Haxanit 1 g / 200 mg
Gemcitabine 1 g/ 200 mg

GP Pharm

Lyophilized Injectable - Intravenous Use
Argentine Industry - Sale under archived prescription

FORMULA

HAXANIT 1 g, each vial contains:

Gemcitabine (as hydrochloride)	1 g
Mannitol	1 g
Sodium acetate	62.5 mg

HAXANIT 200 mg, each vial contains:

Gemcitabine (as hydrochloride)	200 mg
Mannitol	200 mg
Sodium acetate	12.5 mg

ATC code: L01BC05

THERAPEUTIC ACTION: Antineoplastic

INDICATIONS:

Breast cancer - Gemcitabine is indicated in combination with Paclitaxel for the treatment of patients with metastatic breast cancer, after the failure of a previous adjuvant chemotherapy that included anthracyclines, unless these had been clinically contraindicated.

Non-small cell lung cancer - Gemcitabine is indicated in combination with cisplatin for the treatment of patients with inoperable, locally advanced (Stage IIIA or IIIB), or metastatic (Stage IV) non-small cell lung cancer.

Pancreatic Cancer - Gemcitabine is indicated for treatment in patients with locally advanced (unresectable Stage II or Stage III) or metastatic (Stage IV) adenocarcinoma of the pancreas. Gemcitabine is indicated for patients who have previously been treated with 5-FU.

Ovarian cancer - Indicated in combination with carboplatin for recurrent epithelial ovarian carcinoma in patients who have relapsed after at least six months from carboplatin treatment.

Bladder cancer - In combination with cisplatin it is indicated for the treatment of bladder cancer.

CLINICAL PHARMACOLOGY:

Gemcitabine acts specifically at the cellular phase, primarily killing cells undergoing DNA synthesis (S-phase) and also blocking the progression of cells through the G1 / S phase boundary. Gemcitabine (dFdC) is metabolized intracellularly by nucleoside kinases to active nucleoside diphosphate (dFdCDP) and triphosphate (dFdCTP). The cytotoxic action of gemcitabine is attributed to a combination of two actions of diphosphate and nucleosides triphosphate, leading to inhibition of DNA synthesis.

First, Gemcitabine diphosphate inhibits ribonucleotide reductase, which is solely responsible for catalyzing the reactions that deoxynucleoside triphosphates generate for DNA synthesis. Inhibition of this enzyme by the diphosphate nucleoside causes a reduction in deoxynucleoside concentrations in general, including dCTP.

Second, gemcitabine triphosphate competes with dCTP for incorporation into DNA. In this way, the reduction in the intracellular concentration of dCTP (by the action of diphosphate) enhances the incorporation of gemcitabine triphosphate in DNA (self potentiating).

After gemcitabine is incorporated into DNA, an additional nucleotide is added to the growing strands of DNA. After this addition, there is essentially a complete inhibition in the subsequent synthesis of the

DNA. DNA ε-polymerase is fundamentally incapable of removing gemcitabine and repairing the growing DNA strands (covert strand termination). In CEM/T lymphoblastoid cells, gemcitabine induces internucleosomal DNA fragmentation, one of the hallmarks of programmed cell death.

Human Pharmacokinetics - The disposition of gemcitabine was studied, according to published studies, in 5 patients who received a single infusion of 1000 mg / m² / 30 minutes of radiolabelled drug. Within a week, 92% to 98% of the dose was almost completely recovered in the urine. Gemcitabine (< 10%) and the inactive metabolite of uracil-2'-deoxy-2', 2'-difluoruridine (dFdU), accounted for 99% of the excreted dose. The metabolite dFdU is also found in plasma. The binding of Gemcitabine to plasma proteins is negligible.

The half-life of gemcitabine for short infusions ranged from 32 to 94 minutes, and the value for long infusions ranged from 245 to 638 minutes, depending on age and gender, reflecting a greater increase in volume of distribution with more infusions long. Lower clearance in women and older patients results in higher gemcitabine concentrations for any given dose.

The volume of distribution increased with the length of the infusion. The volume of distribution of gemcitabine was 50 L / m², after infusions lasting <70 minutes, indicating that gemcitabine, after short infusions, is not extensively distributed to tissues.

DOSAGE AND METHOD OF ADMINISTRATION

Gemcitabine is for intravenous use only. Adults

Pancreatic cancer - Gemcitabine should be administered by intravenous infusion at a dose of 1000 mg / m² for 30 minutes once a week for up to 7 weeks (or until toxicity necessitates a reduction or maintenance of the dose), followed by a week off. Subsequent cycles should consist of injections once a week for 3 out of 4 consecutive weeks.

Dosage adjustment is applied based on the degree of hematological toxicity experienced by the patient.

Non-small cell lung cancer - **Gemcitabine should be administered by** intravenous infusion at a dose of 1000 mg / m² for 30 minutes once a week for 3 weeks (or until toxicity requires dose reduction or maintenance), followed by one week Rest. Then the 4-week cycle is repeated.

Dosage adjustment is applied based on the degree of hematological toxicity experienced by the patient.

Breast Cancer - Gemcitabine should be administered intravenously at 1000 mg / m² for 30 minutes on days 1, 8, and 15 of each 21-day cycle. Paclitaxel should be administered at a dose of 175 mg / m² on day 1 as an intravenous infusion 3 hours prior to the gemcitabine infusion. Patients should be monitored before each dose with a complete blood count including differential counts. Patients should have an absolute granulocyte count> / = 1500 x 10⁶ / L and a platelet count> / = 100,000 x 10⁶ / L before each cycle.

Ovarian Cancer - Gemcitabine as intravenous infusion 1000 mg / m² over 30 minutes on days 1 and 8 of each 21-day cycle. Carboplatin AUC 4 should be applied after gemcitabine on day 1.

Dosage adjustment is applied based on the degree of hematological toxicity experienced by the patient.

Bladder cancer - Gemcitabine should be administered intravenously at a dose of 1000 mg / m² for 30 minutes on days 1, 8 and 15 of each 28-day cycle in combination with cisplatin. This is given 70 mg / m² on day 1, followed by gemcitabine on day 2 of the 28-day cycle. The 4 week cycle should be repeated.

Dosage adjustment is applied based on the degree of hematological toxicity experienced by the patient.

Dose Modifications - Dosage adjustment is applied based on the degree of hematological toxicity experienced by the patient. Clearance in women and older patients is reduced and women were somewhat less likely to continue cycles later.

Patients receiving gemcitabine should be monitored prior to each dose with a complete blood count (CBC), including differential and platelet counts. If bone marrow suppression is detected, therapy should be modified or suspended according to the guidelines in the table:

Dose reduction guidelines

Absolute granulocyte count (x10⁶/L)		Platelet count (x 10⁶/L)	% of total dose
>/=1000	y	>/= 100.000	100
500-999	o	50.000-99.000	75
<500	o	< 50.000	Suspend

Laboratory evaluation of kidney and liver function, including serum and transaminase clearance, should be performed before starting treatment and periodically thereafter. Gemcitabine should be administered with caution in patients with evidence of renal or hepatic dysfunction.

Instructions for use / handling: The recommended diluent for the reconstitution of Gemcitabine is 0.9% Sodium Chloride Injection without preservatives. Due to solubility considerations, the maximum concentration for gemcitabine at reconstitution is 40 mg / mL. Reconstitution at concentrations greater than 40 mg / mL can result in incomplete dissolution and should be avoided.

To reconstitute, add 5 mL of 0.9% Sodium Chloride solution for injection for the 200 mg vial or 25 mL of 0.9% Sodium Chloride for injection for the 1.00 g vial. Shake to dissolve. Each of these dilutions produces a concentration of 38 mg / mL of gemcitabine, which includes the volume of the lyophilized powder (0.26 mL for the 200 vial or 1.3 mL for the 1 g vial). The total volume after reconstitution will be 5.26 mL or 26.3 mL, respectively. The adequate amount of drug may be administered in the form prepared or diluted with 0.9% sodium chloride injection solution to concentrations as low as 0.1 mg / mL.

Reconstituted gemcitabine is a clear, colorless solution. After reconstitution with 0.9% Sodium Chloride, the pH of the resulting solution is within 2.7 to 3.3. Parenteral drugs should be visually inspected to see if they have particulate matter in suspension, before administration, whenever the solution and the container allow it. If particulate matter is found, it should not be administered.

When prepared according to directions, gemcitabine solutions are stable for 24 hours at controlled room temperature of 20-25 °C. Discard unused portions. Gemcitabine solutions

Reconstituted products should not be refrigerated, as crystallization may occur.

The compatibility of gemcitabine with other drugs has not been studied. No incompatibilities have been observed with infusion bottles or polyvinyl chloride bags and administration sets.

Procedures for the proper handling and disposal of anticancer drugs should be observed.

CONTRAINDICATIONS:

Gemcitabine is contraindicated in those patients with known hypersensitivity to the drug.

WARNINGS:

Prolonged infusion time and increased dose frequency 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.

PRECAUTIONS:

Laboratory tests: Patients receiving gemcitabine should be monitored prior to each dose with a complete blood count (CBC), including differential and platelet counts. The suspension or modification of therapy should be considered when drug-induced spinal depression is detected.

Laboratory tests of kidney and liver function should be performed before starting treatment and periodically thereafter.

Pediatric patients: The effectiveness of gemcitabine in pediatric patients has not been demonstrated.

Patients with impaired renal or hepatic function: Gemcitabine should be used with caution in patients with impaired hepatic function or with pre-existing impaired renal function. Gemcitabine has not been studied in patients with significant hepatic or renal impairment.

Pregnancy and breast-feeding: Pregnancy Category. Gemcitabine may cause fetal harm when administered to pregnant women. Its use in lactation stage should be avoided due to the potential harm to the infant.

Carcinogenesis, mutagenesis, damage to fertility: Gemcitabine has shown reversible dose effects on male fertility in animals, but not on female fertility. There are no long-term studies evaluating the carcinogenic potential of gemcitabine.

Effects on the ability to operate machinery: Patients should be advised of the possibility that gemcitabine may cause mild to moderate drowsiness.

INTERACTIONS:

Concurrent radiation therapy (or less than 7 days apart): Associated toxicity depends on many factors, but clinical studies suggest that gemcitabine has a radiosensitizing effect.

Sequential radiation therapy (more than 7 days apart): There is no data to indicate increased toxicity when gemcitabine is administered more than 7 days apart after radiation therapy. However, soft tissue injuries associated with the simultaneous or non-use of gemcitabine have been reported.

ADVERSE REACTIONS:

General: A flu-like illness has been reported. The most commonly reported symptoms are fever, headache, back pain, chills, myalgia, asthenia, and anorexia. The following symptoms are also commonly reported: cough, rhinitis, malaise, sweating, and insomnia. Anaphylactoid reactions have been reported very infrequently.

Radiation toxicity has been reported (see interactions section).

Hematologic: As gemcitabine is a bone marrow suppressant, anemia, leukopenia, and thrombocytopenia may occur as a result of gemcitabine administration. Febrile neutropenia is also commonly reported.

Gastrointestinal: Abnormalities in liver function tests are very common, but these are usually mild, not progressive and rarely need to stop treatment. However, gemcitabine should be used with caution in patients with impaired liver function.

Nausea and sometimes accompanied by vomiting occur frequently. This adverse effect is rarely dose-limiting, and is easily manageable with standard antiemetic.

Diarrhea and stomatitis have also been frequently reported.

Hepatobiliary: Liver function tests with abnormalities that include increases in the level of aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma-glutamyl transferase (GGT), alkaline phosphatase, and bilirubin have been reported rarely.

Fever: The total incidence was 41%. This contrasts with the 16% infection rate. This suggests that gemcitabine produces fever in the absence of infection. The fever was almost always associated with infection with the influenza virus.

Renal: Moderate proteinuria and hematuria have been reported frequently.

Respiratory: Dyspnea has been frequently reported. Bronchospasm has been reported rarely after gemcitabine infusion. Interstitial pneumonitis has been reported very infrequently.

Pulmonary effects, sometimes severe (such as pulmonary edema, interstitial pneumonitis, or adult respiratory distress syndrome) in association with gemcitabine therapy. If these effects develop, consideration should be given to discontinuation of Gemcitabine treatment.

Early use of supportive measures can improve the condition.

Genito-urinary: Clinical findings consistent with Hemolytic Uremic Syndrome have been rarely reported in patients receiving gemcitabine.

Gemcitabine should be discontinued at the first symptoms of any microangiopathic evidence of hemolytic anemia, such as a rapid fall in hemoglobin concomitant with thrombocytopenia, elevated serum bilirubin, serum creatinine, urea nitrogen, or LDH. Renal failure may not be reversible even with discontinuation of therapy and dialysis may be required.

Cardiovascular: Edema / peripheral edema has been frequently reported. A few cases of hypotension have been reported. Myocardial infarction, congestive heart failure, and arrhythmia have been reported, but there is no clear evidence that gemcitabine causes cardiac toxicity.

Vascular: Very rarely clinical signs of peripheral vasculitis and gangrene have been reported.

Skin and appendages: Rash has been observed, frequently associated with itching.

The rash is usually mild. Alopecia (usually minimal hair loss) has also been reported frequently. Very rarely severe skin reactions, including peeling and rash, have been reported.

OVERDOSE:

There is no antidote for gemcitabine overdose. The main toxicities that were observed were myelosuppression, paraesthesia and severe rash when a single dose as high as 5.7 g / m² was administered by IV infusion over 30 minutes every two weeks; to some patients in a Phase 1 study. Suspected overdose, the patient should be monitored with adequate blood counts and should receive supportive therapy, as necessary.

"In the event of an overdose, go to the nearest Hospital or contact the Poison Control Centers.

Dial 013 if you reside in the interior of the country (011) -4962-2247 or (011) – 4962-6666

R. Gutierrez Children's Hospital, Sanchez de Bustamante 1399 C.A.B.A.

Specialized care for adults:

(011) -4801-7555 Fernandez Hospital, Cervino3356 C.A.B.A

Hospital A. Posadas (011) -4654-6648 / 4658-7777"

PRESENTATION:

HAXANIT 200 mg: Containers containing 1 ampoule vial.

HAXANIT 1 g: Containers containing 1 ampoule vials.

CONSERVATION:

Store at room temperature and humidity between 15 - 30° C (59° - 86° F).

Do not refrigerate. After adding the diluent solution, it can be stored for 24 hours at room temperature. Do not refrigerate after reconstitution. THE UNUSED FRACTION MUST BE DISCARDED.

This medicine must be used exclusively under a medical prescription and cannot be repeated without a new prescription.

KEEP OUT OF THE REACH OF CHILDREN

MEDICINAL SPECIALTY AUTHORIZED BY THE MINISTRY OF HEALTH. CERTIFICATE N°55.445.

If you have any questions, call 0800-777-0018

GP Pharm

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