PROFESSIONAL INFORMATION

SCHEDULING STATUS

S4

1 NAME OF THE MEDICINE

GEMCITABINE 200 mg PHARMA-Q powder for solution for infusion

GEMCITABINE 1 g PHARMA-Q powder for solution for infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

GEMCITABINE 200 mg PHARMA-Q

Each vial contains gemcitabine hydrochloride equivalent to 200 mg gemcitabine.

When reconstituted the solution contains 200 mg gemcitabine per 5 ml

Contains sugar: mannitol 200 mg per vial

GEMCITABINE 1 g PHARMA-Q

Each vial contains gemcitabine hydrochloride equivalent to 1 g gemcitabine.

When reconstituted the solution contains 1 g gemcitabine per 25 ml

Contains sugar: mannitol 1 000 mg per vial

For full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Powder for solution for infusion

White to off white lyophilised plug contained in a flint glass vial.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

GEMCITABINE PHARMA-Q is indicated for the treatment of patients with locally advanced or metastatic non-small cell lung cancer.

GEMCITABINE PHARMA-Q is indicated as first-line treatment for patients with locally

advanced (non-resectable Stage II or Stage III) or metastatic (Stage IV) adenocarcinoma of the pancreas. GEMCITABINE PHARMA-Q is indicated for patients previously treated with 5-FU.

GEMCITABINE PHARMA-Q is indicated for treatment of patients with transitional cell bladder cancer.

GEMCITABINE PHARMA-Q, 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 contra-indicated.

GEMCITABINE PHARMA-Q, alone or in combination, is indicated for the treatment of patients with recurrent epithelial ovarian carcinoma who have relapsed following platinum-based chemotherapy.

4.2 Posology and method of administration

Posology

GEMCITABINE PHARMA-Q is for intravenous use only.

Non-small cell lung cancer

Adults: The recommended monochemotherapy dosage is 1 000 mg/m^2, given by 30-minute intravenous infusion. This should be repeated once weekly for three weeks, followed by a one week rest period. This four week cycle is then repeated. Dosage reduction with each cycle or within a cycle may be applied based upon the amount of toxicity experienced by the patient.

GEMCITABINE PHARMA-Q may be used in combination with cisplatin using either a three week or a four-week schedule. One of the following regimens is suggested:

3-week schedule: GEMCITABINE PHARMA-Q 1 250 mg/m², given by 30-minute intravenous infusion on days 1 and 8 of every 21-day cycle and cisplatin 100 mg/m² on day 1. Dosage reduction with each cycle or within a cycle may be applied based upon

the amount of toxicity experienced by the patient.

4-week schedule: GEMCITABINE PHARMA-Q 1 000 mg/m2 on days 1, 8 and 15 of every 28-day cycle and cisplatin 100 mg/m2 on either day 1, 2 or 15 of therapy. Dose reduction with each cycle or within a cycle may be applied based upon the amount of toxicity experienced by the patient.

Pancreatic cancer

Adults: The recommended dose of GEMCITABINE PHARMA-Q is 1 000 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 amount of toxicity experienced by the patient.

Bladder cancer

Adults: The recommended monochemotherapy dosage of GEMCITABINE PHARMA-Q is 1 250 mg/m², given by 30-minute intravenous infusion. The dose should be given on days 1, 8 and 15 of each 28 day cycle. This four week cycle is then repeated. Dosage reduction with each cycle or within a cycle may be applied based upon the amount of toxicity experienced by the patient.

GEMCITABINE PHARMA-Q may be used in combination with cisplatin. The recommended dose of GEMCITABINE PHARMA-Q is 1 000 mg/m², given by 30-minute infusion. The dose should be given on days 1, 8 and 15 of each 28 day cycle in combination with cisplatin. Cisplatin is given at a recommended dose of 70 mg/m² on day 1 following GEMCITABINE PHARMA-Q or day 2 of each 28-day cycle. This four week cycle is then repeated. Dosage reduction with each cycle or within a cycle may be applied based upon the amount of toxicity experienced by the patient. A clinical trial

showed more myelosuppression when cisplatin was used in doses of 100 mg/m².

Breast cancer

Adults: GEMCITABINE PHARMA-Q 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 PHARMA-Q (1 250 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 amount 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 PHARMA-Q + paclitaxel combination.

Ovarian cancer

Single agent use

Adults: The recommended dose of GEMCITABINE PHARMA-Q is 800 to 1 250 mg/m^2, given by a 30-minute intravenous infusion. The dose should be given on days 1, 8 and 15 of each 28 day cycle. This four week cycle is then repeated. Dosage reduction with each cycle or within a cycle may be applied based upon the amount of toxicity experienced by the patient.

Combination use

Adults: GEMCITABINE PHARMA-Q in combination with carboplatin is recommended using GEMCITABINE PHARMA-Q 1 000 mg/m^2 administered on days 1 and 8 of each 21-day cycle as a 30-minute intravenous infusion. After GEMCITABINE PHARMA-Q, carboplatin will be given on day 1 consistent with a target AUC of 4,0 g/ml/min. Dosage reduction with each cycle or within a cycle may be applied based upon the amount of toxicity experienced by the patient.

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

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

Periodic physical examination and checks of renal and hepatic function should be made to detect non-haematologic toxicity. Dosage reduction with each cycle or within a cycle may be applied based upon the amount of toxicity experienced by the patient. Doses should be withheld until toxicity has resolved in the opinion of the medical practitioner.

GEMCITABINE PHARMA-Q is well tolerated during the infusion, with only a few cases of injection site reaction reported. GEMCITABINE PHARMA-Q can be easily administered on an outpatient basis.

Special populations

Patients with hepatic or renal impairment

GEMCITABINE PHARMA-Q should be used with caution in patients with hepatic insufficiency or with impaired renal function as no studies have been done in patients with significant renal or hepatic impairment. There is insufficient information from clinical studies to allow clear dose recommendation for this patient population.

Elderly patients

GEMCITABINE PHARMA-Q has been well tolerated in patients over the age of 65. There is no evidence to suggest that dose adjustments are necessary in the elderly, although GEMCITABINE PHARMA-Q clearance and half-life are affected by age.

Instructions for reconstitution

The only approved diluent for reconstitution of GEMCITABINE PHARMA-Q is 0,9 % sodium chloride injection without preservatives. It is not recommended that GEMCITABINE PHARMA-Q be mixed with other medicines when reconstituted. Due to solubility considerations, the maximum concentration for GEMCITABINE PHARMA-Q upon reconstitution is 40 mg/ml. Reconstitution at concentrations greater than 40 mg/ml may result in incomplete dissolution and should be avoided.

To reconstitute, add at least 5 ml of 0,9 % sodium chloride injection without preservatives to the 200 mg vial or at least 25 ml of 0,9 % sodium chloride injection without preservatives to the 1 g vial. Shake to dissolve. The appropriate amount of medicine may be administered as prepared or further diluted with 0,9 % sodium chloride injection without preservatives.

4.3 Contraindications

- Hypersensitivity to gemcitabine or to any of the excipients of GEMCITABINE PHARMA-Q (see section 6.1)
- Pregnancy and lactation: The safety of GEMCITABINE PHARMA-Q in human pregnancy and lactation has not been established.
- Usage in children: Safety and effectiveness in children have not been established.

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 PHARMA-Q can suppress bone marrow function as manifested by leucopoenia, thrombocytopenia and anaemia. Myelosuppression is usually mild to moderate and is more pronounced for the granulocyte count.

Patients receiving GEMCITABINE PHARMA-Q should be monitored prior to each dose for platelet, leucocyte and granulocyte counts. Suspension or modification of therapy should be considered when medicine-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 PHARMA-Q administration has been stopped. In patients with impaired bone marrow function, the treatment should be started with caution. The risk of cumulative bone-marrow suppression must be considered when GEMCITABINE PHARMA-Q treatment is given together with other chemotherapy.

Renal toxicity

Renal failure and haemolytic uraemic syndrome (HUS) have been reported rarely. GEMCITABINE PHARMA-Q should be administered with caution to patients with impaired renal function. GEMCITABINE PHARMA-Q should be discontinued at the first signs 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 even with discontinuation of therapy and dialysis may be required.

Pulmonary toxicity

Pulmonary effects, sometimes severe (such as pulmonary oedema, interstitial pneumonitis or adult respiratory distress syndrome (ARDS)) have been reported in

association with GEMCITABINE PHARMA-Q therapy. In such cases, GEMCITABINE PHARMA-Q treatment must be stopped. Steroids may relieve the symptoms in such situations. Starting supportive treatment at an early stage may improve the situation.

Carcinogenesis, mutagenesis, impairment of fertility

Cytogenic damage has been produced by GEMCITABINE PHARMA-Q in an *in vivo* assay. GEMCITABINE PHARMA-Q induced forward mutation *in vitro* in a mouse lymphoma assay. The influence of GEMCITABINE PHARMA-Q on fertility has not been established in humans. The carcinogenic potential of GEMCITABINE PHARMA-Q has not been established.

In fertility studies GEMCITABINE PHARMA-Q caused hypo spermatogenesis in male mice. Therefore, men being treated with GEMCITABINE PHARMA-Q are advised not to father a child during and up to 6 months after treatment and to seek further advice regarding cry conservation of sperm prior to treatment because of the possibility of infertility due to therapy with GEMCITABINE PHARMA-Q (see section 4.6).

Patients with renal or hepatic impairment

GEMCITABINE PHARMA-Q should be used with caution in patients with impaired renal function or hepatic impairment as there is insufficient information from clinical studies to allow clear dose recommendation for this patient population.

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

Administration of GEMCITABINE PHARMA-Q 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.

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 PHARMA-Q (see section 4.5).

Cardiovascular

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

Capillary leak syndrome (CLS)

Capillary leak syndrome has been reported in patients receiving GEMCITABINE PHARMA-Q as single agent or in combination with chemotherapeutic agents. The condition is usually treatable if recognised early and managed appropriately, but fatal cases have been reported. The condition involves systemic capillary hyperpermeability during which fluid and proteins from the intravascular space leak into the interstitium. The clinical features include generalised oedema, weight gain, hypoalbuminaemia, severe hypotension, acute renal impairment and pulmonary oedema. GEMCITABINE PHARMA-Q should be discontinued, and supportive measures implemented if capillary leak syndrome develops during therapy. Capillary leak syndrome can occur in later cycles and has been associated in the literature with adult respiratory distress syndrome.

Posterior reversible encephalopathy syndrome (PRES)

Reports of posterior reversible encephalopathy syndrome (PRES) with potentially severe consequences have been reported in patients receiving gemcitabine as single agent or in combination with other chemotherapeutic medicines.

Acute hypertension and seizure activity were reported in most GEMCITABINE PHARMA-

Q patients experiencing PRES, but other symptoms such as headache, lethargy, confusion and blindness could also be present. Diagnosis is optimally confirmed by magnetic resonance imaging (MRI). PRES was typically reversible with appropriate supportive measures. GEMCITABINE PHARMA-Q should be permanently discontinued, and supportive measures implemented, including blood pressure control and anti-seizure therapy, if PRES develops during therapy.

GEMCITABINE PHARMA-Q contains mannitol and may have a laxative effect.

Severe cutaneous adverse reactions (SCARs)

Severe cutaneous adverse reactions (SCARs) such as toxic epidermal necrolysis (TEN), Steven-Johnson syndrome (SJS), acute generalised exanthematous pustulosis (AGEP), eosinophilia and systemic (DRESS)/ Drug-induced hypersensitivity syndrome (DHIS) and fixed drug eruptions (FDE) have been reported in patients treated with gemcitabine containing medicines. If a patient develops SCAR, treatment with GEMCITABINE PHARMA-Q must be immediately be discontinued and appropriate treatment instituted.

4.5 Interaction with other medicines and other forms of interaction

Radiotherapy

Concurrent (given together or ≤ 7 days apart) - toxicity associated with this multimodality therapy is dependent on many different factors, including dose of gemcitabine injection, frequency of gemcitabine injection administration, dose of radiation, radiotherapy planning technique, the target tissue, and target volume. Clinical studies have shown that gemcitabine injection has radio sensitising activity. When gemcitabine injection was administered at a dose of 1 000 mg/m^2 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

esophagitis, and pneumonitis are observed, particularly in patients receiving large volumes of radiotherapy (median treatment volumes 4 795 cm^3).

The optimum regimen for safe administration of gemcitabine injection with therapeutic doses of radiation has not yet been determined in all tumour types.

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

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 Fertility, pregnancy and lactation

Pregnancy

There are no adequate data from the use of GEMCITABINE PHARMA-Q 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 PHARMA-Q, this medicine should not be used during pregnancy unless clearly necessary (see section 4.3). Women should be advised not to become pregnant during treatment with GEMCITABINE PHARMA-Q and to warn their attending medical practitioner immediately, should this occur after all.

Breastfeeding

It is not known whether GEMCITABINE PHARMA-Q is excreted in human milk and adverse effects on the suckling child cannot be excluded. Breastfeeding must be discontinued during GEMCITABINE PHARMA-Q therapy (see section 4.3).

Fertility

In fertility studies GEMCITABINE PHARMA-Q caused hypo spermatogenesis in male mice. Therefore, men being treated with GEMCITABINE PHARMA-Q are advised not to father a child during and up to 6 months after treatment and to seek further advice regarding cry conservation of sperm prior to treatment because of the possibility of infertility due to therapy with GEMCITABINE PHARMA-Q (see section 4.4).

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

a. Summary of the safety profile

The most commonly reported adverse drug reactions associated with GEMCITABINE PHARMA-Q treatment include nausea with or without vomiting, raised liver transaminases (AST/ALT) and alkaline phosphatase, reported in approximately 60 % of patients, proteinuria and haematuria reported in approximately 50 % of patients, dyspnoea reported in 10 to 40 % of patients (highest incidence in lung cancer patients) and allergic skin rashes occurring in approximately 25 % of patients and associated with itching in 10% of patients. The frequency and severity of adverse reactions are affected by the dose, infusion rate and intervals between doses (see section 4.4). Dose-limiting adverse reactions are reductions in platelet, leucocyte and granulocyte counts (see section 4.3).

b. Tabulated summary of adverse reactions

The following listing of undesirable effects and frequencies is based on clinical trial and post-marketing spontaneous reports.

MedDRA system organ class	**Frequency**	**Adverse reactions**
Infections and Infestations	Frequent	Infections
	Frequency unknown	Sepsis
Blood and lymphatic system disorders	Frequent	Leucopenia, thrombocytopenia, anaemia, myelosuppression, febrile neutropenia.
	Less frequent	Thrombocytosis, thrombiotic micro-angiopathy
Immune system disorders	Less frequent	Anaphylactoid reaction
Metabolism and nutrition disorders	Frequent	Anorexia
Nervous system disorders	Frequent	Headache, insomnia, somnolence
	Less frequent	Posterior reversible encephalopathy syndrome (see section 4.4)
	Frequency unknown	Cerebrovascular accident
Cardiac disorders	Less frequent	Myocardial infarct, heart failure, arrhythmia (predominantly supraventricular in nature).
	Frequency unknown	Dysrythmias (predominantly supraventricular in nature), heart failure.
Vascular disorders	Less frequent	Hypotension, clinical signs of peripheral vasculitis and gangrene. Capillary leak

MedDRA system organ class	**Frequency**	**Adverse reactions**
		syndrome (see section 4.4)
Respiratory, thoracic and mediastinal disorders	Frequent	Dyspnoea, cough, rhinitis
	Less frequent	Bronchospasm, interstitial pneumonitis (with associated pulmonary infiltrates), adult respiratory distress syndrome (ARDS) (see section 4.4)
	Frequency unknown	Pulmonary oedema, adult respiratory distress syndrome (see section 4.4)
Gastrointestinal disorders	Frequent	Nausea, vomiting, stomatitis, diarrhoea, constipation.
	Frequency unknown	Ischaemic colitis
Hepato-biliary disorders	Frequent	Elevation of liver transaminases (AST and ALT) and alkaline phosphatase, increased bilirubin.
	Less frequent	Increased gamma-glutamyl transferase (GGT).
	Frequency unknown	Serious hepatotoxicity, including liver failure and death
Skin and subcutaneous tissue disorders	Frequent	Allergic skin rash, frequently associated with pruritus, alopecia, sweating, itching
	Less frequent	Scaling, vesicle and sore formation, ulceration, severe skin reactions, including desquamation and bullous skin eruptions

MedDRA system organ class	**Frequency**	**Adverse reactions**
	Frequency unknown	Pseudocellulitis, Lyell's Syndrome, Steven-Johnson Syndrome, acute generalised exanthematous pustulosis (AGEP)
Musculoskeletal and connective tissue disorders	Frequent	Back pain, myalgia
Renal and urinary disorders	Frequent	Mild proteinuria and haematuria
	Frequency unknown	Renal failure (see section 4.4) Haemolytic uraemic syndrome (HUS) (see section 4.4)
General disorders and administration site conditions	Frequent	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.
	Less frequent	Injection site reactions-mainly mild in nature.
Injury, poisoning and procedural complications	Less frequent	Radiation toxicity, radiation recall (see section 4.5)

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are requested to report any suspected adverse drug reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website.

4.9 Overdose

There is no known antidote for overdose of gemcitabine. 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

Category and class; A 26 Cytostatic agents

Pharmacotherapeutic group: pyrimidine analogues ATC code: L01BC05

Cellular metabolism and mechanism of action

Gemcitabine (dFdC) is metabolised intracellularly by nucleoside kinases to mono-, di- and triphosphates (dFdCMP, dFdCDP and dFdCTP) of which dFdCDP and dFdCTP are active. The cytotoxic action of gemcitabine appears to be due to inhibition of DNA synthesis by two actions of dFdCDP and dFdCTP. Firstly, dFdCDP inhibits ribonucleotide reductase which is uniquely responsible for catalysing the reactions that generate the deoxynucleoside triphosphates for DNA synthesis. Inhibition of this enzyme by dFdCDP causes a reduction in the concentrations of deoxynucleosides in general, and especially in that of dCTP. Secondly, dFdCTP competes with dCTP for incorporation into DNA. Likewise, a small amount of gemcitabine may also be incorporated into RNA. Thus, the reduction in the intracellular concentration of dCTP potentiates the

incorporation of dFdCTP into DNA (self-potentiation). DNA polymerase epsilon is essentially unable to remove gemcitabine and repair the growing DNA strands. After gemcitabine is incorporated into DNA, one additional nucleotide is added to the growing DNA strands. After this addition there is essentially a complete inhibition in further DNA synthesis (masked chain termination). After incorporation into DNA, gemcitabine appears to induce the programmed cellular death process known as apoptosis.

Cytotoxic activity in cell culture models

Gemcitabine exhibits significant cytotoxicity activity against a variety of cultured murine and human tumour cells. It exhibits cell phase specificity, primarily killing cells undergoing DNA synthesis (S-phase) and under certain conditions blocking the progression of cells through the G1/S-phase boundary. *In vitro* the cytotoxic action of gemcitabine is both concentration and time dependent.

Antitumour activity in preclinical models

In animal tumour models, the antitumour activity of gemcitabine is schedule dependent. When administered daily, gemcitabine causes death in animals with minimal antitumour activity. If, however, gemcitabine is given every third or fourth day, it can be given at non-lethal doses that have excellent antitumour activity against a broad range of mouse tumours.

5.2 Pharmacokinetic properties

Absorption

The pharmacokinetics of gemcitabine appear to be linear over the doses examined.

The following pharmacokinetic parameters were obtained for doses ranging from 500 to 2 592 mg/m^2 that were infused over 0,4 to 1,2 hours:

Peak plasma concentrations (obtained within 5 minutes of end of the infusion): 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

Volume of distribution of central compartment (Vc): 12,4 l/m^2 for women and 17,5 l/m^2 for men (inter-individual variability was 91,9 %). Volume of distribution of peripheral compartment (Vp): 47,4 l/m^2. The volume of peripheral compartment was not sensitive to gender.

Half-life: 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.

Plasma protein binding: Negligible.

Biotransformation

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.

Formation of dFdU from parent compound ranges from 91 % to 98 %. Tissue distribution of dFdU is extensive.

Excretion

Systemic clearance*:* 29,2 l/hr/m^2 to 92,2 l/hr/m^2 depending on gender and age (inter-

individual variability was 52,2 %). Clearance for women is approximately 25 % lower than the values for men. Although rapid, clearance for both men and women appears to decrease with age. For the recommended gemcitabine dose of 1 000 mg/m^2 given as a 30-minute infusion, lower clearance for women or the elderly should not necessitate a decrease in the gemcitabine dose.

Urinary excretion: Less than 10 % is excreted unchanged.

Mean renal clearance: 2 to 7 l/hr/m^2.

Overall elimination: Amount recovered in one week following a single 30-minute infusion of 1 000 mg/m^2 of radiolabelled gemcitabine: 92 % to 98 %, of which 99 % is urinary excretion of dFdU; 1 % of the dose is excreted in faeces.

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

Mannitol (E421)

Sodium acetate trihydrate (E262)

Sodium hydroxide (for pH adjustment)

Hydrochloric acid (for pH adjustment)

Water for injection

6.2 Incompatibilities

This medicine must not be mixed with other medicines except those mentioned in section 6.6.

6.3 Shelf life

24 months

6.4 Special precautions for storage

Before reconstitution

Store at or below 25 °C.

After reconstitution

Solutions of GEMCITABINE PHARMA-Q reconstituted with 0,9 % sodium chloride injection without preservatives should be stored at or below 25 °C and should be administered within 24 hours.

Discard unused portion.

Do not refrigerate as crystallisation may occur.

Reconstituted GEMCITABINE PHARMA-Q should be inspected visually for particulate matter and discolouration, prior to administration.

Procedures for proper handling and disposal of anticancer medicines should be considered (see section 6.6).

6.5 Nature and contents of container

GEMCITABINE 200 mg PHARMA-Q:

10 ml clear colourless tubular glass vials, Type I, with 20 mm neck with a 20 mm Lyo

rubber stopper and 20 mm blue flip off seal stored in an outer unit carton.

GEMCITABINE 1 g PHARMA-Q:

50 ml clear colourless molded glass vials, Type I, with 20 mm neck with a 20 mm Lyo rubber stopper and 20 mm blue flip off seal stored in an outer unit carton.

Pack size: 1 vial per pack.

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 1 g vial. The total volume after reconstitution is 5,26 ml (200 mg vial) or 26,3 ml (1 g 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 medicines 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 HOLDER OF CERTIFICATE OF REGISTRATION

Pharma-Q Holdings (Pty) Ltd

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8 REGISTRATION NUMBERS

48/26/0459: 200 mg

48/26/0460: 1 g

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

22 September 2020

10 DATE OF REVISION OF THE TEXT

07 March 2025