1.3.1.1 Professional Information for medicines for human use

SCHEDULING STATUS

S4

1 NAME OF THE MEDICINE

MYLAN GEMCITABINE 200 mg (powder for solution for injection)

MYLAN GEMCITABINE 1 g (powder for solution for injection)

2 QUALITIVE AND QUANTITIVE 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.

Contains sugar:

MYLAN GEMCITABINE 200 mg contains sugar: Mannitol 200 mg/10 ml vial when reconstituted with 5 ml of 0,9 % sodium chloride.

MYLAN GEMCITABINE 1 g contains sugar: Mannitol 1 g/50 ml vial when reconstituted with 25 ml of 0,9 % sodium chloride.

For full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

A white to off-white lyophilised powder.

4 CLINICAL PARTICULARS

4.1 Therapeutic 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 Ill) 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.
- 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.

4.2 Posology and method of administration

Posology

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.

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.

Special populations

Elderly population:

- 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.

Method of administration

For oral use.

Instructions for reconstitution:

1.3.1.1 Professional Information for medicines for human use

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.**

4.3 Contraindications

- MYLAN GEMCITABINE is contraindicated in those patients with a known hypersensitivity to gemcitabine or any of the excipients listed in section 6.1.
- 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.

4.4 Special warnings and precautions for use

RADIOTHERAPY (see section 4.5):

CONCURRENT (GIVEN TOGETHER OR < 7 DAYS APART): TOXICITY ASSOCIATED WITH THIS MULTIMODALITY THERAPY IS DEPENDENT ON MANY DIFFERENT FACTORS,

INCLUDING DOSE OF MYLAN GEMCITABINE, FREQUENCY OF MYLAN GEMCITABINE ADMINISTRATION, DOSE OF RADIATION, RADIOTHERAPY PLANNING TECHNIQUE, THE TARGET TISSUE, AND TARGET VOLUME. 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.

RADIATION INJURY HAS BEEN REPORTED ON TARGETED TISSUES (e.g. ESOPHAGITIS, COLITIS AND PNEUMONITIS) IN ASSOCIATION WITH BOTH CONCURRENT AND NON-CONCURRENT USE OF MYLAN GEMCITABINE.

General:

- Patients receiving therapy with MYLAN GEMCITABINE 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.
- Prolongation of the infusion time and increased dosing frequency has been shown to increase toxicity.

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- 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 section 4.2 and 4.8 - Haematological toxicity).
- 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 section 4.2. Peripheral blood counts may continue to fall after the medicine is stopped.

Renal toxicity:

- Renal failure and haemolytic uraemic syndrome (HUS) have been reported rarely.
- MYLAN GEMCITABINE should be administered with caution to patients with impaired renal function (see section 4.4 - 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 adult respiratory distress syndrome (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.
- Administration of MYLAN 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.

Live vaccinations:

- Yellow fever vaccine and other live attenuated vaccines are not recommended in patients treated with MYLAN GEMCITABINE (see section 4.5).

Cardiovascular:

- Due to the risk of cardiac and/or vascular disorders with MYLAN GEMCITABINE, 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 MYLAN GEMCITABINE 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.
- MYLAN 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.

Posterior reversible encephalopathy syndrome (PRES):

- Reports of posterior reversible encephalopathy syndrome (PRES) with potentially severe consequences have been reported in patients receiving MYLAN

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.
- MYLAN GEMCITABINE should be permanently discontinued and supportive measures implemented, including blood pressure control and antiseizure therapy, if PRES develops during therapy.

Skin and subcutaneous tissue:

- Severe cutaneous adverse reactions (SCARs) including Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), and acute generalised 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.

MYLAN GEMCITABINE contains mannitol:

MYLAN GEMCITABINE contains mannitol and may have a laxative effect.

4.5 Interaction with other medicines and other forms of Interaction

Radiotherapy (see section 4.4):

CONCURRENT (GIVEN TOGETHER OR < 7 DAYS APART): TOXICITY ASSOCIATED WITH THIS MULTIMODALITY THERAPY IS DEPENDENT ON MANY DIFFERENT FACTORS,

INCLUDING DOSE OF MYLAN GEMCITABINE, FREQUENCY OF MYLAN GEMCITABINE ADMINISTRATION, DOSE OF RADIATION, RADIOTHERAPY PLANNING TECHNIQUE, THE TARGET TISSUE, AND TARGET VOLUME. 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.

RADIATION INJURY HAS BEEN REPORTED ON TARGETED TISSUES (e.g. ESOPHAGITIS, COLITIS AND PNEUMONITIS) IN ASSOCIATION WITH BOTH CONCURRENT AND NON-CONCURRENT USE OF MYLAN 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

Women of childbearing potential/Contraception in males and females

Women should be advised not to become pregnant during treatment with MYLAN GEMCITABINE and to warn their attending medical practitioner immediately, should this occur after all.

Pregnancy

The safety of MYLAN GEMCITABINE in human pregnancy has not been established. See section 4.3.

Breastfeeding

The safety of MYLAN GEMCITABINE in lactation has not been established. See section 4.3.

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 MYLAN GEMCITABINE.

4.7 Effects on ability to drive and use machines

MYLAN GEMCITABINE has been reported to cause mild to moderate somnolence. Patients should be cautioned against driving, operating machinery, activities requiring mental alertness, judgment and/or sound coordination and vision 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 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 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).

b) Tabulated list of adverse reactions

Blood and lymphatic system disorders	**Frequent** Leucopaenia Neutropaenia Bone-marrow suppression • Thrombocytopaenia • Anaemia • Febrile neutropaenia **Less frequent** Thrombocytosis Thrombotic microangiopathy
Infections and infestations	**Frequent** Infections **Frequency unknown** Sepsis

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 **Frequency unknown** Cerebrovascular accident
Cardiac disorders	**Less frequent** Myocardial infarct
	Frequency unknown Dysrythmias, predominantly supraventricular in nature Heart failure
Vascular disorders	**Less frequent** Hypotension Capillary leak syndrome **Frequency unknown** Clinical signs of peripheral vasculitis and gangrene
Respiratory, thoracic and mediastinal disorders	**Frequent** Dyspnoea Cough Rhinitis **Less frequent** Interstitial pneumonitis

	Bronchospasm **Frequency unknown** Pulmonary oedema Adult respiratory distress syndrome
Gastrointestinal disorders	**Frequent** Vomiting Nausea Diarrhoea 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 Alopecia Itching Sweating **Less frequent** Ulceration Vesicle and sore formation Scaling Severe skin reactions, including desquamation and bullous skin eruptions

	Pseudocellulitis **Frequency** **unknown** Lyell's Syndrome Steven- Johnson Syndrome Acute generalised exanthematous pustulosis.
Musculoskeletal and connective tissue disorders	**Frequent** Back pain Myalgia
Renal and urinary disorders	**Frequent** Haematuria Mild proteinuria **Frequency** **unknown** Renal failure Haemolytic uraemic syndrome
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. Oedema/peripheral oedema including facial oedema. Fever Asthenia Chills **Less frequent** Injection site reactions-mainly mild in nature
Injury, poisoning, and procedural Complications	**Frequency unknown** Radiation toxicity Radiation recall

1.3.1.1 Professional Information for medicines for human use

Description of selected adverse reactions

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. Healthcare 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

In overdose, side effects can be precipitated and/or be of increased severity (*see section 4.8)*.

Treatment should be symptomatic and supportive.

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.

1.3.1.1 Professional Information for medicines for human use

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

PHARMACOLOGICAL CLASSIFICATION:

A 26 Cytostatic agents

Pyrimidine analogues, ATC code: L01BC05

Pharmacotherapeutic group and ATC code:

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 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 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.

5.2 Pharmacokinetic properties

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 appear 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.

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.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

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

6.2 Incompatibilities

This medicine must not be mixed with other medicines except those mentioned in section 4.2.

6.3 Shelf life

Unopened vials:

24 months

Reconstituted solution:

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.

6.4 Special precautions for storage

Store at or below 25 °C.

Reconstituted solutions must not be refrigerated as crystallisation may occur.

For storage conditions after dilution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

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

or

1.3.1.1 Professional Information for medicines for human use

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

6.6 Special precautions for disposal of a used medicine or waste materials derived from such medicine and other handling of the product

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

7 HOLDER OF THE CERTIFICATE OF REGISTRATION

Viatris South Africa (Pty) Ltd

4 Brewery Street,

Isando

Johannesburg,

1609

8 REGISTRATION NUMBER(S)

MYLAN GEMCITABINE 200 mg: 43/26/0068

MYLAN GEMCITABINE 1 g: 43/26/0046

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

20 April 2012

10 DATE OF REVISION OF TEXT

02 March 2024