SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Gemcitabine; Lyophilized powder for injection 200 mg/vial

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains:
Gemcitabine hydrochloride equivalent to gemcitabine 200 mg

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Lyophilized powder for injection

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

- Gemcitabine is indicated for the treatment of locally advanced or metastatic bladder cancer in combination with cisplatin.
- Gemcitabine is indicated for the treatment of patients with locally advanced or metastatic adenocarcinoma of the pancreas.
- Gemcitabine, in combination with cisplatin is indicated as the first line treatment of patients with locally advanced or metastatic non-small cell lung cancer (NSCLC). Gemcitabine monotherapy can be considered in elderly patients or those with performance status 2.
- Gemcitabine, in combination with paclitaxel, is indicated for the treatment of patients with unresectable, locally recurrent or metastatic breast cancer who have relapsed following adjuvant/neoadjuvant chemotherapy. Prior chemotherapy should have included an anthracycline unless clinically contraindicated.
- Gemcitabine is indicated for the treatment of patients with locally advanced or metastatic epithelial ovarian carcinoma, in combination with carboplatin, in patients with relapsed disease following a recurrence-free interval of at least 6 months after platinum-based, first-line therapy.

4.2 Posology and method of administration

Gemcitabine should only be prescribed by a physician qualified in the use of anticancer chemotherapy.

Recommended posology

Bladder cancer

Combination use

The recommended dose for gemcitabine is 1,000 mg/m^2, given by 30-minutes infusion. The dose should be given on day 1, 8 and 15 of each 28-days 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-days cycle. This 4-weeks cycle is then repeated. Dosage reduction with each cycle or within a cycle may be applied based upon the grade of toxicity experienced by the patient.

Pancreatic cancer

The recommended dose of gemcitabine is 1,000 mg/m^2, given by 30-minutes 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 grade of toxicity experienced by the patient.

Non-small cell lung cancer
Monotherapy
The recommended dose of gemcitabine is 1,000 mg/m^2, given by 30-minutes intravenous infusion. This should be repeated once weekly for 3 weeks, followed by a 1-week rest period. This 4-weeks cycle is then repeated. Dosage reduction with each cycle or within a cycle may be applied based upon the grade of toxicity experienced by the patient.

Combination use
The recommended dose for gemcitabine is 1,250 mg/m^2 body surface area given as a 30-minutes intravenous infusion on day 1 and 8 of the treatment cycle (21 days). Dosage reduction with each cycle or within a cycle may be applied based upon the grade of toxicity experienced by the patient. Cisplatin has been used at doses between 75-100 mg/m^2 once every 3 weeks.

Breast cancer
Combination use
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 (1,250 mg/m^2) as a 30-minutes intravenous infusion on day 1 and 8 of each 21-days cycle. Dose reduction with each cycle or within a cycle may be applied based upon the grade of toxicity experienced by the patient. Patients should have an absolute granulocyte count of at least 1,500 (x 10^6/l) prior to initiation of gemcitabine + paclitaxel combination.

Ovarian cancer
Combination use
Gemcitabine in combination with carboplatin is recommended using gemcitabine 1,000 mg/m^2 administered on day 1 and 8 of each 21-days cycle as a 30-minutes intravenous infusion. After gemcitabine, carboplatin will be given on day 1 consistent with a target Area Under Curve (AUC) of 4.0 mg/ml.minute. Dosage reduction with each cycle or within a cycle may be applied based upon the grade of toxicity experienced by the patient.

Monitoring for toxicity and dose modification due to toxicity
Dose modification due to nonhematological toxicity
Periodic physical examination and checks of renal and hepatic functions should be made to detect nonhematological toxicity. Dosage reduction with each cycle or within a cycle may be applied based upon the grade of toxicity experienced by the patient. In general, for severe (Grade 3 or 4) nonhematological toxicity, except nausea/vomiting, therapy with gemcitabine should be withheld or decreased depending on the judgement of the treating physician. Doses should be withheld until toxicity has resolved in the opinion of the physician.

For cisplatin, carboplatin, and paclitaxel dosage adjustment in combination therapy, please refer to the corresponding Summary of Product Characteristics.

Dose modification due to hematological toxicity

Initiation of a cycle

For all indications, the patient must be monitored before each dose for platelet and granulocyte counts. Patients should have an absolute granulocyte count of at least 1,500 (x 10^6/l) and platelet account of 100,000 (x 10^6/l) prior to the initiation of a cycle.

Within a cycle

Dose modifications of gemcitabine within a cycle should be performed according to the following tables:

Dose modification of gemcitabine within a cycle for bladder cancer, NSCLC, and pancreatic cancer, given in monotherapy or in combination with cisplatin			
Absolute granulocyte count (x 10^6/l)		**Platelet count (x 10^6/l)**	**Percentage of standard dose of gemcitabine (%)**
≥1,000	and	≥100,000	100
500- <1,000	or	50,000- <100,000	75
<500	or	<50,000	Omit dose*

*Treatment omitted will not be re-instated within a cycle before the absolute granulocyte count reaches at least 500 (x10^6/l) and the platelet count reaches 50,000 (x10^6/l).

Dose modification of gemcitabine within a cycle for breast cancer, given in combination with paclitaxel			
Absolute granulocyte count (x 10^6/l)		**Platelet count (x 10^6/l)**	**Percentage of standard dose of gemcitabine (%)**
≥1,200	and	>75,000	100
1,000- <1,200	or	50,000- 75,000	75
700- <1,000	and	≥50,000	50
<700	or	<50,000	Omit dose*

*Treatment omitted will not be re-instated within a cycle. Treatment will start on day 1 of the next cycle once the absolute granulocyte count reaches at least 1,500 (x10^6/l) and the platelet count reaches 100,000 (x10^6/l).

Dose modification of gemcitabine within a cycle for ovarian cancer, given in combination with carboplatin			
Absolute granulocyte count (x 10^6/l)		**Platelet count (x 10^6/l)**	**Percentage of standard dose of gemcitabine (%)**
≥1,500	and	≥100,000	100
1,000- <1,500	or	75,000- <100,000	50
<1,000	or	<75,000	Omit dose*

*Treatment omitted will not be re-instated within a cycle. Treatment will start on day 1 of the next cycle once the absolute granulocyte count reaches at least 1,500 (x10^6/l) and the platelet count reaches 100,000 (x10^6/l).

Dose modifications due to hematological toxicity in subsequent cycles, for all indications

The gemcitabine dose should be reduced to 75% of the original cycle initiation dose, in the case of the following hematological toxicities:

- Absolute granulocyte count < 500 x 10^6/l for more than 5 days
- Absolute granulocyte count < 100 x 10^6/l for more than 3 days
- Febrile neutropenia
- Platelets < 25,000 x 10^6/l
- Cycle delay of more than 1 week due to toxicity.

Method of administration

Gemcitabine is tolerated well during infusion and may be administered ambulant. If extravasation occurs, generally the infusion must be stopped immediately and started again in another blood vessel. The patient should be monitored carefully after the administration.

For instructions on reconstitution of the medicinal product before administration, see section 6.6.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients.
- Breast-feeding.

4.4 Special warnings and precautions for use

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

Hematological toxicity

Gemcitabine can suppress bone marrow function as manifested by leucopenia, thrombocytopenia, and anemia. Patients receiving gemcitabine should be monitored prior to each dose for platelet, leucocyte, and granulocyte counts. Suspension or modification of therapy should be considered when drug-induced bone marrow depression is detected (see **Dosage and administration**).

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

Hepatic insufficiency
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.
Laboratory evaluation of renal and hepatic function (including virological tests) should be performed periodically.
Gemcitabine should be used with caution in patients with hepatic insufficiency or with impaired renal function as there is insufficient information to allow clear dose recommendation for this patient population (see **Dosage and administration**).

Concomitant radiotherapy
Concomitant radiotherapy (given together or ≤7 days apart): Toxicity has been reported (see **Drug interactions** for details and recommendations for use).

Live vaccinations
Yellow fever vaccine and other live attenuated vaccines are not recommended in patients treated with gemcitabine (see **Drug interactions**).

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

Capillary leak syndrome (CLS)
Capillary leak syndrome has been reported in patients receiving gemcitabine as single agent or in combination with chemotherapeutic agents. The condition is usually treatable if recognized early and managed appropriately, but fatal cases have been reported. The condition involves systemic capillary hyperpermeability during which fluid and protiens from the intravascular space leak into the interstitium. The clinical features include generalized edema, weight gain, hypoalbuminemia, severe hypotension, acute renal impairment, and pulmonary edema. Gemcitabine should be discontinued and supportive measures implemented if capillary leak syndrome develops during therapy. Capillary leak syndrome can occur in later cycles and has been associated in the literature with acute respiratory distress syndrome.

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

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

Pulmonary

Pulmonary effects, sometimes severe (such as pulmonary fibrosis, pulmonary edema, interstitial pneumonitis, or acute 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 therapy. Early use of supportive care measure may help ameliorate the condition.

Renal

Hemolytic uremic syndrome

Clinical findings consistent with the hemolytic uremic syndrome (HUS) were rarely reported in patients receiving gemcitabine (see **Adverse reactions**). 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 with discontinuation of therapy and dialysis may be required.

Sodium

Gemcitabine 200 mg lyophilized powder for injection contains 4.66 mg (<1 mmol) sodium per vial. This should be taken into consideration by patients on a controlled sodium diet.

4.5 Interaction with other medicinal products and other forms of interaction

When calcium folinate is given in conjuction with a folic acid antagonist (e.g., co-trimoxazole, pyrimethamine), the efficacy of the folic acid antagonist may either be reduced or completely neutralized.

Calcium folinate may diminish the effect of antiepileptic substances: phenobarbital, primidone, phenytoin, and succinimides, and may increase the frequency of seizures (a decrease of plasma levels of enzymatic inductor anticonvulsant drugs may be observed because the hepatic metabolism is increased as folates are one of the cofactors.

(see Warnings and precautions and Adverse reactions)

Concomitant administration of calcium folinate with 5-fluorouracil has been shown to enhance the efficacy and toxicity of 5-fluorouracil.

(see Dosage and administrations, Warnings and precautions, and Adverse reactions).

4.6 Fertility, pregnancy and lactation

Fertility

Gemcitabine caused hypospermatogenesis in male mice. Therefore, men being treated with gemcitabine are advised not to father a child during and up to 6 months after treatment and to seek further advice regarding cryoconservation of sperm prior to treatment because of the possibility of infertility due to therapy with gemcitabine.

Pregnancy
There are no adequate data from the use of gemcitabine in pregnant women. This substance should not be used during pregnancy unless clearly necessary. Women should be advised not to become pregnant during treatment with gemcitabine and to warn their attending physician immediately, should this occur after all.

Breast-feeding
It is not known whether gemcitabine is excreted in human milk and adverse effects on the suckling child cannot be excluded. Breast-feeding must be discontinued during gemcitabine therapy.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. However, gemcitabine has been reported to cause mild to moderate somnolence, especially in combination with alcohol consumption. Patients should be cautioned against driving or operating machinery until it is established that they do not become somnolent.

4.8 Undesirable effects

The most commonly reported adverse drug reactions associated with gemcitabine treatment include: nausea with or without vomiting, raised liver transaminases (AST/ALT) and alkaline phosphatase; proteinuria and hematuria; dyspnea (highest incidence in lung cancer patients); allergic skin rashes and are associated with itching.

The frequency and severity of the adverse reactions are affected by the dose, infusion rate, and intervals between doses (see **Warnings and precautions**). Dose-limiting adverse reactions are reductions in thrombocyte, leucocyte, and granulocyte counts (see **Dosage and administration**).

Frequencies are defined as:
- Very common (≥1/10)
- Common (≥1/100 to <1/10)
- Uncommon (≥1/1,000 to <1/100)
- Rare (≥1/10,000 to <1/1,000)
- Very rare (<1/10,000)
- Not known (cannot be estimated from the available data*)*

The following list of adverse reactions within each frequency grouping is presented in order of decreasing seriousness.

Blood and lymphatic system disorders
- *Very common*: leucopenia (neutropenia grade 3 and 4), bone-marrow suppression is usually mild to moderate and mostly affects the granulocyte

count (see **Dosage and administration** and **Warnings and precautions**), thrombocytopenia, anemia.
- *Common*: febrile neutropenia.
- *Very rare*: thrombocytosis, thrombotic microangiopathy.

Immune system disorders
- *Very rare*: anaphylactoid reaction.

Infections and infestations
- *Common*: infections.
- *Not known*: sepsis.

Metabolism and nutrition disorders
- *Common*: anorexia.

Nervous system disorders
- *Common*: headache, insomnia, somnolence.
- *Very rare*: posterior reversible encephalopathy syndrome (see **Warnings and precautions**).
- *Not known*: cerebrovascular accident.

Cardiac disorders
- *Rare*: myocardial infarction.
- *Not known*: arrhythmias, predominantly supraventricular in nature, heart failure.

Vascular disorders
- *Rare*: hypotension.
- *Very rare*: capillary leak syndrome (see **Warnings and precautions**).
- *Not known*: clinical signs of peripheral vasculitis and gangrene.

Respiratory, thoracic, and mediastinal disorders
- *Very common*: dyspnea (usually mild and passes rapidly without treatment).
- *Common*: cough, rhinitis.
- *Uncommon*: interstitial pneumonitis (see **Warnings and precautions**), bronchospasm (usually mild and transient but may require parenteral treatment).
- *Not known*: pulmonary edema, acute respiratory distress syndrome (see **Warnings and precautions**).

Gastrointestinal disorders
- *Very common*: vomiting, nausea.
- *Common*: diarrhea, stomatitis and ulceration of the mouth, constipation.
- *Not known*: ischemic colitis.

Hepatobiliary disorders
- *Very common*: elevation of liver transaminases (AST and ALT) and alkaline phosphatase.
- *Common*: increased bilirubin.

- *Rare*: increased gamma-glutamyl transferase (GGT).
- *Not known*: serious hepatotoxicity, including liver failure and death.

Skin and subcutaneous tissue disorders
- *Very common*: allergic skin rash frequently associated with pruritus, alopecia.
- *Common*: itching, sweating.
- *Rare*: ulceration, vesicle and sore formation, scaling.
- *Very rare*: severe skin reactions, including desquamative and bullous skin eruptions.
- *Not known*: pseudocellulitis, Lyell's syndrome, Stevens-Johnson syndrome.

Musculoskeletal and connective tissue disorders
- *Common*: back pain, myalgia.

Renal and urinary disorders
- *Very common*: hematuria, mild proteinuria.
- *Not known*: renal failure (see **Warnings and precautions**), hemolytic uremic syndrome (see **Warnings and precautions**).

General disorders and administration site conditions
- *Very common*: influenza-like symptoms (the most common symptoms are fever, headache, chills, myalgia, asthenia, and anorexia). Cough, rhinitis, malaise, perspiration, and sleeping difficulties have also been reported. Edema/peripheral edema including facial edema. Edema is usually reversible after stopping treatment.
- *Common*: fever, asthenia, chills.
- *Rare*: injection site reactions (mainly mild in nature).

Injury, poisoning, and procedural complications
- Radiation toxicity (see **Drug interactions**)
- *Not known*: radiation recall.

Combination use in breast cancer
The frequency of grade 3 and 4 hematological toxicities, particularly neutropenia, increases when gemcitabine is used in combination with paclitaxel. However, the increase in these adverse reactions is not associated with an increased incidence of infections or hemorrhagic events. Fatigue and febrile neutropenia occur more frequently when gemcitabine is used in combination with paclitaxel. Fatigue, which is not associated with anemia, usually resolves after the first cycle.
The adverse reactions of combination use in breast cancer are as follows:
- Anemia
- Thrombocytopenia
- Neutropenia
- Febrile neutropenia
- Fatigue
- Diarrhea
- Motor neuropathy
- Sensory neuropathy.

Combination use in bladder cancer
The adverse reactions of combination use in bladder cancer are as follows:
- Anemia
- Thrombocytopenia
- Nausea and vomiting
- Diarrhea
- Infection
- Stomatitis.

Combination use in ovarian cancer
The adverse reactions of combination use in ovarian cancer are as follows:
- Anemia
- Neutropenia
- Thrombocytopenia
- Leucopenia
- Hemorrhage
- Febrile neutropenia
- Infection without neutropenia.

4.9 Overdose

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group*:*
Pyrimidine analogues

ATC code:
L01BC05

Mechanism of action and pharmacodynamic effects

Cytotoxic activity in cell cultures
Gemcitabine shows significant cytotoxic effects against a variety of cultured murine and human tumor cells. Its action is phase-specific such that gemcitabine primarily kills cells that are undergoing DNA synthesis (S-phase) and, under certain circumstances, blocks the progression of cells at the junction of the G1/S phase boundary. *In vitro*, the cytotoxic effect of gemcitabine is dependent on both concentration and time.

Antitumoral activity in preclinical models
In animal tumor models, antitumoral activity of gemcitabine is schedule-dependent. When gemcitabine is administered daily, high mortality among the animals but minimal antitumoral activity is observed. If, however, gemcitabine is

given every third or fourth day, it can be administered in non-lethal doses with substantial antitumoral activity against a broad spectrum of mouse tumors.

Mechanism of action

Cellular metabolism and mechanism of action: gemcitabine (dFdC), which is a pyrimidine antimetabolite, is metabolized intracellularly by nucleoside kinase to the active diphosphate (dFdCDP) and triphosphate (dFdCTP) nucleosides. The cytotoxic effect of gemcitabine is due to inhibition of DNA synthesis by two mechanisms of action by dFdCDP and dFdCTP. First, dFdCDP inhibits ribonucleotide reductase, which is uniquely responsible for catalyzing the reactions that produce deoxynucleoside triphosphates (dCTP) for DNA synthesis. Inhibition of this enzyme by dFdCDP reduces the concentration of deoxynucleosides in general and, in particular, dCTP. Second, dFdCTP competes with dCTP for incorporation into DNA (self-potentiation).

Likewise, 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 lacks the ability to eliminate gemcitabine and to 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 appears to induce the programmed cell death process known as apoptosis.

5.2 Pharmacokinetic properties

Absorption

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

Distribution

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

The plasma protein binding was considered to be negligible.

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

Metabolism

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

Elimination

Systemic clearance ranged from 29.2 l/hour/m^2 to 92.2 /hour/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 1,000 mg/m^2 given as a 30-minutes infusion, lower clearance values for women and men should not necessitate a decrease in the gemcitabine dose.

Urinary excretion: Less than 10% is excreted as unchanged drug. Renal clearance was 2 to 7 l/hour/m^2.

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

5.3 Preclinical safety data

Not applicable

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Mannitol
Sodium acetate trihydrate
Sodium hydroxide 1 N
Hydrochloric acid 1 N
Water for injection

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section ***Method of administration***.

6.3 Shelf life

2 years.

Shelf-life after reconstitution

From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at room temperature, unless reconstitution (and further dilution, if applicable) has taken place in controlled and validated aseptic conditions.

Solutions of reconstituted gemcitabine should not be refrigerated, as crystallization may occur.

6.4 Special precautions for storage

Store at temperatures below 30°C.

For storage conditions after reconstitution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

10 ml type I clear glass vials with neck 20 mm closed with 20 mm bromo butyl lyo rubber stopper and sealed with 20 mm flip off seal.

6.6 Special precautions for disposal and other handling

Handling

The normal safety precautions for cytostatic agents must be observed when preparing and disposing of the infusion solution. Handling of the solution for infusion should be done in a safety box and protective coats and gloves should be used. If no safety box is available, the equipment should be supplemented with a mask and protective glasses.

If the preparation comes into contact with the eyes, this may cause serious irritation. The eyes should be rinsed immediately and thoroughly with water. If there is lasting irritation, a doctor should be consulted. If the solution is spilled on the skin, rinse thoroughly with water.

Instructions for reconstitution (and further dilution, if performed)

The only approved diluent for reconstitution of gemcitabine sterile powder is sodium chloride 9 mg/ml (0.9%) solution for 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.

- Use aseptic technique during the reconstitution and any further dilution of gemcitabine for intravenous infusion administration.
- To reconstitute, add 5 ml of sterile sodium chloride 9 mg/ml (0.9%) solution for injection, without preservative, to the 200 mg vial. The total volume after reconstitution is 5.26 ml. This yields a gemcitabine concentration of 38 mg/ml, which includes accounting for the displacement volume of the lyophilized powder. Shake to dissolve. Further dilution with sterile sodium chloride 9 mg/ml (0.9%) solution for injection, without preservative can be done. Reconstituted solution is a clear colorless to light straw-colored solution.
- Parenteral medicinal products should be inspected visually for particulate matter and discoloration prior to administration. If particulate matter is observed, do not administer.

Any unused product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Bahary Pharmacy Limited
Pugu Road, Industrial Area, P.O.Box 40591, Dar es Salaam, Tanzania
Telephone : +255 22 2182859
+255 22 2180076

Manufacturing site :
PT Fonko International Pharmaceuticals
Kawasan Industri Jababeka II, Jl. Industri Selatan V, Blok PP No.7, Cikarang Selatan,
Bekasi, Indonesia
Telephone : +62-21 29566111

8. MARKETING AUTHORISATION NUMBER(S)

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10. DATE OF REVISION OF THE TEXT