APPROVED PROFESSIONAL INFORMATION FOR CYTIGEM

SCHEDULING STATUS: **S4**

1 NAME OF THE MEDICINE

CYTIGEM 200 mg (Powder for solution for infusion)

CYTIGEM 1 g (Powder for solution for infusion)

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

CYTIGEM 200 mg (10 mL vial): Each vial contains gemcitabine hydrochloride equivalent to 200 mg gemcitabine free base.

CYTIGEM 1 g (50 mL vial): Each vial contains gemcitabine hydrochloride equivalent to 1 g gemcitabine free base.

When reconstituted, yields a final concentration of 40 mg/mL gemcitabine solution for infusion.

Excipients with known effect

Contains sodium:

- CYTIGEM 200 mg contains 3,5 mg (< 1 mmol) sodium per vial.
- CYTIGEM 1 g contains 17,5 mg (< mmol) sodium per vial.

Contains sugar (mannitol):

- CYTIGEM 200 mg contains 200 mg mannitol per vial.
- CYTIGEM 1 g contains 1 000 mg mannitol per vial.

For full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Powder for solution for infusion

CYTIGEM 200 mg: A white to off white lyophilized powder in a clear glass vial. Reconstitution with 0,9 % sodium chloride injection without preservatives produces a clear, colourless to light straw coloured solution for injection.

CYTIGEM 1 g: A white to off white lyophilized powder in a clear glass vial. Reconstitution with 0,9 % sodium chloride injection without preservatives produces a clear, colourless to light straw coloured solution for injection.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

CYTIGEM is indicated for the treatment of patients with locally advanced or metastatic non-small cell lung cancer**.**

CYTIGEM 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. CYTIGEM is indicated for patients previously treated with 5-FU.

CYTIGEM is indicated for treatment of patients with transitional cell bladder cancer.

CYTIGEM, 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.

CYTIGEM, 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

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. CYTIGEM 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: CYTIGEM 1 250 mg/m^2, given by 30 minute intravenous infusion on days 1 and 8 of every 21 day cycle and cisplatin 100 mg/m^2 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: CYTIGEM 1 000 mg/m^2 on days 1, 8 and 15 of every 28 day cycle and cisplatin 100 mg/m^2 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 CYTIGEM 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 CYTIGEM is 1 250 mg/m^2, 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. CYTIGEM may be used in combination with cisplatin. The recommended dose of CYTIGEM is 1 000 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 CYTIGEM 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/m^2.

Breast cancer:

Adults: CYTIGEM 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 CYTIGEM (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 106/L) prior to initiation of CYTIGEM + paclitaxel combination.

Ovarian Cancer: Single medicine use:

Adults: The recommended dose of CYTIGEM is 800 – 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: CYTIGEM in combination with carboplatin is recommended using CYTIGEM 1 000 mg/m^2 administered on days 1 and 8 of each 21 day cycle as a 30 minute intravenous infusion. After CYTIGEM, 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 CYTIGEM should be monitored prior to each dose for platelet, leucocyte and granulocyte counts and, if necessary, the dose of CYTIGEM 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

Special populations

Patients with hepatic or renal impairment:

CYTIGEM 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.

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 physician.

Elderly patients:

CYTIGEM 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 clearance and half-life are affected by age.

Method of administration

CYTIGEM is for intravenous use only.

CYTIGEM is well tolerated during the infusion, with only a few cases of injection site reaction reported. There have been no reports of injection site necrosis. CYTIGEM can be easily administered on an outpatient basis.

For information on instructions for preparation of and reconstitution, see **section 6.6**.

4.3 Contraindications

CYTIGEM is contra-indicated in those patients with a known hypersensitivity to gemcitabine or to any of the excipients in CYTIGEM (see **section 6.1**)

Pregnancy and lactation: The safety of CYTIGEM 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

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

Myelosuppression is usually mild to moderate and is more pronounced for the granulocyte count (see **section 4.2 and 4.8– Investigations**).

Peripheral blood counts may continue to deteriorate after CYTIGEM 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 CYTIGEM treatment is given together with other chemotherapy medicines.

Laboratory tests

Therapy should be started cautiously in patients with compromised bone marrow function. As with other oncolytics, the possibility of cumulative bone marrow suppression when using combination or sequential chemotherapy should be considered.

Guidelines regarding dose modifications when medicine-induced marrow depression is detected are provided under Posology and method of administration (see **section 4.2**). Peripheral blood counts may continue to fall after the medicine is stopped.

Hepatic and renal impairment insufficiency

Administration of CYTIGEM 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.

CYTIGEM should be used with caution in patients with impaired renal function or hepatic insufficiency. No studies have been done in patients with significant renal or hepatic impairment. Mild to moderate renal insufficiency (GFR from 30 mL/min to 80 mL/min) has no consistent, significant effect on CYTIGEM pharmacokinetics.

Patients receiving therapy with CYTIGEM must be monitored closely.

Laboratory facilities should be available to monitor patient status (see **section 4.2**) for evaluation of renal and hepatic function. Treatment for a patient compromised by medicine toxicity may be required.

Severe cutaneous adverse reactions

Severe cutaneous adverse reactions (SCARs) including Stevens-Johnson syndrome (SJS) and acute generalized exanthematous pustulosis (AGEP), which can be life-threatening or fatal, have been reported in association with gemcitabine treatment. Patients should be advised of the

signs and symptoms and monitored closely for skin reactions. If signs and symptoms suggestive of these reactions appear, CYTIGEM should be withdrawn immediately.

Concomitant radiotherapy:

Concurrent (given together or < 7 days apart): Toxicity (radiosensitising activity) 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 CYTIGEM (see **section 4.5)**

Cardiovascular

Due to the risk of cardiac and/or vascular disorders with CYTIGEM, 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 CYTIGEM as single medicine or in combination with chemotherapeutic medicines. 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. CYTIGEM 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 medicine or in combination with other chemotherapeutic medicines. Acute hypertension and seizure activity were reported in most gemcitabine 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. CYTIGEM should be permanently discontinued and supportive measures implemented, including blood pressure control and antiseizure therapy, if PRES develops during therapy.

Renal toxicity:

Haemolytic uraemic syndrome

Renal failure and haemolytic uraemic syndrome (HUS) have been reported rarely. CYTIGEM should be administered with caution to patients with impaired renal function. CYTIGEM 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:

Interstitial pneumonitis together with pulmonary infiltrates has been seen in less than 1 % of patients. In such cases, CYTIGEM treatment must be stopped. Steroids may relieve the symptoms in such situations. Severe rarely fatal pulmonary effects, such as pulmonary oedema, interstitial pneumonitis and ARDS have been reported as less common or rare. In such cases, cessation of CYTIGEM treatment is necessary. Starting supportive treatment at an early stage may improve the situation.

Carcinogenesis, mutagenesis, impairment of fertility:

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

Excipients with known effect

CYTIGEM 200 mg contains 3,5 mg (less than 1 mmol) sodium per 200 mg vial and is essentially ‘sodium free’.

CYTIGEM 1 g contains 17,5 mg of sodium per 1 000 mg vial and is essentially sodium free.

The sodium content should be taken into account by patients on a controlled sodium diet.

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 CYTIGEM, frequency of CYTIGEM administration, dose of radiation, radiotherapy planning technique, the target tissue, and target volume. It has been reported in pre-clinical and clinical studies that gemcitabine has radiosensitizing activity.

When CYTIGEM at a dose of 1 000 mg/m^2 was administered concurrently for up to six 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). The optimum regimen for safe administration of CYTIGEM with therapeutic doses of radiation has not yet been determined.

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.

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

CYTIGEM should not be used during pregnancy as safety has not been established (see **section 4.3)**. There are no adequate data from the use of gemcitabine in pregnant women. Studies in animals have shown reproductive toxicity. Women should be advised not to become pregnant during treatment with CYTIGEM and to warn their attending medical practitioner immediately, should this occur after all.

Breast-feeding

CYTIGEM should not be used during breastfeeding as safety has not been established (see **section 4.3)**.

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

Fertility

In fertility studies gemcitabine caused hypospermatogenesis in male mice. 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 CYTIGEM.

4.7 Effects on ability to drive and use machines

CYTIGEM 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

Summary of the safety profile

The most commonly reported adverse drug reactions associated with CYTIGEM 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 – 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 4.2**).

Tabulated summary of adverse reactions

MedDRA system organ class	**Frequency**	**Side effects**
Blood and lymphatic system disorders	Frequent	• Leucopaenia. • Thrombocytopaenia. • Anaemia. • Neutropaenia (Grade 3 = 19,3 %; Grade 4 = 6 %). • Myelosuppression is usually transient and does not result in dose reductions and rarely in discontinuation. • Febrile neutropaenia.
	Less frequent	• Thrombocytosis. • Thrombotic microangiopathy.
Infections and infestations	Frequent	• Infections.
	Frequency unknown	• Sepsis.
Immune system disorders	Less frequent	• Anaphylactoid reaction (see **section 4.3**).
Metabolism and nutrition disorders	Frequent	• Anorexia.
Nervous system disorders	Frequent	• Headache. • Insomnia. • Somnolence.

	Less frequent	• Posterior reversible encephalopathy syndrome (PRES).
	Frequency unknown	• Cerebrovascular accident.
Cardiac disorders	Less frequent	• Myocardial infarction.
	Frequency unknown	• Heart failure. • Dysrhythmia (predominantly supraventricular in nature).
Vascular disorders	Less frequent	• Hypotension. • Capillary leak syndrome.
	Frequency unknown	• Clinical signs of peripheral vasculitis and gangrene.
Respiratory, thoracic and mediastinal disorders	Frequent	• Dyspnoea which is usually mild and short-lived, rarely dose-limiting, and usually abates without any specific therapy. • Cough. • Rhinitis.
	Less frequent	• Bronchospasm which is usually mild and transient, but parenteral therapy may be required.

		• Interstitial pneumonitis (with associated pulmonary infiltrates).
	Frequency unknown	• Pulmonary oedema. • Adult respiratory distress syndrome (ARDS) (see **section 4.4**).
Gastrointestinal disorders	Frequent	• Nausea, vomiting (These adverse events require therapy in about 20 % of patients, are rarely dose-limiting and are easily manageable with standard antiemetic). • Stomatitis and ulceration of the mouth. • Constipation.
	Frequency unknown	• Ischaemic colitis.
Hepatobiliary 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 (The rash is usually mild, not dose-limiting and responsive to local therapy). • Alopecia. • Itching. • Sweating.
	Less frequent	• Scaling. • Vesicle and sore formation. • Ulceration. • Severe skin reactions, including desquamation and bullous skin eruptions. • Pseudocellulitis.
	Frequency unknown	• 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 (Rarely clinically significant and not usually associated with any change in serum creatinine or blood urea nitrogen).
	Frequency unknown	• Renal failure (aetiology unknown). • 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, back pain, shivering, muscle pain, asthenia and anorexia. Cough, rhinitis, malaise, perspiration and sleeping difficulties. • Oedema/peripheral oedema (Usually mild to moderate, rarely dose-limiting, and usually

		reversible after stopping CYTIGEM treatment. The mechanism of the toxicity is unknown. It is not associated with any evidence of cardiac, hepatic or renal failure). • Fever. • Asthenia. • Chills.
	Less frequent	• Injection site reactions which are mainly mild in nature.
Investigations	Frequent	• Elevation of liver transaminases and alkaline phosphatase (usually mild and non-progressive and rarely necessitating stopping of treatment). • Myelotoxicity has been reported to be modest even at high doses with gemcitabine. • Oedema (including pulmonary oedema). • Hypotension. • Alopecia.

		• Somnolence. • Severe toxicity in the form of potentially life-threatening oesophagitis and pneumonitis. • Haemolytic uraemic syndrome leading to irreversible renal failure.
Injury, poisoning and procedural complications	Frequency unknown	• Radiosensitisation (radiation toxicity). • Radiation recall. (see **section 4.4**)

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.

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

asked to report any suspected adverse reactions to SAHPRA via the "**6.04 Adverse Drug Reactions Reporting Form**", found online under SAHPRA's publications:

https://www.sahpra.org.za/Publications/Index/8

4.9 Overdose

There is no antidote for overdosage of CYTIGEM. In the event of suspected overdose, the patient should be monitored with appropriate blood counts and should receive supportive therapy, as necessary.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacological classification: A 26 Cytostatic agents

Pharmacotherapeutic group: pyrimidine analogues

ATC code: L01BC05

Cellular metabolism and mechanism of action: Gemcitabine (dFdC) is metabolized 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. However, when an every third or fourth day dosing schedule is used, gemcitabine can be given at non-lethal doses that have excellent antitumour activity against a broad range of mouse tumours.

5.2 Pharmacokinetic properties

Parent compound pharmacokinetics:

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

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.

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.

Plasma protein binding: Negligible.

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: 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.

Systemic metabolism: Gemcitabine is rapidly metabolised by cytidine deaminase in the liver, kidney, blood and other tissues.

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.

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.

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.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Mannitol

Sodium acetate trihydrate

Sodium hydroxide

Hydrochloric acid 37 %

Water for injection

6.2 Incompatibilities

Not applicable

6.3 Shelf life

36 months

6.4 Special precautions for storage

Before reconstitution: Store at or below 25 °C.

After reconstitution: Solutions of CYTIGEM reconstituted with 0,9 % sodium chloride injection without preservatives should be stored below 25 °C and should be administered within 24 hours. Discard unused portion. Do not refrigerate as crystallisation may occur.

6.5 Nature and contents of container

CYTIGEM 1 g**:** An outer carton containing one 50 mL USP type 1 clear colourless glass vial with a 20 mm grey bromobutyl rubber stopper and 20 mm aluminium flip off lavender seal/20 mm plain aluminium flip off lavender seal.

CYTIGEM 200 mg**:** An outer carton containing one 10 mL USP type 1 clear colourless glass vial with a 20 mm grey bromobutyl rubber stopper and 20 mm aluminium flip off royal blue seal/20 mm plain aluminium flip off Royal blue seal.

6.6 Special precautions for disposal and other handling

Reconstituted CYTIGEM should be inspected visually for particulate matter and discolouration, prior to administration. Procedures for proper handling and disposal of anti-cancer drugs should be considered.

Instructions for reconstitution: The only approved diluent for reconstitution of CYTIGEM is 0,9 % sodium chloride injection without preservatives.

It is not recommended that CYTIGEM be mixed with other medicines when reconstituted. Due to solubility considerations, the maximum concentration for CYTIGEM 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 further diluted with 0,9 % sodium chloride injection without preservatives.

7 HOLDER OF CERTIFICATE OF REGISTRATION

EUROLAB (PTY) LTD

Woodmead Office Park,

3 Stirrup Lane, Van Reenens Avenue,

Woodmead,

2144

8 REGISTRATION NUMBER(S)

CYTIGEM 200 mg: 42/26/0089

CYTIGEM 1 g: 42/26/0902

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

09 October 2009

10 DATE OF REVISION OF THE TEXT

01 October 2024