especially in combination with alcohol consumption. Patients should be cautioned against driving or operating machinery until it is established that they do not become somnolent.

Interaction of Other Medicaments

No specific interaction studies have been performed

Radiotherapy

Concurrent (given together or ≤7days apart)-Toxicity associated with this multimodality therapy is dependent on many different factors, including dose of gemcitabine, frequency of gemcitabine administration, dose of radiation, radiotherapy planning technique, the target tissue and target volume. The optimum regimen for safe administration of gemcitabine with therapeutic doses of radiation has not yet been determined in all tumor types.

Non-concurrent (given >7 days apart)-Analysis of the data does not indicate any enhanced toxicity when gemcitabine is administered more than 7 days before or after radiation, other than radiation recall.

Radiation injury has been reported on targeted tissues (e.g. esophagitis, colitis and pneumonitis) in association with both concurrent and non- concurrent use of gemcitabine.

Others

Yellow fever and other live attenuated vaccines are not recommended due to the risk of system ic, possibly fatal, disease, particularly in immunosuppressed patients.

Incompatibilities

This medicinal product must not be mixed with other medicinal products.

Pregnancy and Lactation

Pregnancy

There are no or limited amount of data from the use of gemcitabine in pregnant women. As a precautionary measure, it is preferable to avoid the use of gemcitabine during pregnancy.

Lactation

It is unknown whether gemcitabine is excreted in human milk. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from gemcitabine therapy taking into account the benefit of therapy for the woman.

Side Effects

The most commonly reported adverse drug reactions associated with Gemcitabine treatment include: nausea with or without vomiting, raised liver transaminases (AST/ALT) and alkaline phosphatase. The frequency and severity of the adverse reactions will affect by the dose, infusion rate and intervals between doses. Dose-limiting adverse reactions are reductions in thrombocyte, leucocyte and granulocyte counts.

SYSTEM ORGAN CLASS	FREQUENCY GROUPING
Blood and lymphatic system disorders	***Very Common*** • *Leucopaenia.* Bone-marrow suppression is usually mild to moderate and mostly affects the granulocyte count • Thrombocytopaenia • Anaemia ***Common*** • Febrile neutropaenia ***Very rare*** • Thrombocytosis
Immune system disorders	***Very rare*** • Anaphylactoid reaction
Metabolism and nutrition disorders	***Common*** • Anorexia
Nervous system disorders	***Common*** • Headache

Symptoms and Treatment of Overdose

There is no known antidote for overdose of gemcitabine. Doses as high as 5,700 mg/m^2 have been administered by intravenous infusion over 30 minutes every 2 weeks with clinically acceptable toxicity. In the event of suspected overdose, the patient should be monitored with appropriate blood counts and receive supportive therapy, as necessary."

	• Insomnia • Somnolence ***Uncommon*** • Cerebrovascular accident ***Very rare*** • Posterior reversible encephalopathy syndrome
Cardiac disorders	***Uncommon*** • Arrhythmias, predominately supraventricular in nature • Heart failure ***Rare*** • Myocardial infarct
Vascular disorders	***Rare*** • Clinical signs of peripheral vasculitis and gangrene • Hypotension ***Very rare*** • Capillary leak syndrome
Respiratory, thoracic and mediastinal disorders	***Very Common*** • Dyspnoea - usually mild and passes rapidly without treatment ***Common*** • Cough • Rhinitis ***Uncommon*** • Interstitial pneumonitis • Bronchospasm - usually mild and transient but may require parenteral treatment ***Rare*** • Pulmonary oedema • Adult respiratory distress syndrome
Gastrointestinal disorders	***Very Common*** • Vomiting • Nausea ***Common*** • Diarrhoea • Stomatitis and ulceration of the mouth • Constipation ***Very rare*** • Ischaemic colitis
Hepatobiliary disorders	***Very Common*** • Elevation of liver transaminases (AST and ALT) and alkaline phosphatase ***Common*** • Increased bilirubin ***Uncommon*** • Serious hepatotoxicity, including liver failure and death ***Rare*** • Increased gamma-glutamyl transferase (GGT)
Skin and subcutabeous tissue disorders	***Very common*** • Allergic skin rash frequently associated with pruritus • Alopecia ***Common*** • Itching • Sweating ***Rare*** • Severe skin reactions, including desquamation and bullous skin eruptions

	• Ulceration • Vesicle and sore formation • Scaling ***Very rare*** • Toxic epidermal necrolysis • Stevens-Johnson Syndrome
Musculoskeletal and connective tissue disorders	***Common*** • Back pain • Myalgia
Renal and urinary disorders	***Very Common*** • Haematuria • Mild proteinuria ***Uncommon*** • Renal failure • Hemolytic uraemic syndrome
General disorders and administration site conditions	***Very Common*** • Influenza-like symptoms - the most common symptoms are fever, headache, chills, myalgia, asthenia and anorexia. Cough, rhinitis, malaise, perspiration and sleeping difficulties have also been reported. • Oedema.peripheral oedema, including facial oedema. Oedema is usually reversible after stopping treatment ***Common*** • Fever • Asthenia • Chills ***Rare*** • Injection site reactions - mainly mild in nature
Injury, poisoning and procedural complications	***Rare*** • Radiation toxicity • Radiation recall

Storage Condition

Storage Condition for Unopened Vial : Store below 30ºC, Protect from light. Keep out of reach of children.

Storage condition of reconstitution Solution : Chemical and physical in-use stability has been demonstrated for 24 hours at 30ºC, From a microbiological point of view, the product should be used immediately. If not used immediately, in- use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at room temperature, unless reconstitution (and further dilution, if applicable) has taken place in controlled and validated aseptic conditions. Solutions of reconstituted Gemcitabine should not be refrigerated, as crystallization may occur.

Presentation

GEMCITABINE 200MG/VIAL is packaged in clear glass vials (type I) with 10ml nominal capacity with reinforced Non PVC base which are stoppered with slotted rubber plugs, cramped with seals and tampered with flip - off - tops.

GEMCITABINE 1000MG/VIAL is packaged in clear glass vials (type I) with 50ml nominal capacity with reinforced Non PVC base which are stoppered with slotted rubber plugs, cramped with seals and tampered with flip - off - tops.

Shelf-Life: Unopened vial : 36 Months from date of manufacturing
After reconstituted solution : 24 hours at 30°C

Mal No.: MAL17035039AZ, MAL17035044AZ

Product Registration Holder:
Unimed Sdn Bhd
53, Jalan Tembaga SD 5/2B, Bandar Sri Damansara, 52200, Kuala Lumpur, Malaysia

Manufactured by :
VENUS REMEDIES LIMITED
Hill Top Industrial Estate,
Near Jharmajri EPIP, Phase-I (Extention),
Bhatoli Kalan, Baddi, Distt. Solan,
Himachal Pradesh-173205, INDIA

B81/GM200/0846-02, B81/GM1000/0847-02
Revised Date: 15/05/2023

VENUS
Caring Innovation

CITABOL (Gemcitabine Powder for Solution for Infusion 1000 mg/vial)
CITABOL (Gemcitabine Powder for Solution for Infusion 200 mg/vial)

Composition

CITABOL (Gemcitabine Powder for Solution for Infusion 1000 mg/vial)
Each Vial Contains:
Gemcitabine hydrochloride Ph.Eur 1149mg
Equivalent to gemcitabine 1000mg

CITABOL (Gemcitabine Powder for Solution for Infusion 200 mg/vial)
Each Vial Contains:
Gemcitabine hydrochloride Ph.Eur 230mg
Equivalent to gemcitabine 200mg

Product Description

Description of Finished Product - White lypophilised mass after reconstituted form a clear colourless solution.

Description After Reconstitution Solution-
0.9 % w/v Sodium Chloride Injection – Clear colourless solution

The recommended diluent for reconstitution of this drug is 0.9% Sodium Chloride Injection without preservatives. The solution should be inspected visually for particulate matter and discoloration, prior to administration, whenever solution or container permits. Finished product is supplied without diluent/reconstitution.

Pharmacodynamics

Mechanism of Action:

Gemcitabine kills cells undergoing DNA synthesis and blocks the progression of cells through the G1/S-phase boundary. Gemcitabine (dFdC), which is a pyrimidine antimetabolite, is metabolized intracellularly by nucleoside kinases to the active diphosphate and triphosphate nucleosides. Gemcitabine diphosphate inhibits ribonucleotide reductase, an enzyme responsible for catalyzing the reactions that generate deoxynucleoside triphosphates for DNA synthesis, resulting in reductions in deoxynucleotide concentrations, including dCTP. Gemcitabine triphosphate competes with dCTP for incorporation into DNA. The reduction in the intracellular concentration of dCTP by the action of the diphosphate enhances the incorporation of gemcitabine triphosphate into DNA (self potentiation). After the gemcitabine nucleotide is incorporated into DNA, only one additional nucleotide is added to the growing DNA strands, which eventually results in the initiation of apoptotic cell death. Cytotoxic activity in cell cultures Gemcitabine shows significant cytotoxic effects against a variety of cultured murine and human tumor cells. Its action is phase-specific such that Gemcitabine primarily kills cells that are undergoing DNA synthesis (S-phase) and under certain circumstances, blocks the progression of cells at the junction of the G1/S phase boundary. In vitro, the cytotoxic effect of Gemcitabine is dependent on both concentration and time.

Pharmacokinetics Absorption

Peak plasma concentrations (obtained within 5 minutes of the end of the infusion) were 3.2 to 45.5 µg/ml. Plasma concentrations of the parent compound following a dose of 1,000 mg/m^2/30-minutes are greater than 5 µg/ml for approximately 30-minutes after the end of the infusion and greater than 0.4µg/ml for an additional hour.

Distribution

The volume of distribution of the central compartment was 12.4 l/m^2 for women and 17.5 l/m^2 for men (inter-individual variability was 91.9%). The volume of distribution of the peripheral compartment was 47.4 l/m^2. The volume of the peripheral compartment was not sensitive to gender. The plasma protein binding was considered to be negligible.

Half-life: This ranged from 42 to 94 minutes depending on age and gender. For the recommended dosing schedule, gemcitabine elimination should be virtually complete within 5 to 11 hours of the start of the infusion. Gemcitabine does not accumulate when administered once weekly.

Biotransformation

Gemcitabine is rapidly metabolised by cytidine deaminase in the liver, kidney, blood

and other tissues. Intracellular metabolism of gemcitabine produces the gemcitabine mono, di and triphosphates (dFdCMP, dFdCDP and dFdCTP) of which dFdCDP and dFdCTP are considered active. These intracellular metabolites have not been detected in plasma or urine. The primary metabolite, 2'-deoxy-2', 2'-difluorouridine (dFdU), is not active and is found in plasma and urine.

Elimination

Systemic clearance ranged from 29.2 l/hr/m^2 to 92.2 l/hr/m^2 depending on gender and age (interindividual variability was 52.2%). Clearance for women is approximately 25% lower than the values for men. Although rapid, clearance for both men and women appears to decrease with age. For the recommended gemcitabine dose of 1000 mg/m2 given as a 30-minute infusion, lower clearance values for women and men should not necessitate a decrease in the gemcitabine dose. Urinary excretion: Less than 10% is excreted as unchanged drug.

Renal clearance was 2 to 7 l/hr/m^2.

During the week following administration, 92 to 98% of the dose of gemcitabine administered is recovered, 99% in the urine, mainly in the form of dFdU and 1% of the dose is excreted in faeces.

dFdCTP kinetics

This metabolite can be found in peripheral blood mononuclear cells and the information below refers to these cells. Intracellular concentrations increase in proportion to gemcitabine doses of 35-350 mg/m^2/30-minutes which give steady state concentrations of 0.4-5µg/ml. At gemcitabine plasma concentrations above 5µg/ml dFdCTP levels do not increase suggesting that the formation is saturable in these cells.

Half-life of terminal elimination: 0.7-12 hours.

dFdU kinetics

Peak plasma concentrations (3-15 minutes after end of 30-minute infusion, 1000 mg/m^2): 28-52µg/ml. Trough concentration following once weekly dosing: 0.07-1.12µg/ml with no apparent accumulation. Triphasic plasma concentration versus time curve, mean half-life of terminal phase 65 hours (range 33-84 hr).

Formation of dFdU from parent compound: 91%-98%.

Mean volume of distribution of central compartment: 18 l/m^2 (range 11-22 l/m^2).

Mean steady state volume of distribution (Vss): 150 l/m^2 (range 96-228 l/m^2).

Tissue distribution: Extensive.

Mean apparent clearance: 2.5 l/hr/m^2 (range 1-4 l/hr/m^2).

Urinary excretion: All.

Gemcitabine and Paclitaxel combination therapy

Combination therapy did not alter the pharmacokinetics of either gemcitabine or paclitaxel.

Gemcitabine and Carboplatin combination therapy

When given in combination with carboplatin the pharmacokinetics of gemcitabine were not altered.

Renal impairment

Mild to moderate renal insufficiency (GFR from 30 ml/min to 80 ml/min) has no consistent, significant effect on gemcitabine pharmacokinetics.

Indication

Gemcitabine is indicated for the treatment of locally advanced or metastatic non-small cell-lung cancer, Gemcitabine is indicated for the treatment of adult patients with locally advanced or metastatic adenocarcinoma of the pancreas. Gemcitabine is indicated for patients with 5-FU refractory pancreatic cancer, Gemcitabine is indicated for the treatment of patients suffering from bladder cancer, at the invasive stage, Gemcitabine, in combination with paclitaxel, is indicated for the treatment of patients with unrespectable, locally recurrent or metastatic breast cancer who have relapsed following adjuvant/neoadjuvant chemotherapy. Prior chemotherapy should have included an anthracycline unless clinically contraindicated, Gemcitabine, in combination with carboplatin, is indicated for the treatment of patients with recurrent epithelial ovarian carcinoma, who have relapse > 6 months, following platinumbase therapy."

Recommended Dose

Dosage

Adults

-Non small-cell lung cancer

Single agent use

The recommended dose is 1000 mg/m^2, given by intravenous infusion.

The administration must be repeated once weekly for three weeks, followed by a one-week rest period. This four-week cycle is then repeated. A dose reduction or delay before each administration of the chemotherapy may be applied, based upon the amount of toxicity experienced by the patient.

Combination use:

Gemcitabine in combination with cisplatin can be administered using two dosage regimens one regimen use a three-week schedule, the other uses a four-week schedule. The three-week schedule is the usual regimen; this three-week cycle uses gemcitabine 1250 mg/m^2 given by 30 minutes intravenous infusion on days 1 and 8, followed by one-week rest period. This threeweek cycle is then repeated. A dosage reduction or delay before each administration of the chemotherapy may be applied, based upon the amount of toxicity experienced by the patient.

The four-week cycle uses Gemcitabine 1000 mg/m^2 given by 30 minutes intravenous infusion on days 1, 8 and 15, followed by one-week rest period. This four-week cycle is then repeated. A dosage reduction or delay before each administration of the chemotherapy may be applied, based upon the amount of toxicity experienced by the patient.

Pancreatic adenocarcinoma

The recommended dose is 1000 mg/m^2, given by 30 minutes intravenous infusion This should be repeated once weekly for 7 weeks, followed by a week rest Subsequent cycles should consist of injections once weekly for 3 consecutive weeks out of every 4 weeks. A dosage reduction or delay before each administration of the chemotherapy may be applied, based upon the amount of toxicity experienced by the patient.

- Bladder cancer, at the invasive stage

The recommended dose of Gemcitabine in combination with cisplatin, is 1000 mg/m^2, given by 30 minutes intravenous infusion on days 1, 8 and 15, followed by one-week rest period for a 28 day cycle. Cisplatin is given at a recommended dose of 70 mg/m^2 on day 2. This four-week cycle is then repeated. A dosage reduction or delay before each administration of the chemotherapy 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 100mg/m^2.

- Breast cancer

Paclitaxel (175 mg/m^2) administered on Day 1 over approximately 3 hours as an intravenous infusion, followed by Gemcitabine (1250 mg/m^2) as a 30-minute intravenous infusion on Days 1 and 8 of each 21 day cycle. Dose reduction with each cycle or within a cycle may be applied based upon the amount of toxicity experienced by the patient.

Ovarian Cancer

Gemcitabine in combination with carboplatin is recommended using Gemcitabine 1000 mg/m^2 administered on Days 1 and 8 of each 21-day cycle as a 30-minute intravenous infusion. After Gemcitabine, carboplatin should be given on Day 1 to attain a target AUC of 4.0 mg/mL/min. Dosage reduction with each cycle or within a cycle may be applied based upon the amount of toxicity experienced by the patient.

For all indications

Patients receiving Gemcitabine should be monitored prior to each dose for platelet, leukocyte and granulocyte counts and, if necessary, the dose of Gemcitabine may be either reduced or withheld in the presence of hematologic toxicity, according to the following scale:

Absolute granulocyte count (x 10^6/l)		Platelet count (x 10^6/l)	% of total dose
>1,000	and	>100,000	100
500-1,000	or	50,000-100,000	75
<500	or	<50,000	0

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

Elderly patients

Gemcitabine has been well tolerated by patients over 65 years of age. The pharmacokinetic data suggest that the metabolism of the drug is not affected by age.

Patients with hepatic or renal impairment

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

Children

Gemcitabine has been studied in limited Phase I and II trials in children in a variety of tumor types. These studies did not provide sufficient data to establish the efficacy and safety of Gemcitabine in children.

Method of Administration

Intravenous route

Gemcitabine is well tolerated during infusion and is usually easy to administer. Reactions at the site of injection are rare: no case of cutaneous necrosis has been reported. If extravasation, the administration must be stopped immediately.

Handling

It is compulsory that injectable solutions of cytotoxic agents be prepared by specialised, trained staff with knowledge of the drugs used, under conditions which ensure protection of the environment, and particularly of the drug handling staff. Preparation requires a room reserved for this purpose. Smoking, eating and drinking are prohibited in this room. The handling staff must have a set of appropriate equipment for handling, particularly long-sleeved coats, protective masks, caps, protective goggles, sterile disposable gloves, worktop protection sheets and waste collection containers and bags. Excreta and vomitus must be handled with care. Pregnant women must be warned and avoid handling cyto-toxic agents. All broken containers must be treated with the same precautions and regarded as contaminated waste. Contaminated waste is to be disposed of by incineration in rigid containers labelled for this purpose.

Instructions for use and handling

The only approved diluent for reconstitution of Gemcitabine sterile powder is 0.9% Sodium Chloride Injection without preservatives. Although no incompatibility has been demonstrated, it is none-the-less recommended that mixing gemcitabine solutions with those of other drugs should be avoided. Due to solubility considerations, the maximum concentration for 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 to the 200 mg vial and at least 25 ml of 0.9% Sodium Chloride Injection to the 1000 mg vial. Shake to dissolve. The appropriate amount of drug may be administered as prepared or further diluted with 0.9% Sodium Chloride Injection. Parenteral drugs should be inspected visually for particulate matter and discoloration, prior to administration. As other cystostatics, Gemcitabine hydrochloride must be handled with care. Unused products must be destroyed according to hospital procedures of cytotoxic waste deal.

Route of Administration

-Parenteral

Contraindication

Concomitant administration of gemcitabine and radiotherapy contarindicated, due to the risk of radiosensitization and of onset of severe pulmonary and oesophageal fibrosis. Cisplatin/Gemcitabine contraindicated in patient with severe renal failure."

Hypersensitivity to the active substance or to any of the excipients

Warning and Precautions

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

Haematological toxicity

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

Patients receiving gemcitabine should be monitored prior to each dose for platelet, leucocyte and granulocyte counts. Suspension or modification of therapy should be considered when drug-induced bone marrow depression is detected.

However, myelosuppression is short-lived and usually does not result in dose reduction and rarely in discontinuation. Peripheral blood counts may continue to deteriorate after gemcitabine administration has been stopped. In patients with impaired bone marrow function, the treatment should be started with caution. As with other cytotoxic treatments, the risk of cumulative bone-marrow suppression must be considered when

gemcitabine treatment is given together with other chemotherapy.

Hepatic and renal impairment

Gemcitabine should be used with caution in patients with hepatic or renal function impairment as there is insufficient information from clinical studies to allow clear dose recommendation for this patient population Administration of gemcitabine in patients with concurrent liver metastases or a pre-existing medical history of hepatitis, alcoholism or liver cirrhosis may lead to exacerbation of the underlying hepatic impairment. Laboratory evaluation of renal and hepatic function (including virological tests) should be performed periodically.

Concomitant radiotherapy

Concomitant radiotherapy (given together or ≤7 days apart)

Live vaccinations

Yellow fever vaccine and other live attenuated vaccines are not recommended in patients treated with gemcitabine.

Posterior reversible encephalopathy syndrome

Reports of posterior reversible encephalopathy syndrome (PRES) with potentially severe consequences have been reported in patients receiving gemcitabine as single agent or in combination with other chemotherapeutic agents.

Acute hypertension and seizure activity were reported in most gemcitabine patients experiencing PRES but other symptoms such as headache, lethargy, confusion and blindness could also be present. Diagnosis is optimally confirmed by magnetic resonance imaging (MRI). PRES was typically reversible with appropriate supportive measures. Gemcitabine should be permanently discontinued and supportive measures implemented including blood pressure control and anti-seizure therapy, if PRES develops during therapy.

Cardiovascular

Due to the risk of cardiac and/or vascular disorders with gemcitabine, particular caution must be exercised with patients presenting a history of cardiovascular events.

Capillary leak syndrome

Capillary leak syndrome has been reported in patients receiving gemcitabine as single agent or in combination with other chemotherapeutic agents. The condition is usually treatable if recognised early and managed appropriately but fatal cases have been reported. The condition involves systemic capillary hyper permeability during which fluid and proteins from the intravascular space leak into the interstitium. Gemcitabine should be discontinued and supportive measures implemented if capillary leak syndrome develops during therapy. Capillary leak syndrome can occur in later cycles and has been associated in the literature with adult respiratory distress syndrome.

Pulmonary

Pulmonary effects, sometimes severe (such as pulmonary oedema, interstitial pneumonitis or adult respiratory distress syndrome (ARDS)) have been reported in association with gemcitabine therapy. If such effects develop, consideration should be made to discontinuing gemcitabine therapy. Early use of supportive care measure may help ameliorate the condition.

Renal

Haemolytic uraemic syndrome

Gemcitabine should be discontinued at the first signs of any evidence of microangiopathic haemolytic anaemia, such as rapidly falling haemoglobin with concomitant thrombocytopenia, elevation of serum bilirubin, serum creatinine, blood urea nitrogen or LDH. Renal failure may not be reversible with discontinuation of therapy and dialysis may be required.

Fertility

A men being treated with gemcitabine are advised not to father a child during and up to 6 months after treatment and to seek further advice regarding cryoconservation of sperm prior to treatment because of the possibility of infertility due to therapy with gemcitabine.

Sodium

Gemcitabine powder for solution for infusion 200mg contains 3.5mg (<1 mmol) sodium per vial. This should be taken into consideration by patients on a controlled sodium diet. Gemcitabine powder for solution for infusion 1000mg contains 17.5mg (<1 mmol) sodium per vial. This should be taken into consideration by patients on a controlled sodium diet.

Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. However, gemcitabine has been reported to cause mild to moderate somnolence,