

Data Sheet

AS-GEMCITABINE

Powder for Injection, gemcitabine 200 mg , 1 g and 2 g (not marketed)

Presentation

AS-Gemcitabine vials 200 mg (not marketed)

Each vial contains gemcitabine hydrochloride equivalent to 200 mg gemcitabine (expressed as free base) in the form of a white to off-white lyophilised sterile powder for reconstitution for intravenous use.

AS-Gemcitabine vials 1 g (not marketed)

Each vial contains gemcitabine hydrochloride equivalent to 1 g gemcitabine (expressed as free base) in the form of a white to off-white lyophilised sterile powder for reconstitution for intravenous use.

AS-Gemcitabine vials 2 g (not marketed)

Each vial contains gemcitabine hydrochloride equivalent to 2 g gemcitabine (expressed as free base) in the form of a white to off-white lyophilised sterile powder for reconstitution for intravenous use.

Uses

Gemcitabine is a nucleoside analogue that exhibits antitumour activity.

Actions

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-potential). 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.

Pharmacokinetics

The following pharmacokinetic parameters were obtained for gemcitabine doses ranging from 500 to 2,592 mg/m² that were infused from 0.4 to 1.2 hours.

Peak Plasma Concentrations (obtained within 5 minutes of the end of the infusion):
3.2 to 45.5 micrograms/mL.

Volume of Distribution of the Central Compartment: 12.4 L/m² for women and 17.5 L/m² for men (inter-individual variability was 91.9%).

Volume of Distribution of the Peripheral Compartment: 47.4 L/m². The volume of the peripheral compartment was not sensitive to gender.

Plasma Protein Binding: negligible.

Systemic Clearance: ranged from 29.2 L/hr/m² to 92.2 L/hr/m² 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 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 medicine.

Renal Clearance: 2 to 7 L/hr/m².

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 to 12 hours.

Intracellular concentrations increase in proportion to gemcitabine doses of 35 to 350 mg/m²/30 min, which give steady state concentrations of 0.4 to 5 micrograms/mL. At gemcitabine plasma concentrations above 5 micrograms/mL, dFdCTP levels do not increase, suggesting that the formation is saturable in these cells. Parent plasma concentrations following a dose of 1000 mg/m²/30 min are greater than 5 micrograms/mL for approximately 30 minutes after the end of the infusion, and greater than 0.4 micrograms/mL for an additional hour.

dFdU Kinetics

Peak plasma concentrations 3 to 15 minutes after end of 30-minute infusion (1000 mg/m²): 28 to 52 micrograms/mL.

Trough concentration following once weekly dosing: 0.07 to 1.12 micrograms/mL, with no apparent accumulation.

Triphasic plasma concentration versus time curve, mean half-life of terminal phase: 65 hours (range 33 to 84 hr).

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

Mean volume of distribution of central compartment: 18 L/m² (range 11 to 22 L/m²).

Mean steady state volume of distribution (V_{ss}): 150 L/m² (range 96 to 228 L/m²).

Tissue distribution: extensive.

Mean apparent clearance: 2.5 L/hr/m² (range 1 to 4 L/hr/m²).

Urinary excretion: all.

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

Indications

Non-Small Cell Lung Cancer

Gemcitabine, alone or in combination with cisplatin, is indicated for the first line treatment of patients with locally advanced or metastatic non-small cell lung cancer.

Pancreatic Cancer

Gemcitabine is indicated for treatment of patients with locally advanced or metastatic adenocarcinoma of the pancreas. Gemcitabine is indicated for patients with 5-FU refractory pancreatic cancer. Patients treated with gemcitabine may derive improvement in survival, significant clinical benefit, or both.

Bladder Cancer

Gemcitabine is indicated for the treatment of patients with bladder cancer.

Breast Cancer

Gemcitabine, in combination with paclitaxel, is indicated for the first line treatment of patients with unresectable, locally recurrent or metastatic breast cancer who have relapsed following adjuvant/neoadjuvant chemotherapy, containing anthracycline, unless clinically contraindicated.

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 and 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/m², 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 other used a four week schedule.

The three-week schedule used gemcitabine 1250 mg/m², 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/m², 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/m², 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/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.

Bladder Cancer (Combination use)

Adults - the recommended dose for gemcitabine is 1000 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 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. More myelosuppression may be expected when cisplatin is used in doses of 100 mg/m².

Breast Cancer (Combination Use)

Adults - gemcitabine in combination with paclitaxel is recommended using paclitaxel (175 mg/m²) administered on Day 1 over approximately 3 hours as an intravenous infusion, followed by gemcitabine (1250 mg/m²) 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/m² 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 (x 10⁶/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.

Children

There is insufficient data to establish the efficacy and safety of gemcitabine in children.

Contraindications

Gemcitabine is contraindicated in those patients with a known hypersensitivity to gemcitabine or any of the excipients in AS-Gemcitabine.

Warnings and Precautions

Warnings

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

Gemcitabine can suppress bone marrow function as manifested by leukopenia, thrombocytopenia and anaemia. However, myelosuppression is short-lived and usually does not result in dose reductions and rarely in discontinuation (see Dosage and Administration and Adverse Effects - Haematological).

Precautions

General

Patients receiving therapy with gemcitabine must be monitored closely. Laboratory facilities should be available to monitor patient status. Treatment for a patient compromised by gemcitabine 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.

Patients receiving gemcitabine should be monitored prior to each dose for platelet, leukocyte, and granulocyte counts. Suspension or modification of therapy should be considered when medicine-induced marrow depression is detected (see Dosage and Administration). Peripheral blood counts may continue to fall after the medicine is stopped.

Laboratory evaluation of renal and hepatic functions should be performed periodically.

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 insufficiency.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term duration animal studies have not been conducted to evaluate the carcinogenic potential of gemcitabine. Cytogenetic damage has been produced by gemcitabine in an *in vivo* assay. Gemcitabine induced forward mutation *in vitro* in a mouse lymphoma (L5178Y) assay. Gemcitabine causes a reversible, dose- and schedule-dependent hypospermatogenesis in male mice. Although animal studies have shown an effect of gemcitabine on male fertility, no effect has been demonstrated on female fertility.

Use During Pregnancy and Lactation

Pregnancy

Category D. Because of the potential for abnormalities with cytotoxic therapy, particularly during the first trimester, gemcitabine must not be used during pregnancy. Studies in experimental animals (mice and rabbits at doses up to 4.5 and 1.6 mg/m²/day IV respectively, administered during the period of organogenesis) have shown teratogenicity and embryotoxicity. Peri- and postnatal studies in mice at doses up to 4.5 mg/m²/day have shown retarded physical development in the offspring.

Women of childbearing age receiving gemcitabine should be advised to avoid becoming pregnant, and to inform the treating physician immediately should this occur.

Lactation

It is not known whether gemcitabine is excreted in human milk, however, studies in lactating rats have shown gemcitabine and/or its metabolites in the milk 10 minutes after an IV dose to the dam. The use of gemcitabine should be avoided in nursing women because of the potential hazard to the infant.

Usage in Children

There is insufficient data to establish the efficacy and safety of gemcitabine in children.

Patients with Renal and Hepatic Impairment

Gemcitabine should be used with caution in patients with impaired renal function or hepatic insufficiency. No studies have been done in patients with significant renal or hepatic impairment. The patient must be advised of the lack of information in patients with significant renal or hepatic impairment (see Dosage and Administration).

Effects on the Ability to Drive and Use Machines

Gemcitabine has been reported to cause mild to moderate somnolence. Patients should be cautioned against driving or operating machinery until it is established that they do not become somnolent.

Adverse Effects

Haematological Toxicity

Because gemcitabine is a bone marrow suppressant, anaemia, leukopenia, and thrombocytopenia can occur as a result of administration of gemcitabine (see Warnings). 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/mm³ and only 0.1% discontinued for leukopenia. Sixty-four percent of patients have reduced granulocyte counts and almost 25% drop below 1000 cells/mm³. 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.

Thrombocytopenia 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 (see Precautions).

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 90% 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.

Mild constipation is reported in 6% of patients.

Renal Toxicity

See Precautions. Clinical findings consistent with the haemolytic uraemic syndrome (HUS) were rarely reported in patients receiving gemcitabine. 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 even with discontinuation of therapy, and dialysis may be required.

Genito-Urinary

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. 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 even with discontinuation of therapy, and dialysis may be required.

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.

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

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 (see 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 (see Precautions).

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.

Other Adverse 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.
- 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. Arrhythmias, predominantly supraventricular in nature, have been reported.
- Radiation toxicity and radiation recall reactions have been reported (see Interactions section).
- Hypersensitivity: anaphylactoid reaction has been reported very rarely.
- Clinical signs of peripheral vasculitis and gangrene have been reported very rarely.
- Severe skin reactions, including desquamation and bullous skin eruptions, have been reported very rarely.

Interactions

Radiotherapy

Concurrent (given together or less than or equal to 7 days 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.

Gemcitabine has radiosensitising activity. In a single trial, where gemcitabine at a dose of 1000 mg/m² 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 4795 cm³). 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 (600 mg/m², four times) and cisplatin (80 mg/m², twice) during 6 weeks. The optimum regimen for safe administration of gemcitabine with therapeutic doses of radiation has not yet been determined in all tumour types.

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

Sequential (given >7 days apart)

Available information does not indicate any enhanced toxicity with administration of gemcitabine in patients who received 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.

Overdosage

There is no antidote for overdosage of gemcitabine. Single doses as high as 5.7 g/m² have been administered by IV 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 should receive supportive therapy, as necessary.

Pharmaceutical Precautions

After reconstitution, vials should be stored at room temperature (15 to 30°C) and should be administered within 24 hours. Discard unused portion. Solutions of reconstituted gemcitabine should not be refrigerated, as crystallisation may occur.

Instructions for Use/Handling

The only approved diluent for reconstitution of sterile gemcitabine hydrochloride is 0.9% Sodium Chloride Injection without preservatives. 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 5 mL of 0.9% Sodium Chloride Injection to the 200 mg vial, 25 mL of 0.9% Sodium Chloride Injection to the 1 g vial or 50 mL of 0.9% Sodium Chloride Injection to the 2 g vial. Shake to dissolve. These dilutions each yield a gemcitabine concentration of 38 mg/mL, which includes accounting for the displacement volume of the lyophilised powder (0.26 mL for the 200 mg vial, 1.3 mL for the 1 g vial or 2.6 mL for the 2 g vial). The total volume upon reconstitution will be 5.26 mL, 26.3 mL or 52.6 mL, respectively.

Complete withdrawal of the vial contents will provide 200 mg, 1 g or 2 g of gemcitabine, respectively. The appropriate amount of medicine may be administered as prepared or further diluted with 0.9% Sodium Chloride Injection.

Solutions of reconstituted gemcitabine should be stored at room temperature (15° to 30°C) and should be administered within 24 hours. Discard unused portion. Solutions of reconstituted gemcitabine should not be refrigerated as crystallisation may occur. Parenteral medicines should be inspected visually for particulate matter and discolouration, prior to administration, whenever solution or container permits.

Procedures for proper handling and disposal of anti-cancer medicines should be considered.

Incompatibilities

The compatibility with other medicines has not been studied.

Medicine Classification

Prescription Medicine

Package Quantities and Storage Conditions

Each AS-Gemcitabine 200 mg , 1 g or 2 g vial is supplied separately.

AS-Gemcitabine for Injection 200 mg, equivalent to 200 mg gemcitabine, is available in a 10 mL glass vial with rubber stopper (not marketed).

AS-Gemcitabine for Injection 1 g, equivalent to 1 g gemcitabine, is available in a 50 mL glass vial with rubber stopper (not marketed).

AS-Gemcitabine for Injection 2 g, equivalent to 2 g gemcitabine, is available in a 100 mL glass vial with rubber stopper (not marketed).

Unconstituted vials of powder for injection, when stored at or below 25°C, have a shelf life of 2 years (24 months from date of manufacture).

Further Information

Description

Gemcitabine hydrochloride is 2'-deoxy-2',2'-difluorocytidine monohydrochloride (β -isomer). The empirical formula for gemcitabine hydrochloride is $C_9H_{11}F_2N_3O_4 \cdot HCl$. It has a molecular weight of 299.66.

Gemcitabine is a white to off-white solid. It is an acidic compound. The free base is soluble in water, slightly soluble in methanol, and practically insoluble in ethanol and polar organic solvents.

After reconstitution with 0.9% Sodium Chloride Injection, the pH of the resulting solution lies in the range of 2.7 to 3.3.

List of Excipients

In addition to the active ingredient gemcitabine hydrochloride, AS-Gemcitabine also contains mannitol and sodium acetate. Hydrochloric acid and/or sodium hydroxide may have been added for pH adjustment.

Preclinical Data

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.

Preclinical Safety Data

In repeat dose studies of up to 6 months in duration in mice and dogs, the principal finding was haematopoietic suppression. These effects were related to the cytotoxic properties of the medicine and were reversible when treatment was withdrawn. The degree of the effect was schedule and dose-dependent.

Name and Address

Saltarello Limited
P. O. Box 51-598
Pakuranga
Auckland 2140

Date of Preparation

9 January 2012