SCHEDULING STATUS: S4

PROPRIETARY NAME AND DOSAGE FORM:

GEMZAR 200 mg (Powder for Injection)

GEMZAR 1 g (Powder for Injection)

COMPOSITION:

Each GEMZAR 200 mg vial contains gemcitabine hydrochloride equivalent to 200 mg of gemcitabine free base.

Each GEMZAR 1 g vial contains gemcitabine hydrochloride equivalent to 1 g of gemcitabine free base.

Gemcitabine hydrochloride is 2'-deoxy-2',2'-difluorocytidine monohydrochloride (β-isomer). The empirical formula for gemcitabine hydrochloride is $C_9H_{11}F_2N_3O_4.HCl$. It has a molecular mass of 299,66.

The clinical formulation is a sterile lyophilised powder for reconstitution with 0,9 % sodium chloride injection. The pH of the resulting solution lies in the range of 2,7 to 3,3. This product is for intravenous use only.

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 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.

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.

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 (V_c): 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 (V_p): 47,4 L/m^2. The volume of peripheral compartment was not sensitive to gender.

Plasma protein binding: Negligible.

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.

INDICATIONS:

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

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

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

GEMZAR, 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.

GEMZAR, 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:

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

Pregnancy and lactation: The safety of GEMZAR 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 have been shown to increase toxicity.

GEMZAR can suppress bone marrow function as manifested by leucopoenia, thrombocytopenia and anaemia. Myelosuppression is usually mild to moderate and is more pronounced for the granulocyte count (see 'DOSAGE AND DIRECTIONS FOR USE' and 'Side effects -Haematological Toxicity').

INTERACTIONS:

RADIOTHERAPY:

CONCURRENT (GIVEN TOGETHER OR ≤7 DAYS APART) - TOXICITY ASSOCIATED WITH THIS MULTIMODALITY THERAPY IS DEPENDENT ON MANY DIFFERENT FACTORS, INCLUDING DOSE OF GEMZAR, FREQUENCY OF GEMZAR

ADMINISTRATION, DOSE OF RADIATION, RADIOTHERAPY PLANNING TECHNIQUE, THE TARGET TISSUE, AND TARGET VOLUME. PRE-CLINICAL AND CLINICAL STUDIES HAVE SHOWN THAT GEMZAR HAS RADIOSENSITIZING ACTIVITY. IN A SINGLE TRIAL, WHEN GEMZAR 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 ESOPHAGITIS, 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 GEMZAR WITH THERAPEUTIC DOSES OF RADIATION HAS NOT YET BEEN DETERMINED IN ALL TUMOUR TYPES.

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

PREGNANCY AND LACTATION:

The safety of GEMZAR in human pregnancy and lactation has not been established. See ‘CONTRA-INDICATIONS’.

DOSAGE AND DIRECTIONS FOR USE:

GEMZAR is for intravenous use only.

Patients with hepatic or renal impairment:

GEMZAR 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.

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.

GEMZAR 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: GEMZAR 1 250 mg/m², given by 30 minute intravenous infusion on days 1 and 8 of every 21 day cycle and cisplatin 100 mg/m² on day 1. Dosage reduction with each cycle or within a cycle may be applied based upon the amount of toxicity experienced by the patient.

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

GEMZAR may be used in combination with cisplatin. The recommended dose of GEMZAR is 1 000 mg/m², given by 30 minute infusion. The dose should be given on days 1, 8 and 15 of each 28 day cycle in combination with cisplatin. Cisplatin is given at a recommended dose of 70 mg/m² on day 1 following GEMZAR or day 2 of each 28 day cycle. This four week cycle is then repeated. Dosage reduction with each cycle or within a cycle may be applied based upon the amount of toxicity experienced by the patient. A clinical trial showed more myelosuppression when cisplatin was used in doses of 100 mg/m².

Breast cancer:

Adults: GEMZAR 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 GEMZAR (1 250 mg/m^2) as a 30 minute intravenous infusion on days 1 and 8 of each 21 day cycle. Dose reduction with each cycle or within a cycle may be applied based upon the amount of toxicity experienced by the patient. Patients should have an absolute granulocyte count of at least 1 500 (x 10^6/L) prior to initiation of GEMZAR + paclitaxel combination.

Ovarian Cancer:

Single agent use:

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

Combination use:

Adults: GEMZAR in combination with carboplatin is recommended using GEMZAR 1 000 mg/m^2 administered on days 1 and 8 of each 21 day cycle as a 30 minute intravenous infusion. After GEMZAR, 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 GEMZAR should be monitored prior to each dose for platelet, leucocyte and granulocyte counts and, if necessary, the dose of GEMZAR may be either reduced or withheld in the presence of haematological toxicity, according to the following scale:

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

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

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

Elderly patients: GEMZAR 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 GEMZAR clearance and half-life are affected by age.

Instructions for reconstitution: The only approved diluent for reconstitution of GEMZAR is 0,9% sodium chloride injection without preservatives. It is not recommended that GEMZAR be mixed with other medicines when reconstituted. Due to solubility considerations, the maximum concentration for GEMZAR 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.

SIDE EFFECTS AND SPECIAL PRECAUTIONS:

Side effects:

The most commonly reported adverse drug reactions associated with GEMZAR treatment include nausea with or without vomiting, raised liver transaminases (AST/ALT) and alkaline phosphatase,

reported in approximately 60 % of patients, proteinuria and haematuria reported in approximately 50% of patients, dyspnoea reported in 10 to 40 % of patients (highest incidence in lung cancer patients) and allergic skin rashes occurring in approximately 25 % of patients and associated with itching in 10% of patients. The frequency and severity of adverse reactions are affected by the dose, infusion rate and intervals between doses (see 'WARNINGS'). Dose-limiting adverse reactions are reductions in platelet, leucocyte and granulocyte counts (see 'DOSAGE AND DIRECTIONS FOR USE').

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

Blood and Lymphatic System Disorders

Very Common (>1:10):

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'.)

Common (>1:100, <1:10):

Febrile neutropenia.

Immune System Disorders

Very Rare (<1:10 000):

Anaphylactoid reaction (see 'CONTRA-INDICATIONS').

Nervous System Disorders

Common (>1:100, <1:10):

Somnolence.

Cardiac Disorders

Rare (>1:10 000, <1:1 000):

Myocardial infarct, heart failure, arrhythmia (predominantly supraventricular in nature).

Vascular Disorders

Rare (>1:10 000, <1:1 000):

Hypotension.

Very Rare (<1:10 000):

Clinical signs of peripheral vasculitis and gangrene.

Respiratory, Thoracic and Mediastinal Disorders

Very Common (>1:10):

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

Uncommon (>1:1 000, <1:100):

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

GEMZAR should not be administered in patients with a known hypersensitivity to this medicine (see 'CONTRA-INDICATIONS').

Rare (>1:10 000, <1:1 000):

Pulmonary oedema, interstitial pneumonitis (with associated pulmonary infiltrates), adult respiratory distress syndrome (ARDS). (See 'PRECAUTIONS'.)

Gastrointestinal Disorders

Very Common (>1:10):

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

Stomatitis.

Common (>1:100, <1:10):

Diarrhoea, constipation.

Hepatobiliary Disorders

Very Common (>1:10):

Elevation of liver transaminases (AST and ALT) and alkaline phosphatase.

Rare (>1:10,000, <1:1,000):

Increased gamma-glutamyl transferase (GGT) and bilirubin.

Skin and Subcutaneous Tissue Disorders

Very Common (>1:10):

Allergic skin rash, frequently associated with pruritus. The rash is usually mild, not dose-limiting and responsive to local therapy.

Alopecia.

Rare (>1:10 000, <1:1 000):

Scaling, vesicle and sore formation, ulceration.

Very Rare (<1:10 000):

Severe skin reactions, including desquamation and bullous skin eruptions.

Renal and Urinary Disorders

Very Common (>1:10):

Mild proteinuria and haematuria. Rarely clinically significant and not usually associated with any change in serum creatinine or blood urea nitrogen.

Rare (>1:10 000, <1:1 000):

Renal failure (aetiology unknown).

Haemolytic uraemic syndrome (HUS) (see 'PRECAUTIONS' - 'Renal toxicity').

GEMZAR should be used with caution in patients with impaired renal function (see 'PRECAUTIONS' – 'Patients with renal or hepatic impairment').

General Disorders and Administration Site Conditions

Very Common (>1:10):

Oedema/peripheral oedema

Usually mild to moderate, rarely dose-limiting, and usually reversible after stopping GEMZAR 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 have also been reported. Fever and asthenia also occur as isolated symptoms. The mechanism of this toxicity is unknown.

Common (>1:100, <1:10):

Fever, asthenia.

Very Rare (<1:10 000):

Facial oedema.

Injury, Poisoning and Procedural Complications

Radiosensitisation and radiation recall reactions have been reported (also see 'INTERACTIONS').

Precautions:

General: Patients receiving therapy with GEMZAR 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. GEMZAR should be administered with caution to patients with impaired renal function (see 'PRECAUTIONS' – 'Patients with renal or hepatic impairment'). GEMZAR 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, GEMZAR 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 GEMZAR 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 GEMZAR in an *in vivo* assay. GEMZAR induced forward mutation *in vitro* in a mouse lymphoma assay. The influence of GEMZAR on fertility has not been established in humans. The carcinogenic potential of GEMZAR has not been established.

Patients with renal or hepatic impairment: GEMZAR should be used with caution in patients with impaired renal function or hepatic insufficiency as there is insufficient information from clinical studies to all clear dose recommendation for this patient population.
Mild to moderate renal insufficiency (GFR from 30 ml/min to 80 ml/min) has no consistent, significant effect on GEMZAR pharmacokinetics.

Administration of GEMZAR 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.

Effects on the ability to drive and use machines: GEMZAR 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:
There is no antidote for overdosage of GEMZAR. In the event of suspected overdose, the patient should be monitored with appropriate blood counts and should receive supportive therapy, as necessary.

IDENTIFICATION:

GEMZAR 200 mg (Powder for Injection), VL 7501, is a 10 ml size flint glass vial sealed with a rubber stopper and an aluminium seal, combined with a polypropylene cap. It contains a sterile lyophilized white to off-white plug or powder for injection.

Reconstitution with 0,9 % sodium chloride injection without preservatives produces a clear, colourless to light straw-coloured solution for injection.

GEMZAR 1 g (Powder for Injection), VL 7502, is a 50 ml size flint glass vial sealed with a rubber stopper and an aluminium seal, combined with a polypropylene cap. It contains a sterile lyophilized white to off-white plug or powder for injection.

Reconstitution with 0,9 % sodium chloride injection without preservatives produces a clear, colourless to light straw-coloured solution for injection.

PRESENTATION:

GEMZAR 200 mg and 1 g (Powder for Injection) vials are supplied in cartons containing singles.

STORAGE INSTRUCTIONS:

Before reconstitution: Store below 30 °C.

After reconstitution: Solutions of GEMZAR reconstituted with 0,9 % sodium chloride injection without preservatives should be stored below 30 °C and should be administered within 24 hours. Discard unused portion. Do not refrigerate as crystallization may occur. Reconstituted GEMZAR 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.
Keep out of reach of children.

REGISTRATION NUMBERS:

200 mg vials: 29/26/0306

1 g vials: 29/26/0307

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

Eli Lilly (S.A.) (Pty) Limited

1 Petunia Street,

Private Bag X119

Bryanston, 2021

DATE OF PUBLICATION OF THIS PACKAGE INSERT:

04 December 2009

Botswana Registration Details: S2	
Gemzar 200 mg powder for injection	Gemzar 1 g powder for injection
Reg. No.: R9800291	Reg. No.: R9800292

Namibian Registration Details: S4	
Gemzar 200 mg powder for injection	Gemzar 1 g powder for injection
Reg. No.: 04/26/0644	Reg. No.: 04/26/0643

SKEDULERINGSTATUS : S4

EIENDOMSNAAM EN DOSEERVORM:

GEMZAR 200 mg (Poeier vir Inspuiting)

GEMZAR 1 g (Poeier vir Inspuiting)

SAMESTELLING :

Elke GEMZAR 200 mg flessie bevat gemsitabienhidrochloried gelykstaande aan 200 mg gemsitabienbasis.

Elke GEMZAR 1 g flessie bevat gemsitabienhidrochloried gelykstaande aan 1 g gemsitabienbasis.

Gemsitabienhidrochloried is 2'-deoksi-2',2'-difluorositidienmonohidrochloried (β-isomeer). Die empiriese formule vir gemsitabienhidrochloried is $C_9H_{11}F_2N_3O_4.HCl$. Dit het 'n molekulêre massa van 299,66.

Die kliniese formulering is 'n steriele gevriesdroogde poeier vir hersamestelling met 0,9% natriumchloriedinspuiting. Die toebereide oplossing het 'n pH van 2,7 tot 3,3. Hierdie produk is alleenlik vir intraveneuse gebruik.

FARMAKOLOGIESE KLASSIFIKASIE :

A 26 Sitostatiese middels

FARMAKOLOGIESE WERKING :

Farmakodinamika:

Sellulêre metabolisme en meganisme van werking: Gemsitabien (dFdC) word intrasellulêr deur nukleosiedkinases na mono-, di-, en trifosfate (dFdCMF, dFdCDF en dFdCTF) gemetaboliseer,

waarvan dFdCDF en dFdCTF aktief is. Die sitotoksiese werking van gemsitabien is klaarblyklik die gevolg van inhibering van DNS-sintese deur twee aksies van dFdCDF en dFdCTF. Eerstens inhibeer dFdCDF ribonukleotiedreduktase wat op 'n unieke wyse verantwoordelik is vir die katalisering van die reaksies wat die deoksi-nukleosiedtrifosfate genereer vir DNS-sintese. Inhibering van hierdie ensiem deur dFdCDF veroorsaak 'n vermindering in die konsentrasies van deoksinukleosiede in die algemeen en veral in dié van dCTF. Tweedens, kompeteer dFdCTF en dCTF vir inkorporering in DNS. Op 'n soortgelyke wyse kan 'n klein hoeveelheid gemsitabien ook in RNS geïnkorporeer word. Derhalwe potensieer die vermindering in die intrasellulêre konsentrasie van dCTF die inkorporering van dFdCTF in DNS (selfpotensiëring). DNS polimerase epsilon is vir alle praktiese doeleindes nie in staat om gemsitabien te verwyder en die groeiende DNS-stringe te herstel nie. Nadat gemsitabien in DNS geïnkorporeer is, word een addisionele nukleotied by die groeiende DNS stringe bygevoeg. Na hierdie toevoeging is daar dus 'n volledige inhibering van verdere DNS-sintese (gemaskeerde kettingterminering). Na inkorporering in DNS, induseer gemsitabien klaarblyklik die geprogrammeerde sellulêre sterfproses bekend as apoptose.

Sitotoksiese aktiwiteit in selkultuurmodelle: Gemsitabien vertoon 'n uitgesproke sitotoksiese werking teen 'n verskeidenheid van gekweekte muis- en menslike tumorselle. Dit vertoon selfase-spesifisiteit deur hoofsaaklik selle te dood wat DNS-sintese ondergaan (S-fase) en deur onder sekere toestande die progressie van selle deur die G1/S-fase-grens te blokkeer. Die *in vitro* sitotoksiese werking van gemsitabien is van konsentrasie sowel as tyd afhanklik.

Antitumoraktiwiteit in prekliniese modelle: Die antitumorwerking van gemsitabien in diertumormodelle is skedule-afhanklik. Wanneer dit daagliks toegedien word, veroorsaak gemsitabien die dood by diere met minimale antitumorwerking. Gemsitabien kan egter in nie-dodelike dosisse toegedien word wat uitstekende antitumoraktiwiteit teen 'n groot verskeidenheid muistumore het, wanneer 'n dosisskedule van elke derde of vierde dag gebruik word.

Moederverbinding-farmakokinetika: Die farmakokinetika van gemsitabien blyk lineêr te wees vir dosisse wat bestudeer is.

Die volgende farmakokinetiese parameters is verkry vir dosisse van 500 tot 2 592 mg/m² wat deur infusie oor 'n tydperk van 0,4 tot 1,2 uur toegedien is:

Piekplasmakonsentrasies (verkry binne 5 minute nadat die infusie gestaak is): 3,2 tot 45,5 µg/ml.

Halfleeftyd: 42 tot 94 minute afhangende van ouderdom en geslag. Vir die aanbevole doseerleefreël behoort gemsitabien eliminasie feitlik volledig te wees binne 5 tot 11 uur na aanvang van die infusie. Gemsitabien hoop nie op wanneer dit een maal per week toegedien word nie.

Volume van distribusie van die sentrale kompartement (V_s): 12,4 L/m^2 vir vrouens en 17,5 L/m² vir mans (inter-individuele variasie was 91,9 %).

Volume van distribusie van die perifere kompartement (V_p) : 47,4 L/m². Die volume van die perifere kompartement was nie sensitief vir geslag nie.

Plasmaproteïenbinding: Onbeduidend.

Sistemiese opruiming: 29,2 L/hr/m² tot 92,2 L/hr/m² afhangend van geslag en ouderdom (inter-individuele variasie was 52,2 %). Die opruiming by vroue is ongeveer 25 % laer as by mans. Alhoewel dit vinnig geskied, wil dit voorkom asof vinnige opruiming by beide mans en vrouens afneem met ouderdom. Vir die aanbevole gemsitabiendosis van 1 000 mg/m² toegedien as 'n infusie oor 'n tydperk van 30 minute, behoort die laer opruiming by vroue of by bejaardes nie 'n vermindering van die gemsitabien-dosis te noodsaak nie.

Urienuitskeiding: minder as 10 % word onveranderd uitgeskei.

Gemiddelde renale opruiming: 2 tot 7 L/h/m^2.

Sistemiese metabolisme: Gemsitabien word vinnig deur sitidien-deaminase in die lewer, niere, bloed en ander weefsels gemetaboliseer.

Die primêre metaboliet, 2'-deoksi-2',2'-difluorouridien (dFdU) is onaktief en word in die plasma en urien gevind. Die vorming van dFdU vanaf die moederverbinding wissel van 91% tot 98%. Die weefselverspreiding van dFdU is uitgebreid.

Algehele eliminasie: Hoeveelhede wat binne een week na 'n enkele 30 minute infusie van 1 000 mg/m^2 radiogemerkte gemsitabien herwin is, is 92 % tot 98 %, waarvan 99 % urienuitskeiding van dFdU is; 1 % van die dosis word in die feses uitgeskei.

INDIKASIES :

GEMZAR is aangedui vir die behandeling van pasiënte met plaaslike gevorderde of metastatiese nie-kleinsellongkanker.

GEMZAR is aangedui as eerste-linie behandeling by pasiënte met plaaslik gevorderde (nie-resekteerbare Stadium II of Stadium III) of metastatiese (Stadium IV) adenokarsinoom van die pankreas. GEMZAR is aangedui vir pasiënte wat voorheen met 5-FU behandel is.

GEMZAR is aangedui vir die behandeling van pasiënte met oorgangsel blaaskanker.

GEMZAR**,** in kombinasie met paklitaksel, word aangedui vir die behandeling van pasiënte met nie-resekteerbare, lokaal-herhalende of metastatiese borskanker wat na adjuvante/ neo-adjuvante

chemoterapie teruggeval het. Tensy klinies teenaangedui is 'n antrasiklien veronderstel om by vorige chemoterapie ingesluit te word.

GEMZAR, alleen of in kombinasie, is aangedui vir die behandeling van pasiënte met epiteel ovariumkarsinoom, wat na platinum-gebaseerde chemoterapie teruggeval het.

KONTRA-INDIKASIES :

GEMZAR is teenaangedui by pasiënte met 'n bekende hipersensitiwiteit vir die medisyne.

Swangerskap en borsvoeding: Die veiligheid van GEMZAR tydens menslike swangerskap en laktasie is nog nie vasgestel nie.

Gebruik by kinders: Die veiligheid en effektiwiteit by kinders is nog nie vasgestel nie.

WAARSKUWINGS :

Daar is aangetoon dat verlenging van die infusietyd en verhoogde doseringsfrekwensie toksisiteit verhoog.

GEMZAR kan beenmurgfunksie onderdruk, wat manifesteer as leukopenie, trombositopenie en anemie. Miëlo-onderdrukking is gewoonlik lig tot matig en is meer uitgesproke vir die granulosiettelling (sien 'DOSERING EN GEBRUIKSAANWYSINGS' en 'Newe-effekte - Hematologiese Toksisiteit').

INTERAKSIES:

RADIOTERAPIE:

GELYKTYDIG (SAAM TOEGEDIEN OF < 7 DAE UITMEKAAR) – GEBASSEER OP RESULTATE VAN PRE-KLINIESE EN KLINIESE STUDIES, BESKIK GEMZAR OOR BESTRALINGSENSITASIE-AKTIWITEIT. TOE GEMZAR TEEN 'N DOSIS VAN 1 000 mg/m^2 SAAM MET TERAPEUTIESE BESTRALING VAN DIE BORSKAS VIR TOT EN MET SES WEKE AAN PASIËNTE MET NIE-KLEINSELLONGKANKER TOEGEDIEN IS, IS BEDUIDENDE TOKSISITEIT IN DIE VORM VAN ERNSTIGE EN POTENSIEËL LEWENSBEDRYGENDE MUKOSITIS VERAL SLUKDERMONTSTEKING EN LONGONTSTEKING WAARGENEEM, SPESIFIEK BY PASIËNTE WAT GROOT HOEVEELHEDE RADIOTERAPIE ONTVANG HET (GEMIDDELDE BEHANDELING VOLUMES 4 795 cm^3). DIE OPTIMALE DOSEERLEEFREËL VIR VEILIGE GESAMENTLIKE TOEDIENING VAN GEMZAR EN TERAPEUTIESE BESTRALINGSDOSISSE IS NOG NIE VASGESTEL IN AL DIE TUMOR TIPES NIE.

BESTRALING BESERING IS AANGEMELD IN TEIKENORGAAN WEEFSELS (bv. ESOFAGITIS, KOLITIS, EN PNEUMONITIS) IN ASSOSIASIE MET BEIDE GESAMENTLIKE EN NIE-GESAMENTLIKE GEMZAR TOEDIENING.

SWANGERSKAP EN LAKTASIE:

Die veiligheid van GEMZAR in menslike swangerskap en laktasie is nie vasgestel nie. Sien ‘KONTRA-INDIKASIES’.

DOSERING EN GEBRUIKSAANWYSINGS :

GEMZAR is slegs vir intraveneuse gebruik.

Pasiënte met hepatiese- of nier inkorting:

GEMZAR moet met versigtigheid gebruik word in pasiënte met lewerontoereikenheid of ingekorte nierfunksie omdat daar geen studies in hierdie populasie groepe gedoen is nie. Daar is onvoldoende informasie van kliniese studies om duidelike riglyne aangaande dosering in hierdie pasiënt populasie aan te beveel.

Nie-kleinsellongkanker:

Volwassenes: Die aanbevole mono-chemoterapie dosis van GEMZAR is 1 000 mg/m^2, toegedien deur intraveneuse infusie oor 30 minute. Die prosedure moet een maal per week vir drie weke herhaal word, gevolg deur 'n rusperiode van een week. Hierdie vierweeklikse siklus word dan herhaal. Dosisvermindering met elke siklus of tydens 'n siklus kan gebaseer word op die hoeveelheid toksisiteit wat die pasiënt ervaar.

GEMZAR kan in kombinasie met cisplatin op 'n drie weeklikse- of vier weeklikse siklus gebruik word. Een van die volgende doseerleefreëls word aanbeveel:

3 week skedule: GEMZAR 1 250 mg/m^2, toegedien deur intraveneuse infusie oor 30 minute op dag 1 en 8 van elke 21 dag siklus en cisplatin 100 mg/m^2 op dag 1. Dosisvermindering met elke siklus of tydens 'n siklus kan gebaseer word op die hoeveelheid toksisiteit wat die pasiënt ervaar.

4 week skedule: GEMZAR 1 000 mg/m² op dag 1, 8 en 15 van elke 28 dag siklus en cisplatin 100 mg/m² op dag 1, 2 of 15 van behandeling. Dosisvermindering met elke siklus of tydens 'n siklus kan gebaseer word op die hoeveelheid toksisiteit wat die pasiënt ervaar.

Pankreaskanker:

Volwassenes: Die aanbevole dosis van GEMZAR is 1 000 mg/m² toegedien deur intraveneuse infusie oor 30 minute. Dit moet een maal per week vir tot en met sewe weke herhaal word, gevolg deur 'n rusperiode van een week. Daaropvolgende siklusse moet bestaan uit inspuitings een maal per week vir drie agtereenvolgende weke uit elke vier weke. Dosisvermindering met elke siklus of tydens 'n siklus kan gebaseer word op die hoeveelheid toksisiteit wat die pasiënt ervaar.

Blaaskanker:

Volwassenes: Die aanbevole mono-chemoterapie dosis van GEMZAR is 1 250 mg/m^2 toegedien deur intraveneuse infusie oor 30 minute. Die dosis moet op dag 1, 8 en 15 van elke 28 dag siklus toegedien word. Hierdie vierweeklikse siklus word dan herhaal. Dosisvermindering met elke siklus of tydens 'n siklus kan gebaseer word op die hoeveelheid toksisiteit wat die pasiënt ervaar.

GEMZAR kan in kombinasie met cisplatin gebruik word. Die aanbevole dosis van GEMZAR is 1 000 mg/m^2 toegedien deur intraveneuse infusie oor 30 minute. Die dosis moet op dag 1, 8 en 15 van elke 28 dag siklus in kombinasie met cisplatin toegedien word. Cisplatin moet teen 'n aanbevole dosis van 70 mg/m^2 op dag 1 na die GEMZAR dosis, of op dag 2 van elke 28 dag siklus toegedien word. Hierdie vierweeklikse siklus word dan herhaal. Dosisvermindering met elke siklus of tydens 'n siklus kan gebaseer word op die hoeveelheid toksisiteit wat die pasiënt ervaar. 'n Kliniese proef het op meer miëlo-onderdrukking gedui indien cisplatin teen 'n dosis van 100 mg/m^2 gebruik word.

Borskanker:

Volwassenes: GEMZAR in kombinasie met paklitaksel word aanbeveel deur van paklitaksel (175 mg/m^2) gebruik te maak wat op dag 1 oor ongeveer 3 uur as ‘n intraveneuse infusie toegedien word, gevolg deur GEMZAR (1 250 mg/m^2) as 'n 30-minuut intraveneuse infusie op dae 1 en 8 van elke siklus van 21 dae. Dosisvermindering met elke siklus of tydens 'n siklus mag toegepas word soos bepaal deur die hoeveelheid toksisiteit wat deur die pasiënt ondervind word.

Pasiënte behoort ‘n absolute granulosiet-telling van ten minste 1 500 (x 10^{10}/L) te hê voordat die GEMZAR + paklitaksel kombinasie ingestel word.

Ovariumkanker:

Enkelagent gebruik:

Volwassenes: Die aanbevole dosering van GEMZAR is 800-1 250 mg/m^2, toegedien deur 30 minute intraveneuse infusie. Die dosering moet gegee word op dag 1, 8 en 15 van elke 28 dag siklus. Hierdie vierweeklikse siklus word dan herhaal. Doseringvermindering met elke siklus of tydens 'n siklus kan gebaseer word op die hoeveelheid toksisiteit wat die pasiënt ervaar.

Kombinasie gebruik:

Volwassenes: Die aanbevole dosis van GEMZAR in kombinasie met carboplatin, is 1 000mg/m^2 toegedien op dag 1 en 8 van elke 21 dag siklus deur 30 minute intraveneuse infusie. Na GEMZAR, sal carboplatin op dag 1 aanhoudend toegedien word met 'n teiken AOK van 4,0 mg/ml/min. Doseringvermindering met elke siklus of tydens 'n siklus kan gebaseer word op die hoeveelheid toksisiteit wat die pasiënt ervaar.

Pasiënte wat GEMZAR ontvang moet voor elke dosis gemonitor word vir bloedplaatjie-, leukosiet- en granulosiettellings en, indien nodig, kan die dosis van GEMZAR in die teenwoordigheid van hematologiese toksisiteit volgens die volgende skaal óf verminder óf onttrek word:

Absolute granulosiettelling (x 10^6/L)		**Plaatjietelling (x 10^6/L)**	**% van volle dosis**
>1 000	en	>100 000	100
500 - 1 000	of	50 000 - 100 000	75
<500	of	<50 000	onttrek

Periodieke fisieke ondersoeke en lewer- en nierfunksietoetse moet ook uitgevoer word om nie-hematologiese toksisiteit te evalueer. Dosisvermindering met elke siklus of tydens 'n siklus kan gebaseer word op die hoeveelheid toksisiteit wat die pasiënt ervaar. Dosisse moet weerhou word totdat die toksisiteit in die opinie van die geneesheer opgeklaar het.

GEMZAR word goed verdra tydens die infusie, met slegs enkele gevalle van inspuitplekreaksies wat aangemeld is. Geen gevalle van inspuitpleknekrose is aangemeld nie. GEMZAR kan maklik op 'n buitepasiëntbasis toegedien word.

Bejaardes: GEMZAR word goed verdra by pasiënte ouer as 65. Hoewel gemsitabien opruiming en halfleeftyd deur ouderdom beinvloed word, is daar geen getuienis wat daarop dui dat dosisaanpassings by bejaardes nodig is nie.

Instruksies vir hersamestelling: Die enigste goedgekeurde verdunningsmiddel vir die toebereiding van GEMZAR is 0,9 % Natriumchloriedinspuiting sonder preserveermiddels. Vermenging van GEMZAR met ander geneesmiddels tydens toebereiding word nie aanbeveel nie. As gevolg van oplosbaarheidsoorwegings, is die maksimum konsentrasie van GEMZAR na toebereiding 40 mg/ml. Toebereiding teen konsentrasies hoër as 40 mg/ml kan tot onvolledige oplossing aanleiding gee en moet vermy word.

Om toe te berei, voeg ten minste 5 ml 0,9 % natriumchloriedinspuiting sonder preserveermiddels by die 200 mg flessie of ten minste 25 ml 0,9 % natriumchloriedinspuiting sonder preserveermiddels by die 1 g flessie. Skud om op te los. Die toepaslike hoeveelheid medisyne kan toegedien word soos toeberei, of verder verdun word met 0,9 % natriumchloriedinspuiting sonder preserveermiddels.

NEWE-EFFEKTE EN SPESIALE VOORSORGMAATREËLS :

Newe-effekte:

Die nadelige geneesmiddelreaksies geassosieer met GEMZAR-behandeling wat mees algemeen aangemeld is, sluit in naarheid, met of sonder braking, verhoogde lewer-transaminases (AST/ALT) en alkaliese fosfatase, aangemeld in ongeveer 60 % van pasiënte, proteïenurie en hematurie aangemeld in ongeveer 50 % van pasiënte, dispnee aangemeld in 10-40 % van pasiënte (hoogste voorkoms in longkankerpasiënte), en allergiese veluitslae wat in ongeveer 25% van pasiënte voorkom en met jeuk in 10 % van pasiënte geassosieer word. Die frekwensie en erns van die nadelige reaksies word deur die dosis, infusietempo en intervalle tussen dosisse beïnvloed (sien 'WAARSKUWING'). Vermindering in plaatjie-, leukosiet- en granulosiet-tellings word as dosisbeperkende nadelige reaksies beskou (sien 'DOSERING EN GEBRUIKSAANWYSINGS').

Die volgende lys van ongewenste uitwerkings en frekwensies is gegrond op kliniese proewe en spontane nabemarking-berigte.

Afwykings van die Bloed en Limfatiese Sisteem

Baie Algemeen (>1:10)

Leukopenie, trombositopenie, anemie.

(Neutropenie Graad 3 = 19,3 %; Graad 4 = 6 %).

Miëlo-onderdrukking is gewoonlik verbygaande, veroorsaak meestal nie dosisverminderings nie, en veroorsaak selde staking. Dosisvermindering of -omissie mag by ernstige beenmurgonderdrukking noodsaaklik wees (sien 'DOSERING EN GEBRUIKSAANWYSINGS'.)

Algemeen (>1:100; <1:10)

Febriele neutropenie.

Afwykings van die Immuunsisteem

Baie seldsaam (<1:10 000)

Anafilaktoïed reaksie (sien ‘KONTRA-INDIKASIES’).

Afwykings van die Senusisteem

Algemeen (>1:100, <1:10)

Slaperigheid.

Hartafwykings

Seldsaam (>1:10 000, <1:1 000)

Miokardiale infarksie, hartversaking, aritmie (hoofsaaklik supraventrikulêr van aard).

Vaskulêre Afwykings

Seldsaam (>1:10 000, <1:1 000)

Hipotensie.

Baie Seldsaam (<1:10 000)

Kliniese tekens van perifere vaskulitis en gangreen

Respiratoriese, Torakale en Mediastinale Afwykings

Baie Algemeen (>1:10)

Dispnee. Gewoonlik lig en kortstondig, selde dosisbeperkend, en bedaar gewoonlik sonder enige spesifieke terapie.

Ongewoon (>1:1 000, <1:100)

Brongospasma. Gewoonlik lig en verbygaande, maar parenterale terapie mag nodig wees. GEMZAR moet nie aan pasiënte met 'n bekende hipersensitiwiteit teen hierdie medisyne, toegedien word nie (sien ‘KONTRA-INDIKASIES’).

Seldsaam (>1:10 000, <1:1 000)

Pulmonale edeem, interstisiële pneumonitis (met geassosieerde pulmonale infiltrate), volwasse respiratoriese nood sindroom (ARDS). (Sien ‘VOORSORGMAATREËLS’).

Gastroïntestinale Afwykings

Baie Algemeen (>1:10)

Naarheid, braking. Hierdie nadelige insidente benodig terapie in ongeveer 20 % van pasiënte, is selde dosisbeperkend en kan maklik met standaard anti-emetika beheer word.
Stomatitis.

Algemeen (>1:100, <1:10)

Diarree, hardlywigheid.

Hepato-biliêre Afwykings

Baie Algemeen (>1:10)

Verhoging van lewer transaminase (AST en ALT) en alkaliese fosfatase.

Seldsaam (>1:10 000; <1:1 000)

Verhoogde gamma-glutamiel transferase (GGT) en bilirubien.

Afwykings van die Vel en Onderhuidse Weefsels

Baie Algemeen (>1:10)

Allergiese veluitslag, dikwels geassosieer met pruritus. Die veluitslag is gewoonlik lig, nie dosisbeperkend nie en reageer op lokale terapie.

Alopesie.

Seldsaam (>1:10 000, <1:1 000)

Skubvorming, vesikel- en seervorming, ulserasie.

Baie Seldsaam (<1: 10 000)

Erge vel reaksies, insluitend vel afskilfering en blaas veluitslag.

Renale en Urinêre Afwykings

Baie Algemeen (>1:10)

Ligte proteïenurie en hematurie. Selde klinies beduidend, en gewoonlik nie gekoppel aan enige veranderings in serumkreatinien, of bloedureumstikstof nie.

Seldsaam (>1:10 000, <1:1 000)

Nierversaking (etiologie onbekend).

Hemolitiese uremiese sindroom (HUS) (sien 'VOORSORGMAATREËLS' - Renale toksisiteit').

GEMZAR moet versigtig gebruik word in pasiënte met ingekorte nierfunksie (sien 'VOORSORGMAATREËLS' - Pasiënte met renale of hepatiese inkorting').

Algemene Afwykings en Toedieningsplek-toestande

Baie Algemeen (>1:10)

Edeem/ perifere edeem

Gewoonlik lig tot matig, selde dosisbeperkend, en gewoonlik omkeerbaar na staking van GEMZAR-behandeling. Die meganisme van toksisiteit is onbekend. Dit word nie met enige tekens van hart-, lewer- of nierversaking geassosieer nie.

Griepagtige simptome

Die mees algemene simptome is koors, hoofpyn, rugpyn, bewing, spierpyn, astenie en anoreksie. Hoes, rinitis, malaise, sweet en probleme met slaap is ook aangemeld. Koors en astenie kom ook as geïsoleerde simptome voor. Die meganisme van hierdie toksisiteit is onbekend.

Algemeen (>1:100, <1:10)

Koors, astenie.

Baie Seldsaam (<1:10 000)

Edeem van die gesig.

Besering, Vergiftiging en Prosedure Komplikasies

Radiosensitisering en herroeping van bestraling reaksies is aangemeld (sien ook ‘WAARSKUWINGS’).

Voorsorgmaatreëls:

Algemeen: Pasiënte wat met GEMZAR behandel word moet noukeurig dopgehou word. Laboratoriumfasiliteite moet beskikbaar wees om die status van die pasiënt te monitor. Sien 'DOSERING EN GEBRUIKSAANWYSINGS' aangaande evaluering van nier- en lewerfunksies. Behandeling van 'n pasiënt wat deur medisynetoksisiteit gekompromitteer is, kan nodig wees.

Laboratoriumtoetse: Terapie moet met omsigtigheid 'n aanvang neem by pasiënte met gekompromitteerde beenmurgfunksie. Soos met ander onkolitika, moet die moontlikheid van kumulatiewe beenmurgonderdrukking oorweeg word wanneer kombinasie- of opeenvolgende chemoterapie gebruik word.

Riglyne vir dosismodifisering wanneer medisyne-geïnduseerde murgonderdrukking ervaar word, word verskaf onder 'DOSIS EN GEBRUIKSAANWYSINGS'. Perifere bloedtellings kan verder daal nadat die medisyne gestaak is.

Renale toksisiteit: Nierversaking en HUS (hemolitiese uremiese sindroom) is selde gerapporteer. GEMZAR moet met sorg aan pasiënte met belemmerde nierfunksie toegedien word (Sien 'VOORSORGMAATREELS' – "Pasiënte met belemmerde renale- of hepatiese- funksie"). GEMZAR behandeling moet dadelik met die eerste tekens van mikro-angiopatiese hemolitiese anemie soos vinnig dalende hemoglobien met gepaardgaande trombositopenie, verhoging in serumbilirubien, serumkreatinien, bloed ureum stikstof of LDH gestaak word. Nierversaking mag selfs nie met onttrekking van behandeling omkeerbaar wees nie en dialise mag nodig wees.

Pulmonale toksisiteit: Interstisiële pneumonitis (longontsteking) tesame met pulmonale infiltrate is in minder as 1 % van pasiente gesien. GEMZAR behandeling moet in sulke gevalle dadelik gestaak word. Steroïde mag in hierdie gevalle simptome verlig. Erge, selde dodelike pulmonale effekte soos pulmonale edeem, interstisiële pneumonitis en akute respiratoriese ongemakssindroom (ARDS) is as minder algemeen of skaars gerapporteer. Staking van GEMZAR behandeling in sulke gevalle is nodig. Ondersteunende behandeling, op n vroeë stadium begin, mag die situasie baie verbeter.

Karsinogenese, mutagenese, inkorting van fertiliteit: Sitogenese skade is veroorsaak deur GEMZAR in *in vivo* proewe. GEMZAR het 'n voorwaartse mutasie in 'n *in vitro* muislimfoom toets

geïnduseer. Die invloed van GEMZAR op fertiliteit by mense is nog nie vasgestel nie. Die karsinogeniese potensiaal van GEMZAR is nog nie vasgestel nie.

Pasiënte met nier- en lewerontoereikendheid: GEMZAR moet met omsigtigheid gebruik word by pasiënte met ingekorte nierfunksie of lewerontoereikendheid. Geen studies is nog by pasiënte met uitgesproke nier- of lewerontoereikendheid uitgevoer nie. Ligte tot matige nierontoereikendheid (GFT van 30 ml/min tot 80 ml/min) het geen volgehoue betekenisvolle effek op GEMZAR farmakokinetika nie.

Toediening van GEMZAR in pasiënte met bestaande lewer metastase of ’n bestaande mediese geskiedenis van hepatitis, alkoholisme of lewersirrose mag lei tot ’n verergering van onderliggende lewerinkorting.

Invloed op die vermoë om te bestuur of masjinerie te gebruik: Daar is aangemeld dat GEMZAR ligte tot matige slaperigheid veroorsaak. Pasiënte moet gewaarsku word om nie te bestuur of masjinerie te gebruik totdat daar vasgestel is dat hulle nie slaperig word nie.

BEKENDE SIMPTOME VAN OORDOSERING EN BESONDERHEDE VAN DIE BEHANDELING DAARVAN :

Daar is geen teenmiddel vir oordosering met GEMZAR nie. In geval van vermeende oordosering, moet die pasiënt gemonitor word met toepaslike bloedtellings en moet ondersteunende behandeling soos benodig gegee word.

IDENTIFIKASIE :

GEMZAR 200 mg (Poeier vir Inspuiting), VL 7501, is 'n 10 ml-grootte loodglasflessie verseël met 'n rubberproppie en aluminiumseël, gekombineer met 'n polipropileendoppie. Dit bevat 'n steriele gevriesdroogde wit tot naaswit proppie of poeier vir inspuiting.

Toebereiding met 0,9 % natriumchloriedinspuiting sonder preserveermiddels lewer 'n helder, kleurlose tot ligte strooikleurige oplossing vir inspuiting.

GEMZAR 1 g (Poeier vir Inspuiting), VL 7502, is 'n 50 ml-grootte loodglasflessie verseël met 'n rubberproppie en aluminiumseël, gekombineer met 'n polipropileendoppie. Dit bevat 'n steriele gevriesdroogde wit tot naaswit proppie of poeier vir inspuiting.

Hersamestelling met 0,9 % natriumchloriedinspuiting sonder preserveermiddels lewer 'n helder, kleurlose tot ligte strooikleurige oplossing vir inspuiting.

AANBIEDING :

GEMZAR 200 mg en 1 g (Poeier vir Inspuiting) flessies word verskaf in kartonnetjies wat enkelflessies bevat.

BERGINGSAANWYSINGS :

Voor toebereiding: Berg benede 30 °C.

Na toebereiding: Oplossings van GEMZAR wat met 0,9 % natriumchloriedinspuiting sonder preserveermiddels toeberei is moet benede 30 °C geberg word en moet binne 24 uur toegedien word. Die ongebruikte gedeelte moet weggegooi word. Moenie verkoel nie, omdat kristallisering mag voorkom. Toebereide GEMZAR moet voor toediening visueel ondersoek word vir deeltjies en verkleuring. Daar moet gelet word op prosedures vir die behoorlike hantering en wegdoen van antikankergeneesmiddels.

Hou buite bereik van kinders.

REGISTRASIENOMMERS:

200 mg flessie: 29/26/0306

1 g flessie: 29/26/0307

NAAM EN BESIGHEIDSADRES VAN DIE HOUER VAN DIE SERTIFIKAAT VAN REGISTRASIE:

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