Approved Professional Information for Medicines for Human Use:

PULMOGEM IV

SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

PULMOGEM IV 200 mg/5 mL Concentrate for Solution for Infusion

PULMOGEM IV 1 g/25 mL Concentrate for Solution for Infusion

PULMOGEM IV 2 g/50 mL Concentrate for Solution for Infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each mL of concentrate for solution for infusion contains gemcitabine

hydrochloride equivalent to 40 mg gemcitabine free base.

PULMOGEM IV 200 mg/5 mL Concentrate for Solution for Infusion:

Each 5 mL vial contains 200 mg gemcitabine (as gemcitabine hydrochloride)

PULMOGEM IV 1 g/25 mL Concentrate for Solution for Infusion:

Each 25 mL vial contains 1 g gemcitabine (as gemcitabine hydrochloride)

PULMOGEM IV 2 g/50 mL Concentrate for Solution for Infusion:

Each 50 mL vial contains 2 g gemcitabine (as gemcitabine hydrochloride)

Sugar free.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Concentrate for solution for IV Infusion

The pH of the concentrate is 2,4 ± 0,4 and the osmolarity is 270 – 280 mOsmoL/kg.

Clear, colourless or pale, yellow solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

PULMOGEM IV 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. PULMOGEM IV is indicated for patients previously treated with 5-FU.

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

PULMOGEM IV**,** 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.

PULMOGEM IV**,** 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 1000 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.

PULMOGEM IV, 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:

PULMOGEM IV, 1250 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:

PULMOGEM IV, 1000 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 PULMOGEM IV 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 amount of toxicity experienced by the patient.

Bladder cancer

Adults:

The recommended monochemotherapy dosage of PULMOGEM IV is 1250 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.

PULMOGEM IV may be used in combination with cisplatin. The recommended dose of PULMOGEM IV 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 PULMOGEM IV 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:

PULMOGEM IV in combination with paclitaxel recommended using paclitaxel (175 mg/m^2) administered on day 1 over approximately 3 hours as an intravenous infusion, followed by PULMOGEM IV (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 amount of toxicity experienced by

the patient. Patients should have an absolute granulocyte count of at least 1500 (x 10^6/L) prior to initiation of PULMOGEM IV and paclitaxel combination.

Ovarian cancer

Monotherapy

Adults:

The recommended dose of PULMOGEM IV is 800 to 1250 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:

PULMOGEM IV in combination with carboplatin is recommended using PULMOGEM IV 1000 mg/m^2 administered on days 1 and 8 of each 21-day cycle as a 30-minute intravenous infusion. After PULMOGEM IV, 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 PULMOGEM IV should be monitored prior to each dose for platelet, leucocyte and granulocyte counts and, if necessary, the dose of PULMOGEM IV 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**

> 1000	and	> 100 000	100
500 – 1000	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 physician.

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

Special populations

Patients with hepatic or renal impairment

PULMOGEM IV 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

PULMOGEM IV 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 PULMOGEM IV clearance and half-life are affected by age.

Paediatric population

The safety and efficacy of PULMOGEM IV in children has not been established.

Method of administration

PULMOGEM IV is for intravenous use only.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- The safety in human pregnancy and lactation have not been established (see section 4.6).
- Safety and efficacy 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 can suppress bone marrow function as manifested by leukopenia, thrombocytopenia and anaemia.

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

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

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

Hepatic and renal impairment

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 or renal function impairment 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).

Posterior reversible encephalopathy syndrome

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 agents. 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. Gemcitabine should be permanently discontinued, and supportive measures implemented, including blood pressure control and anti-seizure therapy, if PRES develops during therapy.

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.

Capillary leak syndrome

Capillary leak syndrome has been reported in patients receiving gemcitabine as single agent or in combination with other chemotherapeutic agents (see section 4.8). 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, hypoalbuminemia, severe hypotension, acute renal impairment and pulmonary oedema. Gemcitabine 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

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. If such effects develop, consideration should be made to discontinuing gemcitabine therapy. Early use of supportive care measure may help ameliorate the condition.

Renal

Haemolytic uraemic syndrome

Clinical findings consistent with the haemolytic uraemic syndrome (HUS) were rarely reported (post- marketing data) in patients receiving gemcitabine (see section 4.8). HUS is a potentially life-threatening disorder. Gemcitabine should be discontinued at the first signs of any evidence of microangiopathic haemolytic anaemia, such as rapidly falling haemoglobin with concomitant thrombocytopenia, elevation of serum bilirubin, serum creatinine, blood urea, 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. 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).

Embryofoetal toxicity

PULMOGEM IV can cause foetal harm when administered to a pregnant woman, based on its mechanism of action. Gemcitabine was teratogenic, embryotoxic, and fetotoxic in mice and rabbits. If this medicine is used during pregnancy, or if a

woman becomes pregnant while taking PULMOGEM IV, the patient should be apprised of the potential hazard to a foetus (see section 4.6).

Risk of Severe Cutaneous Adverse Reactions (SCAR's)

Severe cutaneous adverse reactions (SCARs) including Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), 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, gemcitabine should be withdrawn immediately.

4.5 Interaction with other medicines 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, when 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].

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

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 (see section 4.4).

4.6 Fertility, pregnancy and lactation

The safety of PULMOGEM IV in human pregnancy and lactation have not been established (see section 4.3).

Women of childbearing potential/Contraception in males and females

PULMOGEM IV has potential for genotoxicity and can cause foetal harm when administered to a pregnant woman. Therefore, females of childbearing potential must use effective contraception during treatment and for 12 months following final dose (see section 4.4).

Male patients with female partners of childbearing potential must use effective contraception during treatment and for 6 months after the final dose (see section 4.4).

Pregnancy

There are no adequate data from the use of gemcitabine in pregnant women. Studies in animals have shown reproductive toxicity. 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.

Breastfeeding

It is not known whether gemcitabine is excreted in human milk and adverse effects on the suckling child cannot be excluded. Breastfeeding must be discontinued during gemcitabine 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 gemcitabine (see section 4.4).

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 their alertness is not affected.

4.8 Undesirable effects

a) Summary of the safety profile

The most commonly reported adverse drug reactions associated with gemcitabine treatment include: nausea with or without vomiting, raised liver transaminases (AST/ALT) and alkaline phosphatase, reported in approximately 60 % of patients; proteinuria and haematuria reported in approximately 50 % patients; dyspnoea reported in 10 – 40 % of patients (highest incidence in lung cancer patients); allergic skin rashes occur in approximately 25 % of patients and are associated with itching in 10 % of patients.
The frequency and severity of the adverse reactions are affected by the dose, infusion rate and intervals between doses (see section 4.4). Dose-limiting adverse reactions are reductions in thrombocyte, leucocyte and granulocyte counts (see section 4.2).

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.

b) Tabulated list of adverse reactions

System Organ Class	**Frequency**		
	Frequent	**Less Frequent**	**Unknown**
Blood and lymphatic system disorders	• Leukopenia (Neutropenia Grade 3 = 19,3 %; Grade 4 = 6 %).	• Thrombocytosis	

	Bone-marrow suppression is usually mild to moderate and mostly affects the granulocyte count (see section 4.2 and 4.4) • Thrombocytopenia • Anaemia • Febrile neutropenia		
Immune system disorders		• Anaphylactoid reaction	
Metabolism and nutrition disorders	• Anorexia		
Nervous system disorders	• Headache • Insomnia • Somnolence	• Cerebrovascular accident • Posterior reversible encephalopathy syndrome (see section 4.4)	

Cardiac disorders		• Dysrhythmias, predominantly supraventricular in nature • Heart failure • Myocardial infarct	
Vascular disorders		• Clinical signs of peripheral vasculitis and gangrene • Hypotension • Capillary leak syndrome (see section 4.4)	
Respiratory, thoracic and mediastinal disorders	• Dyspnoea –usually mild and passes rapidly without treatment • Cough • Rhinitis	• Interstitial pneumonitis (see section 4.4) • Bronchospasm –usually mild and transient but may require parenteral treatment	

		• Pulmonary oedema • Adult respiratory distress syndrome (see section 4.4)	
Gastrointestinal disorders	• Vomiting • Nausea • Diarrhoea • Stomatitis and ulceration of the mouth • Constipation	• Ischaemic colitis	
Hepatobiliary disorders	• Elevation of liver transaminases (AST and ALT) and alkaline phosphatase • Increased bilirubin	• Serious hepatotoxicity, including liver failure and death • Increased gamma-glutamyl transferase (GGT)	

Skin and subcutaneous tissue disorders	• Allergic skin rash frequently associated with pruritus • Alopecia • Itching • Sweating	• Severe skin reactions, including desquamation and bullous skin eruptions • Ulceration • Vesicle and sore formation • Scaling • Toxic epidermal necrolysis • Stevens-Johnson Syndrome	• Acute generalised exanthematous pustulosis.
Musculoskeletal and connective tissue disorders	• Back pain • Myalgia		
Renal and urinary disorders	• Haematuria • Mild proteinuria	• Renal failure (see section 4.4)	

		• Haemolytic uraemic syndrome (see section 4.4)	
General disorders and administration site conditions	• 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 • Fever	• Injection site reactions-mainly mild in nature	

	• Asthenia • Chills		
Injury, poisoning and procedural complications		• Radiation toxicity (see section 4.5). • Radiation recall	

Combination use in breast cancer

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

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

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

Suspected adverse reactions can also be reported directly to the HCR via medsafety@austell.co.za

Austell Pharmaceuticals, 520315-7, PULMOGEM IV, 200 mg /5 mL, 1 g /25 mL, 2 g/50 mL, Concentrate for solution for infusion

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

Pharmacological Classification/ Category and Class: A 26 Cytostatic agents

Pharmacotherapeutic group: pyrimidine analogues

ATC Code: L01BC05

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.

Pharmacodynamic effects

Cytotoxic activity in cell cultures

Gemcitabine shows significant cytotoxic effects against a variety of cultured murine and human tumour cells. Its action is phase-specific such that gemcitabine primarily kills cells that are undergoing DNA synthesis (S phase) and, under certain circumstances, blocks the progression of cells at the junction of the G1/S phase boundary. In vitro, the cytotoxic effect of gemcitabine is dependent on both concentration and time.

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.

Absorption

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 1000 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 is virtually complete within 5 to 11 hours of the start of the infusion. Gemcitabine does not accumulate when administered once weekly.

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.

Elimination

Systemic clearance ranged from 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 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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Hydrochloric acid (E507) for pH adjustment

Water for injections

6.2 Incompatibilities

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

6.3 Shelf life

Concentrate in unopened vial

2 years.

After first opening

Chemical and physical in use stability has been demonstrated for 28 days at 25 °C.

From a microbiological point of view, unless the method of opening precludes the risk of microbial contamination, the product should be used immediately. If not used immediately, in-use storage times and conditions are the responsibility of the user.

Solution for infusion

Chemical and physical in-use stability has been demonstrated for 28 days at 2 °C to 8 °C and about 25 °C upon dilution in 0,9 % sodium chloride solution to a final concentration in the range between 2 – 25 mg/mL (2,0 mg/mL, 12 mg/mL and 25 mg/mL). The pH of the diluted solution is in the range of 2 - 3 and the osmolality is approximately 285 mOsm/kg. Diluted solutions are stable when packaged into either PVC or PE infusion bags.

From a microbiological point of view, the solution for infusion 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 2 °C to 8 °C unless dilution has taken place in controlled and validated aseptic conditions.

6.4 Special precautions for storage

Store in a refrigerator (2 °C to 8 °C)

For storage conditions after first opening the vial and of the diluted medicine, see section 6.3.

6.5 Nature and contents of container

Colourless glass vial (type I) with bromobutyl rubber stopper and sealed with aluminium caps with polypropylene disc. The vial will be packed with or without a protective plastic overwrap.

Pack sizes

1 x 5 mL vial

1 x 25 mL vial

1 x 50 mL vial

Not all pack sizes may be marketed.

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. Pregnant personnel should not handle the product. 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.

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

Instructions for dilution

The only approved diluent for dilution of Gemcitabine concentrate for solution for infusion is sodium chloride 9 mg/mL (0,9 %) solution for injection (without preservative).

- Use aseptic technique during dilution of gemcitabine for intravenous infusion administration.
- Diluted solution is a clear colourless or light straw-coloured solution.

- 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.

Instructions for reconstitution

The only approved diluent for reconstitution of PULMOGEM IV is sodium chloride injection without preservatives. It is not recommended that PULMOGEM IV be mixed with other medicines when reconstituted. Due to solubility considerations, the maximum concentration for PULMOGEM IV 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.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Austell Laboratories (Pty) Ltd

1 Sherborne Road

Parktown

JOHANNESBURG

2193

South Africa

Tel: 0860287835

8. REGISTRATION NUMBERS

PULMOGEM IV 200 mg/5 mL: 52/26/0315

PULMOGEM IV 1 g/25 mL: 52/26/0316

PULMOGEM IV 2 g/50 mL: 52/26/0317

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

15 June 2020

10. DATE OF REVISION OF THE TEXT

12 February 2024