PACKAGE INSERT

SCHEDULING STATUS:

S4

PROPRIETARY NAME AND DOSAGE FORM:

MYLAN GEMCITABINE 200 mg (Powder for solution for injection)

MYLAN GEMCITABINE 1 g (Powder for solution for injection)

COMPOSITION:

Each 10 ml vial of **MYLAN GEMCITABINE 200 mg** contains gemcitabine hydrochloride equivalent to 200 mg of gemcitabine free base.

Each 50 ml vial of **MYLAN GEMCITABINE 1 g** contains gemcitabine hydrochloride equivalent to 1 g gemcitabine free base.

Excipients:

Mannitol, sodium acetate trihydrate, sodium hydroxide and hydrochloric acid.

PHARMACOLOGICAL CLASSIFICATION:

A 26 Cytostatic agents

PHARMACOLOGICAL ACTION:

Pharmacodynamics:

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 dFdDTP 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

31 August 2023 Signature:

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 significantly cytotoxicity 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 antitumour activity against a broad range of mouse tumours.

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.

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, of Body Surface Area (BSA) for women and 17,5 l/m^2 for men (inter-individual variability was 91,9 %).

Volume of distribution of peripheral compartment (Vd): 47,4 l/m^2, of BSA. The volume of peripheral compartment was not sensitive to gender.

Plasma protein binding: Negligible.

Systemic clearance: 29,2 l/m^2 to 92,2 l/m^2 of BSA depending on gender and age (inter-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/m2, given as 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.

31 August 2023 Signature:

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

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 radio-labelled gemcitabine: 92 % to 98 %, of which 99 % is urinary excretion of dFdU; 1 % of the dose is excreted in faeces.

INDICATIONS:

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

MYLAN GEMCITABINE 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.

MYLAN GEMCITABINE is indicated for patients previously treated with 5-FU.

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

MYLAN GEMCITABINE in combination with paclitaxel, is indicated for treatment of patients with unresectable, local recurrent or metastatic breast cancer who have relapsed following adjuvant/neoadjuvant chemotherapy. Prior chemotherapy should have included an anthracycline unless clinically contra-indicated.

31 August 2023 Signature:

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

CONTRA-INDICATIONS:

MYLAN GEMCITABINE is contra-indicated in those patients with a known hypersensitivity to the medicine.

Pregnancy and lactation: The safety of **MYLAN GEMCITABINE** in human pregnancy and lactation has not been established.

Usage in children: Safety and effectiveness in children have not been established.

WARNINGS:

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

MYLAN GEMCITABINE 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 **DOSAGE AND DIRECTIONS FOR USE** and **SIDE EFFECTS** -Haematological toxicity).

Radiotherapy: Concurrent (given together or < 7 days apart): based on the results of preclinical studies and clinical trials, MYLAN GEMCITABINE has radiosensitising activity. When MYLAN GEMCITABINE at a dose of 1 000 mg/m^2 of BSA 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 MYLAN GEMCITABINE with therapeutic doses of radiation has not been determined.

INTERACTIONS:

Radiotherapy: See **WARNINGS.**

PREGNANCY AND LACTATION:

The safety of **MYLAN GEMCITABINE** in human pregnancy and lactation has not been established. See **CONTRA-INDICATIONS.**

DOSAGE AND DIRECTIONS FOR USE:

MYLAN GEMCITABINE is for intravenous use only.

Non-small cell lung cancer:

Adults:

The recommended monochemotherapy dosage is 1 000 mg/m^2, of Body Surface Area (BSA) 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.

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

3 week schedule: MYLAN GEMCITABINE 1 250 mg/m^2, of BSA 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: MYLAN GEMCITABINE 1 000 mg/m^2 of BSA on days 1, 8 and 15 of every 28 day cycle and cisplatin 100 mg/m^2 of BSA 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 **MYLAN GEMCITABINE** is 1 000 mg/m^2, of BSA 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 **MYLAN GEMCITABINE** is 1 250 mg/m^2, of BSA 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.

MYLAN GEMCITABINE may be used in combination with cisplatin. The recommended dose of **MYLAN GEMCITABINE** is 1 000 mg/m^2, of BSA 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, of BSA on day 1 following **MYLAN GEMCITABINE** 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 of BSA.

Breast cancer:

Adults:

MYLAN GEMCITABINE in combination with paclitaxel is recommended using paclitaxel (175 mg/m^2, of BSA administered on day 1 over approximately 3 hours as an intravenous infusion, followed by **MYLAN GEMCITABINE** (1 250 mg/m^2 of BSA) 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 **MYLAN GEMCITABINE** + paclitaxel combination.

Ovarian cancer: Single agent use:

Adults:

The recommended dose of **MYLAN GEMCITABINE** is 800 -1 250 mg/m^2, of BSA 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.

31 August 2023 Signature:

Combination use:

Adults:

MYLAN GEMCITABINE in combination with carboplatin is recommended using **MYLAN GEMCITABINE** 1 000 mg/m^2 of BSA administered on days 1 and 8 of each 21 day cycle as a 30 minute intravenous infusion. After **MYLAN GEMCITABINE** carboplatin will be given on day 1 consistent with a target AUG 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 **MYLAN GEMCITABINE** should be monitored prior to each dose for platelet, leucocyte and granulocyte counts and, if necessary, the dose of **MYLAN GEMCITABINE** 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 – 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-haematological 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.

Elderly patients:

31 August 2023 Signature:

MYLAN GEMCITABINE 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.

Instructions for reconstitution:

The only approved diluent for reconstitution of **MYLAN GEMCITABINE** is 0,9 % sodium chloride injection without preservatives. It is not recommended that **MYLAN GEMCITABINE** be mixed with other medicines when reconstituted.

Due to solubility considerations, the maximum concentration for **MYLAN GEMCITABINE** 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. **Solutions must be inspected visually for particulate matter and discoloration prior to administration.**

SIDE-EFFECTS AND SPECIAL PRECAUTIONS:

The most commonly reported adverse reactions associated with **MYLAN 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 % of patients, dyspnoea reported in 10-40 % of patients (highest incidence in lung cancer patients) and allergic skin rashes occurring in approximately 25 % of

31 August 2023 Signature: 

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 **WARNINGS**). Dose-limiting adverse reactions are reductions in platelet, leucocyte and granulocyte counts (see **DOSAGE AND DIRECTIONS FOR USE**).

Blood and the lymphatic system disorders:

Frequent: Leucopenia, thrombocytopenia, anaemia

(Neutropenia Grade 3 = 19,3 %; Grade 4 = 6 %)

Myelosuppression is usually transient, usually does not result in dose reductions and rarely results in discontinuation. Dosage reduction or omission may be necessary for severe bone marrow depression (see **DOSAGE AND DIRECTIONS FOR USE**).

Less frequent: Haemorrhage

Immune system disorders:

Less frequent: Anaphylactoid reaction (see **CONTRA-INDICATIONS**)

Nervous system disorders:

Frequent: Somnolence

Less frequent: Paraesthesia

Cardiac disorders:

Less frequent: Myocardial infarct, heart failure, dysrhythmia (predominantly supra ventricular in nature)

Vascular disorders:

Less frequent: Hypotension

Respiratory, thoracic and mediastinal disorders:

Frequent: Dyspnoea. Usually mild and short-lived, rarely dose-limiting, and usually abates without any specific therapy.

Less frequent: Bronchospasm. Usually mild and transient, but parenteral therapy may be required.

MYLAN GEMCITABINE should not be administered in patients with a known hypersensitivity to this medicine (see **CONTRA-INDICATIONS**). Pulmonary oedema, interstitial pneumonitis (with associated pulmonary infiltrates), adult respiratory distress syndrome (ARDS) (see **Special Precautions**).

Gastro-intestinal disorders:

Frequent: Nausea, vomiting. These adverse events require therapy in about 20 % of patients, are rarely dose-limiting and are easily manageable with standard antiemetics; stomatitis; diarrhoea; constipation.

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.

Less frequent: Scaling, vesicle and sore formation, ulceration. Irritation, pain or redness at injection site.

Renal and urinary disorders:

Frequent: Mild proteinuria and haematuria. Rarely clinical significant and not usually associated with any change in serum creatinine or blood urea.

Less frequent: Renal failure (aetiology unknown); haemolytic uraemic syndrome (HUS) - see **Special Precautions.**

MYLAN GEMCITABINE should be used with caution in patients with impaired renal function (see **Special Precautions** - Patients with renal or hepatic impairment)

General disorders and administration site conditions:

Frequent: Oedema/peripheral oedema usually mild to moderate, rarely dose-limiting, and usually reversible after stopping **MYLAN GEMCITABINE** treatment. The mechanism of the toxicity is unknown. It is not associated with any evidence of cardiac, hepatic or renal failure.

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. Fever and asthenia. The mechanism of this toxicity is unknown.

Less frequent: Facial oedema.

Investigations:

Frequent: Elevation of liver transaminases and alkaline phosphatase. Usually mild and non-progressive and rarely necessitating stopping of treatment.

MYLAN GEMCITABINE should be used with caution in patients with impaired liver function (see **Special Precautions** - Patients with renal or hepatic impairment).

Injury and poisoning:

Radiosensitisation and radiation recall (see **WARNINGS**).

Special Precautions:

General:

Patients receiving therapy with **MYLAN GEMCITABINE** must be monitored closely. Laboratory facilities should be available to monitor patient status. See **DOSAGE AND DIRECTIONS FOR USE** for evaluation of renal and hepatic function. Treatment for a patient compromised by medicine toxicity may be required.

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 **DOSAGE AND DIRECTIONS FOR USE.** Peripheral blood counts may continue to fall after the medicine is stopped.

Renal toxicity:

Renal failure and HUS have been reported rarely. **MYLAN GEMCITABINE** should be administered with caution to patients with impaired renal function (see **Special Precautions** - Patients with renal or hepatic impairment). **MYLAN GEMCITABINE** 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, serum creatinine, blood urea 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 **MYLAN GEMCITABINE** treatment should 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 less frequently. In such cases, cessation of **MYLAN GEMCITABINE** 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 **MYLAN GEMCITABINE** in an in vivo assay. **MYLAN GEMCITABINE** induced forward mutation in vitro in a mouse lymphoma assay. The influence of **MYLAN GEMCITABINE** on fertility has not been established in humans. The carcinogenic potential of **MYLAN GEMCITABINE** has not been established.

Patients with renal or hepatic impairment:

MYLAN GEMCITABINE 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 **MYLAN GEMCITABINE** pharmacokinetics.

Effects on the ability to drive and use machines:

MYLAN GEMCITABINE 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.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT:

See **SIDE-EFFECTS AND SPECIAL PRECAUTIONS**

31 August 2023 Signature:

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

IDENTIFICATION:

A white to off-white lyophilised powder.

PRESENTATION:

Clear colourless glass vial, with a grey bromobutyl stopper and a lavender aluminium flip-off seal, packed in a carton.

Or

Clear tubular glass vial with a 20 mm grey siliconised bromobutyl rubber stopper and a 20 mm aluminium flip-off seal.

STORAGE INSTRUCTIONS:

KEEP OUT OF THE REACH OF CHILDREN.

Store at or below 25 °C. Reconstituted solutions (vials) and infusion solutions (in Sodium chloride 0,9 %) must be used immediately or within 12 hours when stored at or below 25 °C.

Reconstituted solutions must not be refrigerated as crystallisation may occur.

REGISTRATION NUMBERS:

MYLAN GEMCITABINE 200 mg: 43/26/0068

MYLAN GEMCITABINE 1 g: 43/26/0046

31 August 2023 Signature: 

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION:

Viatris South Africa (Pty) Ltd

4 Brewery Street,

Isando

Johannesburg,

1609

DATE OF PUBLICATION OF THE PACKAGE INSERT:

20 April 2012

31 August 2023 Signature: