Gemcitabine hydrochloride

1. NAME OF THE MEDICINAL PRODUCT
Gemzar 200 mg, freeze-dried powder for parenteral use (i.v.)
Gemzar 1000 mg, freeze-dried powder for parenteral use (i.v.)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
Gemzar 200 mg
Gemcitabine hydrochloride 228 mg.
Equivalent to gemcitabine 200 mg.
Excipients: mannitol, sodium acetate, hydrochloric acid, sodium hydroxide for 1 vial.

Gemzar 1000 mg
Gemcitabine hydrochloride 1140 mg.
Equivalent to gemcitabine 1000 mg.
Excipients: mannitol, sodium acetate, hydrochloric acid, sodium hydroxide for 1 vial.

3. PHARMACEUTICAL FORM
Freeze-dried powder for parenteral use (i.v.)

4. CLINICAL PARTICULARS
4.1. Therapeutic indications
Gemcitabine is indicated for the treatment of patients suffering from:
- locally advanced or metastatic non-small cell lung cancer,
- locally advanced or metastatic adenocarcinoma of the pancreas,
- bladder cancer, at the invasive stage,
- metastatic breast cancer who have relapsed following adjuvant/neoadjuvant chemotherapy, in combination with paclitaxel. Prior chemotherapy should have included an anthracycline unless clinically contraindicated.

4.2. Posology and administration
Dosage
Adults
Non-small cell lung cancer

Single-agent use
The recommended dose is 1000 mg/m², given by 30 minute intravenous infusion.
The administration must be repeated once a week for three weeks, followed by a 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.

Combination use
Gemcitabine, in combination with cisplatin, can be administered using two dosage regimens: one regimen uses a three-week schedule and the other uses a four-week schedule.
The three-week cycle is the usual regimen: this three-week cycle uses gemcitabine 1250 mg/m² given by 30 minute intravenous infusion on days 1 and 8, followed by one-week rest period for each 21-day cycle.
This three-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.
The four-week uses gemcitabine 1000 mg/m² given by 30 minute intravenous infusion on days 1, 8 and 15, followed by one-week rest period for each 28-day cycle. 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 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. 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**

**Combination use**

The recommended dose of gemcitabine, in combination with cisplatin, is 1000 mg/m² given by 30 minute 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/m² 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 100 mg/m².

**Breast cancer**

**Combination use with paclitaxel**

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.

**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:

<table>
<thead>
<tr>
<th>Absolute granulocyte count (x10⁶/L)</th>
<th>Platelet count (x10⁶/L)</th>
<th>% of total dose</th>
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<tbody>
<tr>
<td>&gt;1000 and</td>
<td>&gt;100,000</td>
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<td>500 - 1000 or</td>
<td>50,000 - 100,000</td>
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<td>&lt;500 or</td>
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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.

**Children**

Gemcitabine has not been studied in children.

**Method of Administration**

Intravenous route only.

Gemcitabine is well tolerated during the infusion and is usually easy to administer. Reactions at the site of injection are rare: no cases of cutaneous necrosis have been reported.

If extravasation occurs, the administration must be stopped immediately.

**Handling Procedures**

It is compulsory that injectable solutions of cytotoxic agents are 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 cytotoxic 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 labeled for this purpose.

These provisions may be envisaged within the context of the cancerology network (circular DGS/DH/98 no. 98/188 of 24th March 1998) in collaboration with any suitable structure that complies with the requisite conditions.

**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 cytostatics, gemcitabine hydrochloride must be handled with care.

Unused products must be destroyed according to hospital procedures of cytotoxic waste deal.

4.3. Contraindications
- Hypersensitivity to any ingredient.
- Concomitant administration of gemcitabine and radiation therapy, due to the risk of radiosensitization and of the onset of severe pulmonary and esophageal fibrosis.
- Cisplatin/gemcitabine combination in patients with severe renal failure.

4.4. Warnings and special precautions

Warnings
When they are used consecutively, the possibility of serious radiosensitization calls for an interval of at least 4 weeks between gemcitabine chemotherapy and radiotherapy. This interval can be shortened if required by the patient’s condition.

Increased toxicity has been reported when infusion time is prolonged and recommended interval between doses is reduced.

Like other cytotoxics, gemcitabine can induce bone-marrow suppression, resulting in anemia, leukopenia and thrombocytopenia. This thrombocytopenia is often severe and platelet transfusions can sometimes be necessary. However, the myelosuppression is of short duration, and does not usually require dosage reduction and rarely requires the discontinuation of treatment.

Hypersensitivity: anaphylactoid reaction has been rarely reported.

Precautions
Patients receiving gemcitabine must be closely monitored. A medical laboratory must check their biological parameters. Treatment may be required if the drug produces any toxic effects.

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.

Patients receiving gemcitabine must undergo hematological tests including a differential white blood cell and platelet count before each administration. It may be necessary to suspend or alter the treatment if bone-marrow toxicity induced by the drug is detected (see 4.2 Posology and administration). Peripheral blood levels may continue to deteriorate after treatment has been stopped.

Gemcitabine must be used with caution in patients with liver failure as no studies have been done in patients with hepatic impairment. Renal failure with creatinine clearance values of between 30 ml/min and 80 ml/min has no significant effect on the pharmacokinetics of gemcitabine.

The use of gemcitabine should be avoided in pregnant or nursing women (see 4.6 Pregnancy and breastfeeding).

4.5. Interactions with other drugs and other types of interaction

4.6. Pregnancy and breast-feeding
The safety of gemcitabine has not been established for pregnant women. The drug has been shown to be embryotoxic, fetotoxic and teratogenic in experimental animal studies and so gemcitabine must not
be used during pregnancy or breast-feeding due to the potential risk for the fetus or infant.

4.7. Effects on the ability to drive vehicles and operate machinery
Gemcitabine can induce drowsiness and so patients must avoid driving a vehicle or operating machinery unless the possibility of an effect of this type has been ruled out.

4.8. Adverse events

* Hematological
Gemcitabine can induce bone-marrow suppression, resulting in anemia, leukocytopenia and thrombocytopenia. The bone-marrow suppression is usually mild and mostly affects the granulocyte count. Thrombocytosis is another commonly reported effect.

* Hepatic
Elevations in hepatic transaminases are observed. They are usually mild, transient and rarely necessitate stopping treatment. However, caution is required in patients whose liver function is compromised.

* Eso-gastro-duodenal
Nausea, sometimes accompanied by vomiting. These side effects may call for therapeutic measures in about 20% of cases, but they rarely necessitate dosage reduction and are easily manageable with standard anti-emetics.
Diarrhea and stomatitis.

* Pulmonary
For a few hours after the injection of gemcitabine, patients may experience dyspnea, which is usually mild and brief. It rarely necessitates dosage reduction and usually disappears without any specific treatment. The mechanism of this effect is unknown and its relationship with gemcitabine is not clear.
Cases of pulmonary edema, interstitial pneumonitis and adult respiratory distress syndrome (ARDS) have been reported in association with gemcitabine therapy. The etiology of these effects is unknown. If such effects develop, consideration should be made to discontinuing gemcitabine.

* Renal
Mild proteinuria and hematuria occur in nearly half of the patients, but are rarely clinically significant. These conditions are usually not combined with changes in serum creatinine or uremia. However, some cases of renal failure of uncertain etiology have been reported. No cumulative renal toxicity has been observed (see Precautions).
Clinical findings consistent with the hemolytic uremic syndrome (HUS) were rarely reported in patients receiving gemcitabine. Gemcitabine should be discontinued at the first signs of any evidence of microangiopathic hemolytic anemia such as rapidly falling hemoglobin 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.

* Allergic
A rash can occur and can be associated with itching. The rash is usually mild, and does not necessitate dosage reduction and responds to local treatment. Desquamation, vesiculation and ulceration have occasionally been reported.
Bronchospasm has sometimes been reported. This bronchospasm is usually moderate and transient, but parenteral treatment may be required. Gemcitabine must not be administered to patients with known hypersensitivity to this drug. Anaphylactoid reaction has been reported rarely.

* Cardiac
Cases of myocardial infarction, congestive heart failure and arrhythmia have been reported. A few cases of hypotension have been reported.

* Cutaneous
Severe cutaneo-muscular signs resembling dermatopolymyositis have been reported at a previously irradiated site after sequential administration of radiotherapy and gemcitabine.

* Others
A flu-like syndrome, which is rarely severe, can occur. It is generally of brief duration and rarely
When gemcitabine is administered daily, high mortality among the animals but minimal antitumoral activity is observed. However, if a therapeutic regimen consisting of one administration every three or four days is given, gemcitabine can be administered at non-lethal doses with excellent antitumor activity against a broad spectrum of mouse tumors.

Cell metabolism and mechanisms of action
Gemcitabine (dFdC) is metabolised intracellularly by nucleoside kinase to the active diphosphate (dFdCDP)- and triphosphate (dFdCTP) nucleosides. The cytotoxic effect of gemcitabine seems to be due to the inhibition of DNA synthesis by two mechanisms of action by dFdCDP and dFdCTP. First, dFdCDP inhibits ribonucleotide reductase, which solely catalyses the reactions that produce deoxynucleoside triphosphates for the DNA synthesis. Inhibition of this enzyme by dFdCDP reduces the concentrations of deoxynucleotides in general and, in particular, dCTP. Second, dFdCTP competes with dCTP for incorporation into DNA (self-potentialisation). In the same way, a small amount of gemcitabine may also be incorporated into RNA. Thus, the reduced intracellular concentration of dCTP potentiates the incorporation of dFdCTP into DNA. DNA polymerase epsilon is not able to displace the gemcitabine and repair DNA strand that is formed. When gemcitabine is incorporated into DNA, the DNA strand is increased by one nucleotide. After this addition, the DNA synthesis is completely inhibited (masked termination of the chain). After being incorporated into DNA, gemcitabine induces the process of programmed cell lysis known as apoptosis.

5.2. Pharmacokinetic properties
Pharmacokinetics of gemcitabine
The plasma peaks found immediately after the administration of a dose of 1000 mg/m² infused over 30 minutes range from 10 to 40 μg/ml. It has a terminal half-life of 17 minutes (range: 11 to 26 minutes). The mean distribution volume of the central compartment is 11 L/m² (range: 5 to 21 L/m²) and the mean distribution volume at steady state (Vss) is 17 L/m² (range: 9 to 30 L/m²). Binding to plasma proteins is requires a dosage reduction. Fever, headache, back pain, chill, 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 as isolated symptoms. The underlying mechanism of this toxicity is unknown. The symptoms may be relieved with paracetamol.

Peripheral edema, very rarely facial edema. Peripheral edema is usually moderate, and rarely necessitates dosage reduction, but may be painful; it is usually reversible after stopping gemcitabine treatment. The underlying mechanism of this toxicity is unknown. This adverse reaction is not associated with signs of cardiac, hepatic or renal insufficiency. The following side effects are also commonly reported: alopecia (usually very slight) and drowsiness.

4.9. Overdose
There is no known antidote to gemcitabine. Single doses of up to 5.7 g/m² have been administered as intravenous infusions over 30 minutes every two weeks with clinically acceptable toxicity. If there is a suspicion of overdose then the patient’s blood counts should be monitored and adequate treatment given as required.

5. PHARMACOLOGICAL PROPERTIES
5.1. Pharmacodynamic properties
Antimetabolite
(L: antineoplastic drugs - immunosuppressants).

In-vitro cytotoxicity activity
Gemcitabine has a significant cytotoxic effect on various murine cells and cultured human tumor cells. Gemcitabine is a specific antimetabolic of the S phase of the cell cycle (DNA synthesis phase); in some circumstances it prevents cells from progressing beyond the G1/S phase. In vitro, the cytotoxic effect of gemcitabine depends on both concentration and time.

Preclinical antitumor activity
In animal models of tumors, antitumoral activity of gemcitabine depends on the administration regimen.
The plasma concentration of gemcitabine following a dose of 1000 mg/m²/30 min remains above 5 μg/ml for nearly 30 minutes after the end of the infusion and over 0.4 μg/ml for the following hour. **Kinetics of dFdU**

The plasma peak occurs 3 to 15 minutes after termination of an infusion of 1000 mg/m² over 30 minutes and ranges from 28 to 52 μg/ml. The lowest concentrations after once weekly dosing range from 0.07 to 1.12 μg/ml, with no apparent accumulation. The plasma concentrations diminish following a three-phase pattern. The mean half-life of the terminal phase is 65 hours (range: 33 to 84 hours). The dFdU formed accounts for 91 to 98% of the clearance of gemcitabine. The mean volume of distribution of the central compartment is 18 L/m² (range: 11 to 22 L/m²) and the mean distribution volume at steady state (Vss) is 150 L/m² (range: 96 to 228 L/m²). The tissue distribution is considerable and the mean apparent clearance corresponds to 2.5 L/h/m² (range: 1 to 4 L/h/m²). It is excreted by urinary route. **Global excretion**

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% is excreted in the feces.

5.3. Preclinical safety data

In repeated-dose studies in the mouse and dog, some of which lasted as long as 6 months, the main observation was suppression of hematopoiesis. These effects were related to the cytotoxic properties of the substance and were reversible when the treatment was stopped. The severity of the effect was dependent on the dose and dosage interval.

**Oncogenicity, mutagenicity, fertility**

In one in vivo test, gemcitabine caused cytogenetic damage. Gemcitabine induced genetic mutations in a mouse lymphoma in-vitro test (L5178Y). Gemcitabine induces reversible low spermatogenesis in male mice, which depends on the dose and dosage interval. Although animal studies demonstrated that gemcitabine has an impact on male fertility, no corresponding effect was seen on female fertility.
6. PHARMACEUTICAL PARTICULARS

6.1. Incompatibilities
Although no incompatibility has been demonstrated, it is none-the-less recommended that mixing gemcitabine solutions with those of other drugs should be avoided.

6.2. Shelf-life
3 years

6.3. Special precautions for storage
This medicinal product must be stored at a temperature which never goes above 30°C.
The reconstituted solutions must be stored at a temperature which never goes above 30°C, and must be used within 24 hours. Solutions of reconstituted gemcitabine should not be refrigerated, as crystallization may occur.

6.4. Nature and contents of the container
Type I glass vial with bromobutyl stopper.

6.5. Instructions for use and handling
A series of precautions are called for when this cytotoxic is handled by the nursing or medical staff, which ensure the protection of the person handling it and the environment (see 4.2 Posology and administration).

7. DATE APPROVED/REVISED
March 2004
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