disposal and other handling

Handling
The normal safety precautions for cytostatic agents must be observed when preparing and disposing of the infusion solution. Handling of the solution for infusion should be done in a safety box and protective coats and gloves should be used. If no safety box is available, the equipment should be supplemented with a mask and protective glasses.
If the preparation comes into contact with the eyes, this may cause serious irritation. The eyes should be rinsed immediately and thoroughly with water. If there is lasting irritation, a doctor should be consulted. If the solution is spilled on the skin, rinse thoroughly with water.

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

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

2. To reconstitute, add 5 ml of sterile sodium chloride 9 mg/ml (0.9 %) solution for injection, without preservative, to the 200 mg vial or 25 ml sterile sodium chloride 9 mg/ml (0.9 %) solution for injection, without preservative, to the 1000 mg vial. The total volume after reconstitution is 5.26 ml (200 mg vial) or 26.3 ml (1000 mg vial) respectively. This yields a gemcitabine concentration of 38 mg/ml, which includes accounting for the displacement volume of the lyophilised powder. Shake to dissolve. Further dilution with sterile sodium chloride 9 mg/ml (0.9 %) solution for injection, without preservative can be done. Reconstituted solution is a clear colourless to light straw-coloured solution.

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

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

7. MARKETING AUTHORISATION HOLDER

[See Annex I - To be completed nationally]

8. MARKETING AUTHORISATION NUMBER

[To be completed nationally]

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

[To be completed nationally]

10. DATE OF REVISION OF THE TEXT

[To be completed nationally]

LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Gemzar 200 mg powder for solution for infusion

Gemzar 1000 mg powder for solution for infusion
Gemcitabine

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each vial contains gemcitabine hydrochloride equivalent to 200 mg gemcitabine.

Each vial contains gemcitabine hydrochloride equivalent to 1000 mg gemcitabine

3. LIST OF EXCIPIENTS

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

4. PHARMACEUTICAL FORM AND CONTENTS

1 vial, powder for solution for infusion

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

Do not refrigerate the reconstituted solution

8. EXPIRY DATE

EXP:

9. SPECIAL STORAGE CONDITIONS

Unopened vial: Store below 30°C

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 appropriately.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

[To be completed nationally]

12. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

13. BATCH NUMBER

Lot

14. CLASSIFICATION FOR SUPPLY

[To be completed nationally]

15. INSTRUCTIONS ON USE

16. INFORMATION ON BRAILLE

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL LABEL

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

Gemzar 200 mg powder for solution for infusion

Gemzar1000 mg powder for solution for infusion

Gemcitabine
For intravenous use after reconstitution

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

200 mg gemcitabine

1000 mg gemcitabine

6. OTHER

PACKAGE LEAFLET

PACKAGE LEAFLET: INFORMATION FOR THE USER

Gemzar 200 mg powder for solution for infusion
Gemzar 1000 mg 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 GEMZAR IS AND WHAT IT IS USED FOR

Gemzar belongs to a group of medicines called "cytotoxics". These medicines kill dividing cells, including cancer cells.

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

Gemzar 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 GEMZAR

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

Take special care with Gemzar:
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 Gemzar. 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 Gemzar. 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 Gemzar should be avoided during pregnancy. Your doctor will discuss with you the potential risk of taking Gemzar during pregnancy.

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

Driving and using machines
Gemzar 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 Gemzar treatment has not made you feel sleepy.

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

3. HOW GEMZAR IS GIVEN

The usual dose of Gemzar 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 Gemzar infusion depends on the type of cancer that you are being treated for.

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

You will always receive Gemzar 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, Gemzar 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 38ºC 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 Gemzar infusion which soon passes, however uncommonly or rarely there can be more severe lung problems)

Side effects with Gemzar 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 mentioned in this leaflet, please tell your doctor.

5. HOW TO STORE GEMZAR

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

Unopened vial: Store below 30°C.

Reconstituted solution: The product should be used immediately. When prepared as directed, chemical and physical in-use stability of reconstituted solutions of gemcitabine were demonstrated for 24 hours at 30°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 Gemzar contains

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

What Gemzar looks like and contents of the pack

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

Marketing Authorisation Holder and Manufacturer

[See Annex I - To be completed nationally]

Manufacturer:
Lilly France S.A.S., rue du Colonel Lilly, F-67640, Fegersheim, France

This leaflet was last approved in

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

Instructions for use, handling and disposal.

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

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

3. Reconstitute 200 mg vials with 5 ml of 9 mg/ml (0.9 %) sterile sodium chloride solution for injection, without preservative, or 25 ml sterile sodium chloride solution for injection, without preservative to the 1000 mg vial. Shake to dissolve. The total volume after reconstitution is 5.26 ml (200 mg vial) or 26.3 ml (1000 mg vial) respectively. This dilution yields a gemcitabine concentration of 38 mg/ml, which includes accounting for the displacement volume of the lyophilised powder. Further dilution with sterile sodium chloride 9 mg/ml (0.9%) solution for injection, without preservative may be done. The resulting solution is clear and ranges in colour from colourless to light straw-coloured.

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

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

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

Preparation and administration precautions

The normal safety precautions for cytostatic agents must be observed when preparing and disposing of the infusion solution. Handling of the solution for infusion should be done in a safety box and protective coats and gloves should be used. If no safety box is available, the equipment should be supplemented with a mask and protective glasses.
If the preparation comes into contact with the eyes, this may cause serious irritation. The eyes should be rinsed immediately and thoroughly with water. If there is lasting irritation, a doctor should be consulted. If the solution is spilled on the skin, rinse thoroughly with water.

Disposal
Any unused product should be disposed of in accordance with local requirements.