Gemoxen
Gemcitabine Hydrochloride USP
Aqua

COMPOSITION

Gemoxen Aqua 1 g Injection: Each 10 mL contains Gemcitabine Hydrochloride USP equivalent to Gemcitabine 1 g.

Gemoxen Aqua 200 Injection: Each 2 mL contains Gemcitabine Hydrochloride USP equivalent to Gemcitabine 200 mg.

PHARMACOLOGY

Mechanism of Action: Gemcitabine (dFdC) is metabolised intracellularly by nucleoside kinases to the active diphosphate (dFdCDP) and triphosphate (dFdCTP) nucleosides. The cytotoxic action of Gemcitabine appears to be due to inhibition of DNA synthesis by two actions of dFdCDP and dFdCTP. First, 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 then appears to induce the programmed cellular death process known as apoptosis.

Pharmacokinetic Properties: Peak plasma concentrations (obtained within 5 minutes of the end of the infusion): 3.2 to 45.5 µg/mL. Volume of distribution of the central compartment: 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 the peripheral compartment: 47.4 l/m^2. The volume of the peripheral compartment was not sensitive to gender. Plasma protein binding: Negligible. Systemic clearance: Ranged from 29.2 l/hr/m^2 to 92.2 l/hr/m^2 depending on gender and age (inter-individual variability was 52.2%). Clearance for women is approximately 25% lower than the values for men. Although rapid, clearance for both men and women appears to decrease with age. For the recommended Gemcitabine dose of 1,000mg/m^2 given as a 30 minute infusion, lower clearance values for women and men should not necessitate a decrease in the Gemcitabine dose. Urinary excretion: Less than 10% is excreted as unchanged drug. Renal clearance: 2 to 7 l/hr/m^2. Half-life: 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. Metabolism: 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. dFdCTP Kinetics: This metabolite can be found in peripheral blood mononuclear cells and the information below refers to these cells. Half-life of terminal elimination: 0.7-12 hours. Intracellular concentrations increase in proportion to Gemcitabine doses of 35-350 mg/m^2/30 min, which give steady-state concentrations of 0.4-5 µg/mL. At Gemcitabine plasma concentrations above 5 µg/mL, dFdCTP levels do not increase, suggesting that the formation is saturable in these cells. Parent plasma concentrations following a dose of 1,000mg/m^2/30 min are greater than 5 µg/mL for approximately 30 minutes after the end of the infusion, and greater than 0.4 µg/mL for an additional hour. dFdU Kinetics: Peak plasma concentrations (3-15 minutes after end of 30 minute infusion, 1,000mg/m^2): 28-52 µg/mL. Trough concentration following once weekly dosing: 0.07-1.12 µg/mL, with no apparent accumulation. Triphasic plasma concentration versus time curve, mean half-life of terminal phase: 65 hours (range 33-84 hours). 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.

Overall Elimination: Amount recovered in one week: 92%-98%, of which 99% is dFdU, 1% of the dose is excreted in faeces.

Gemcitabine and Paclitaxel Combination Therapy: Combination therapy did not alter the pharmacokinetics of either Gemcitabine or paclitaxel.

INDICATIONS

Non-Small Cell Lung Cancer: Gemcitabine, in combination with cisplatin, is indicated as a first-line treatment of patients with locally advanced (inoperable Stage IIIA or IIIB) or metastatic (Stage IV) non-small cell lung cancer. Gemcitabine is indicated for the palliative treatment of adult patients with locally advanced or metastatic non-small cell lung cancer.

Pancreatic 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.

Bladder Cancer: Gemcitabine is indicated for treatment of advanced bladder cancer (muscle invasive Stage IV tumors with or without metastases) in combination with cisplatin therapy.

Breast Cancer: Gemcitabine, in combination with paclitaxel, is indicated for the treatment of patients with metastatic breast cancer who have relapsed following adjuvant/neoadjuvant chemotherapy. Prior chemotherapy should have included an anthracycline, unless clinically contra-indicated.

Ovarian Cancer: Gemcitabine in combination with carboplatin, is indicated for the treatment of patients with recurrent epithelial ovarian carcinoma who have relapsed following platinum-based therapy.

DOSAGE & ADMINISTRATION

Gemcitabine is for intravenous use only.

Standard Dosing

Non-Small Cell Lung Cancer: (Single-agent Use): Adults - the recommended dose of Gemcitabine is 1000 mg/m^2, given by 30-minute intravenous infusion. This should be repeated once weekly for three weeks, followed by a one-week rest period. This four-week cycle is then repeated. Dosage reduction with each cycle or within a cycle may be applied based upon the amount of toxicity experienced by the patient.

Non-Small Cell Lung Cancer: (Combination Use): Adults- Gemcitabine, in combination with cisplatin has been investigated using two dosing regimens. One regimen used a three-week schedule and the over used a four-week schedule.

The three-week schedule used Gemcitabine 1250 mg/m^2, given by 30-minute intravenous infusion, on days 1 and 8 of each 21-day cycle. Dosage reduction with each cycle or within a cycle may be applied based upon the amount of toxicity experienced by the patient.

The four-week schedule used Gemcitabine 1000 mg/ m^2, given by 30-minute intravenous infusion, on days 1, 8, and 15 of each 28-day cycle. Dosage 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 Gemcitabine is 1000 mg/m^2, given by 30-minute intravenous infusion. This should be repeated once weekly for up to 7 weeks followed by a week of rest. Subsequent cycles should consist of injections once weekly for 3 consecutive weeks out of every 4 weeks. Dosage reduction with each cycle or within a cycle may be applied based upon the amount of toxicity experienced by the patient.

Bladder Cancer: (Single agent use): Adults - the recommended dose of Gemcitabine is 1250 mg/m^2, given by 30-minute intravenous infusion. The dose should be given on days 1, 8 and 15 of each 28-day cycle. This 4-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.

Bladder Cancer: (Combination use): Adults - the recommended dose for Gemcitabine is 1000 mg/m^2, given by 30-minute infusion. The dose should be given on days 1, 8 and 15 of each 28-day cycle in combination with cisplatin. Cisplatin is given at a recommended dose of 70 mg/m^2 on day 1 following Gemcitabine or day 2 of each 28-day cycle. This 4-week cycle is then repeated. Dosage reduction with each cycle or within a cycle may be applied based upon the amount of toxicity experienced by the patient. A clinical trial showed more myelosuppression when cisplatin was used in doses of 100 mg/m^2.

Breast Cancer: (Combination Use): Adults- Gemcitabine 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 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. Patients should have an absolute granulocyte count of at least 1,500 (x106/L) prior to initiation of Gemcitabine + paclitaxel combination.

Ovarian Cancer: (Combination use): Adults- 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 consistent with 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.

Monitoring, Dose Adjustment or Titration, Methods of Terminating Treatment

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 haematological toxicity, according to the following scale:

Absolute granulocyte count (x106/L)		Platelet count (x 106/L)	% of full dose
>1000	And	>100,000	100
500 to 1000	Or	50,000 to 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 on the amount of toxicity experienced by the patient. Doses should be withheld until toxicity has resolved in the opinion of the physician.

Gemcitabine is well tolerated during the infusion, with only a few cases of injection site reaction reported. There have been no reports of injection site necrosis. Gemcitabine can be easily administered on an outpatient basis.

Elderly Patients: Gemcitabine has been well tolerated in patients over the age of 65. There is no evidence to suggest that dose adjustments, other than those recommended for all patients, are necessary in the elderly, although Gemcitabine clearance and half-life are affected by age.

Renal and Hepatic Impairment: Gemcitabine should be used with caution in patients with impaired renal function or hepatic insufficiency, as there is insufficient information from clinical studies to allow clear 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 Gemcitabine pharmacokinetics.

Preparation for Intravenous Infusion Administration

- Withdraw the calculated dose from the vial and discard any unused portion.
- Prior to administration, dilute the appropriate amount of drug with 0.9% Sodium Chloride Injection to a minimum final concentration of at least 0.1 mg/mL.
- Store diluted Gemcitabine Injection solution for no more than 24 hours at controlled room temperature of 20° to 25°C (68° to 77°F). Discard if not used within 24 hours after dilution.
- Visually inspect for particulate matter or discoloration prior to administration and discard if particulate matter or discoloration is observed.
- No incompatibilities have been observed with infusion bottles or polyvinyl chloride bags and administration sets.

Guidelines for the Safe Handling of Antineoplastic Agents: Cytotoxic preparations should not be handled by pregnant staff. Trained personnel should reconstitute the drug. This should be performed in a designated area. The work surface should be covered with disposable plastic-backed absorbent paper.

Adequate protective gloves, masks, and clothing should be worn. Precautions should be taken to avoid the drug accidentally coming into contact with the eyes. If accidental contamination occurs, the eye should be washed with water thoroughly and immediately.

Large bore needles are recommended to minimise pressure and the possible formation of aerosols. The latter may also be reduced by the use of a venting needle.

Adequate care and precaution should be taken in the disposal of items used to reconstitute Gemoxen. Any unused dry product or contaminated materials should be placed in a high-risk waste bag. Sharp objects (needles, syringes, vials, etc) should be placed in a suitable rigid container. Personnel concerned with the collection and disposal of this waste should be aware of the hazard involved. Waste material should be destroyed by incineration. Any excess drug solution should be flushed directly into a drain with copious amounts of water.

CONTRAINDICATIONS

Gemcitabine is contraindicated in those patients with a known hypersensitivity to the medicine or any of the excipients in the medicinal product.

WARNINGS

Prolongation of the infusion time beyond 60 minutes and more frequent than weekly dosing have been shown to increase toxicity. Gemcitabine can suppress bone marrow function as manifested by leukopenia, thrombocytopenia and anemia, and myelosuppression is usually the dose-limiting toxicity. Patients should be monitored for myelosuppression during therapy. See Dosage and Administration for recommended dose adjustments. Hemolytic-Uremic Syndrome (HUS) has been reported rarely with the use of Gemcitabine

PRECAUTIONS

General: Patients receiving therapy with Gemcitabine should be monitored closely by a physician experienced in the use of cancer chemotherapeutic agents. Most adverse events are reversible and do not need to result in discontinuation, although doses may need to be withheld or reduced. There was a greater tendency in women, especially older women, not to proceed to the next cycle.

Laboratory Tests: Patients receiving Gemcitabine should be monitored prior to each dose with a complete blood count (CBC), including differential and platelet count. Suspension or modification of therapy should be considered when marrow suppression is detected Laboratory evaluation of renal and hepatic function should be performed prior to initiation of therapy and periodically thereafter.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Long-term animal studies to evaluate the carcinogenic potential of Gemcitabine have not been conducted. Gemcitabine induced forward mutations in vitro in a mouse lymphoma (L5178Y) assay and was clastogenic in an in vivo mouse micronucleus assay. Gemcitabine was negative when tested using the Ames, in vivo sister chromatid exchange, and in vitro chromosomal aberration assays, and did not cause unscheduled DNA synthesis in vitro. Gemcitabine I.P. doses of 0.5 mg/kg/day (about 1/700 the human dose on a mg/m^2 basis) in male mice had an effect on fertility with moderate to severe hypospermatogenesis, decreased fertility, and decreased implantations. In female mice fertility was not affected but maternal toxicities were observed at 1.5 mg/kg/day I.V. (about 1/200 the human dose on a mg/m^2 basis) and fetotoxicity or embryolethality was observed at 0.25 mg/kg/day I.V.(about 1/1300 the human dose on a mg/m^2 basis).

Elderly Patients: Gemcitabine clearance is affected by age. There is no evidence, however, that unusual dose adjustments, (i.e., other than those already recommended in the Dosage and Administration section) are necessary in patients over 65, and, in general adverse reaction rates in the single-agent safety database of 979 patients were similar in patients above and below 65. Grade 3 / 4 thrombocytopenia was more common in the elderly.

Gender: Gemcitabine clearance is affected by gender. In the single agent safety database (N=979 patients), however, there is no evidence that unusual dose adjustments (i.e., other than those already recommended in the Dosage and Administration section) are necessary in women. In general, in single agent studies of Gemcitabine adverse reaction rates were similar in men and women, but women, especially older women, were more likely not to proceed to a subsequent cycle and to experience grade 3 / 4 neutropenia and thrombocytopenia.

Pediatric Patients: Gemcitabine has not been studied in pediatric patients. Safety and effectiveness in pediatric patients have not been established.

Patients with Renal or Hepatic Impairment: Gemcitabine should be used with caution in patients with preexisting renal impairment or hepatic insufficiency. Gemcitabine has not been studied in patients with significant renal or hepatic impairment.

Radiation Therapy: Safe and effective regimens for the administration of Gemcitabine with therapeutic doses of radiation have not yet been determined.

Concurrent (given together or 7 days apart): Based on the result of preclinical studies and clinical trials, Gemcitabine has radiosensitising activity. In a single trial, where Gemcitabine at a dose of 1,000mg/m^2 was administered concurrently for up to 6 consecutive weeks with therapeutic thoracic radiation to patients with non-small cell lung cancer, significant toxicity in the form of severe and potentially life-threatening mucositis, especially oesophagitis and pneumonitis, was observed, particularly in patients receiving large volumes of radiotherapy (median treatment volumes 4,795 cm^3). Studies done subsequently have suggested that it is feasible to administer Gemcitabine at lower doses with concurrent radiotherapy with predictable toxicity, such as a Phase II study in non-small cell lung cancer. Thoracic radiation doses of 66Gy were administered with Gemcitabine (600mg/m^2, four times) and cisplatin (80mg/m^2, twice) during 6 weeks. The optimum regimen for safe administration of Gemcitabine with therapeutic doses of radiation has not yet been determined.

Sequential (given>7 days apart): Available information does not indicate any enhanced toxicity with administration of Gemcitabine in patients who receive prior radiation, other than radiation recall. Data suggest that Gemcitabine can be started after the acute effects of radiation have resolved or at least one week after radiation. Available information does not indicate any enhanced toxicity from radiation therapy following Gemcitabine exposure.

SIDE EFFECTS

Common Side Effects

Haematological Toxicity : Because Gemcitabine is a bone marrow suppressant, anaemia, leukopenia, and thrombocytopenia can occur as a result of administration of Gemcitabine. Myelosuppression is usually mild to moderate and is more pronounced for the granulocyte count. While two-thirds of patients experience some anaemia, only 7% have haemoglobin levels drop below 8 g/100 mL. While 19% of patients received transfusions, only 0.2% of patients discontinued because of anaemia. The white blood cell count is depressed in 61% of patients, however only 9% of patients experience WBC's below 2000 cells/mm^3 and only 0.1% discontinued for leukopenia. Sixty-four percent of patients have reduced granulocyte counts and almost 25% drop below 1000 cells/mm^3. Platelet counts are reduced in 21% of patients but only 5% of patients experience counts below 50,000 cells/mm3 and only 0.4% of patients were discontinued due to thrombocytopenia. Previous therapy with cytotoxic agents appears to increase the frequency and severity of the leukopenia, granulocytopenia, and thrombocytopenia. There is no evidence of cumulative haematological toxicity. Anaemia is manageable with the use of conventional transfusions. Dose reduction or omission may be necessary for severe leukopenia or thrombocytopenia (see Dosage and Administration). Rare cases of haemorrhage occurring simultaneously with thrombocytopenia have been reported, but were usually thought to be disease-related. Thrombocythemia is also commonly reported (7.5% of patients), but no patients were discontinued for this event. Febrile neutropenia is also commonly reported.

Hepatic Toxicity: Abnormalities of liver transaminase enzymes occur in about two-thirds of patients, but they are usually mild, non-progressive, and rarely necessitate stopping treatment. Less than 10% of patients experience elevations greater than 5 times normal and only 0.5% of patients were discontinued for abnormalities in liver function. One patient was discontinued for liver failure, but the assessment was complicated by a history of chronic alcoholism. Alanine transaminase (ALT) effects decline over time despite continued treatment. Elevations of alkaline phosphatase greater than 5 times normal occurred in 6.6% of patients but may have been due to bone disorders. Bilirubin values greater than 5 times normal were observed in 1.5% of patients, but ninety percent of patients had normal bilirubin levels.

Gastrointestinal: Nausea, and nausea accompanied by vomiting are each reported in about one-third of patients, respectively. This adverse event requires therapy in about 20% of patients, is rarely dose-limiting, and is easily manageable with standard antiemetics. Only 0.9% of patients report intractable vomiting and only 0.9% of patients discontinued due to nausea and vomiting. Diarrhoea and stomatitis are commonly reported. Diarrhoea (transient to tolerable) was reported by 7% of patients. Intolerable diarrhoea requiring therapy was reported in 0.5% of patients. No patients discontinued treatment because of diarrhoea.

Genito-Urinary Toxicity: Mild proteinuria and haematuria are reported in approximately half the patients, but are rarely clinically significant, and are not usually associated with any change in serum creatinine or blood urea nitrogen. However, a few cases (0.6% of patients) of renal failure of uncertain aetiology have been reported hence Gemcitabine should be used with caution in patients with impaired renal function (see Precautions). Rare cases (0.4%) of possible haemolytic uraemic syndrome have been reported. Cumulative renal toxicity has not been observed.

Pulmonary Toxicity: Dyspnoea occurring within hours following Gemcitabine injection is reported by approximately 10% of patients. This dyspnoea is usually mild and short-lived, rarely dose-limiting, and usually abates spontaneously without any specific therapy. The mechanism of this toxicity is unknown and the relationship to Gemcitabine is not clear. Only 0.6% of patients discontinued due to dyspnoea and only 0.1% of these were believed to be medicine-related. Interstitial pneumonitis has been reported infrequently.

Allergic Toxicity: A rash is seen in approximately 25% of patients and is associated with pruritus in about 10% of patients. The rash is usually mild, not dose-limiting, and responds to local therapy. Desquamation, vesiculation, and ulceration have been reported rarely. Discontinuations for cutaneous toxicity were reported for only 0.3% of patients. Gemcitabine is well tolerated during the infusion with only a few cases of injection site reaction reported. Gemcitabine does not appear to be a vesicant. There have been no reports of injection site necrosis. Bronchospasm is usually mild and transient, but parenteral therapy may be required. Gemcitabine should not be administered to patients with a known hypersensitivity to the medicine (see Contraindications).

Neurotoxicity: Mild to moderate somnolence occurs in approximately 10% of patients. Only 0.1% of patients discontinued for somnolence. Asthenia is frequently reported with other flu symptoms but is also reported as an isolated symptom. Asthenia was cause for discontinuation by 1.4% of patients. Paresthesias are reported in 3.4% of patients, but only 0.2% report these as severe.

Flu Symptoms: An entity resembling influenza is reported by approximately 20% of patients. This is usually mild, short-lived, and rarely dose-limiting with 1.5% of patients reporting this to be severe. Fever, headache, back pain, chills, myalgia, asthenia, and anorexia are the most commonly reported symptoms. Cough, rhinitis, malaise, sweating and insomnia are also commonly reported. Fever and asthenia are also reported frequently as isolated symptoms. The mechanism of this toxicity is unknown. Reports received indicate that paracetamol may produce symptomatic relief. Only 0.1% of patients reported discontinuation because of the flu symptoms. The percentages of patients who discontinued for fever, malaise, or myalgia are reported as 0.4%, 0.3% and 0.1% respectively.

Oedema/Peripheral Oedema: Oedema/peripheral oedema is reported by approximately 30% of patients. Some cases of facial oedema have also been reported. Pulmonary oedema was reported infrequently (1%). Oedema/peripheral oedema is usually mild to moderate, rarely dose-limiting, is sometimes reported as painful and is usually reversible after stopping Gemcitabine treatment. The mechanism of this toxicity is unknown. However, it was not associated with any evidence of cardiac, renal or hepatic failure. Oedema resulted in the discontinuation of 0.7% of patients.

Alopecia: Overall, 86.7% of patients had no hair loss at all. Minimal to moderate hair loss was reported by 13% of patients. Only 0.5% of patients reported complete but reversible alopecia.

Rare Side Effects

The following adverse effects are also reported. Oral toxicity mainly described as soreness or erythema occurred in 7% of patients, however this only required a liquid diet in 0.2% of patients. Mild constipation is reported by 6% of patients. A few cases of hypotension have been reported with only 0.1% of patients discontinued for this event. Irrespective of medicine causality, some cases of myocardial infarction, congestive heart failure, and arrhythmia have been reported in studies. Radiation toxicity has been reported (see Interactions section). Hypersensitivity: anaphylactoid reaction has been reported very rarely.

Cardiovascular: Heart failure has been reported very rarely. Arrhythmias, predominantly supraventricular in nature, have been reported.

Vascular: Clinical signs of peripheral vasculitis and gangrene have been reported very rarely.

Skin And Appendages: Severe skin reactions, including desquamation and bullous skin eruptions, have been reported very rarely.

Injury, Poisoning and Procedural Complications: Radiation toxicity and radiation recall reactions have been reported.

USE IN PREGNANCY & LACTATION

Pregnancy: Pregnancy Category D. Gemcitabine can cause fetal harm when administered to a pregnant woman. Gemcitabine is embryotoxic causing fetal malformations (cleft palate, incomplete ossification) at doses of 1.5 mg/kg/day in mice (about 1/200 the recommended human dose on a mg/m^2 basis). Gemcitabine is fetotoxic causing fetal malformations (fused pulmonary artery, absence of gall bladder) at doses of 0.1 mg/kg/day in rabbits (about 1/600 the recommended human dose on a mg/m^2 basis). Embryotoxicity was characterized by decreased fetal viability, reduced live litter sizes, and developmental delays. There are no studies of Gemcitabine in pregnant women. If Gemoxen is used during pregnancy, or if the patient becomes pregnant while taking Gemoxen, the patient should be apprised of the potential hazard to the fetus.

Nursing Mothers: It is not known whether Gemcitabine or its metabolites are excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions from Gemcitabine in nursing infants, the mother should be warned and a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother and the potential risk to the infant.

USE IN CHILDREN AND ADOLESCENTS

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

DRUG INTERACTIONS

No confirmed interactions have been reported with the use of Gemcitabine. No specific drug interaction studies have been conducted.

OVERDOSAGE

There is no known antidote for overdoses of Gemcitabine. Myelosuppression, paresthesias and severe rash were the principal toxicities seen when a single dose as high as 5700 mg/m^2 was administered by I.V. infusion over 30 minutes every 2 weeks to several patients in a Phase 1 study. In the event of suspected overdose, the patient should be monitored with appropriate blood counts and should receive supportive therapy, as necessary.

STORAGE

Store the vial in original carton below 25°C. Protect from light. Keep out of the reach of children. Do not refrigerate after reconstitution.

PRESENTATION AND PACKAGING

Gemoxen Aqua 1 g Injection: Each box contains one vial of Gemcitabine 1 g.

Gemoxen Aqua 200 Injection: Each box contains one vial of Gemcitabine 200 mg.

Manufactured By
BEACON Pharmaceuticals PLC
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