PROFESSIONAL INFORMATION FOR HUMAN MEDICINES

SCHEDULING STATUS

S4

1 NAME OF THE MEDICINE

GEMCITABINE 200 mg RTU FRESENIUS

GEMCITABINE 1 g RTU FRESENIUS

GEMCITABINE 2 g RTU FRESENIUS

Concentrate for solution for infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Active ingredient: Each 1 ml of concentrated solution contains 38 mg gemcitabine (as hydrochloride).

Presentation	Strength	Quantity of gemcitabine (as hydrochloride)	Volume of Solution
200 mg/5,3 ml	38 mg/ml	200 mg	5,3 ml
1 g/26,3 ml	38 mg/ml	1 g	26,3 ml
2 g/52,6 ml	38 mg/ml	2 g	52,6 ml

Excipients with known effect: Each ml of concentration contains up to 0,46 mg sodium (see section 4.4).

Sugar-free.

For a full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Concentrate for solution for infusion: A clear, colourless or light straw-coloured solution, practically free from visible particles with a pH of 7,0 to 9,0.

Reconstituted solution: A clear and colourless solution.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

- **GEMCITABINE FRESENIUS RTU** is indicated for the treatment of patients with locally advanced or metastatic non-small cell lung cancer (NSCLC);
- **GEMCITABINE FRESENIUS RTU** is indicated as first-line treatment for patients with locally advanced (non-resectable Stage II or Stage III) or metastatic (Stage IV) adenocarcinoma of the pancreas.
- **GEMCITABINE FRESENIUS RTU** is indicated for patients previously treated with 5-Fluorouracil (5-FU);
- **GEMCITABINE FRESENIUS RTU** is indicated for treatment of patients with transitional cell bladder cancer;
- **GEMCITABINE FRESENIUS RTU**, in combination with paclitaxel, is indicated for the treatment of patients with unresectable, locally recurrent or metastatic breast cancer, in patients who have relapsed following adjuvant/neoadjuvant chemotherapy. Prior chemotherapy should have included an anthracycline, unless clinically contraindicated;
- **GEMCITABINE FRESENIUS RTU**, alone or in combination, is indicated for the treatment of patients with recurrent epithelial ovarian carcinoma who have relapsed following platinum-based chemotherapy.

4.2 Posology and method of administration

GEMCITABINE FRESENIUS RTU should only be prescribed by a medical doctor qualified in the use of anticancer chemotherapy.

Posology

Non-small cell lung cancer

Adults: The recommended monochemotherapy dose of **GEMCITABINE FRESENIUS RTU** is 1 000 mg/m^2, given by 30-minute intravenous infusion. This should be repeated once a week for three consecutive weeks, followed by a 1-week rest period. This 4-week 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.

GEMCITABINE FRESENIUS RTU may be used in combination with cisplatin, using either a 3-week or a 4-week schedule. One of the following regimens is suggested:

3-week schedule: **GEMCITABINE FRESENIUS RTU** 1 250 mg/m^2, given by 30-minute intravenous infusion on days 1 and 8 of every 21-day treatment cycle and cisplatin 100 mg/m^2 on day 1. Dosage reduction with each cycle or within a cycle may be applied based upon the grade of toxicity experienced by the patient.

4-week schedule: **GEMCITABINE FRESENIUS RTU** 1 000 mg/m^2 on days 1, 8, and 15 of every 28 days day cycle

and cisplatin 100 mg/m^2 on either day 1, 2, or 15 of therapy. Dosage reduction with each cycle or within a cycle may be applied based upon the grade of toxicity experienced by the patient.

Pancreatic cancer

Adults: The recommended dose for **GEMCITABINE FRESENIUS RTU** is 1000 mg/m^2, given by 30-minute intravenous infusion. This should be repeated once weekly for up to 7 weeks followed by a week of rest. Subsequently cycles should consist of injections once weekly for three consecutive weeks out of every 4 weeks. Dosage reduction with each cycle or within a cycle may be applied upon the grade of toxicity experienced by the patient.

Bladder cancer

Adults: The recommended monochemotherapy dosage of **GEMCITABINE FRESENIUS RTU** is 1 250 mg/m^2, given by 30-minute intravenous infusion. The dose should be given on days 1, 8 and 15 of each 28-day cycle. This 4-week cycle is then repeated. Dosage reduction with each cycle or within a cycle may be applied based upon the grade of toxicity experienced by the patient.

GEMCITABINE FRESENIUS RTU may be used in combination with cisplatin. The recommended dosage of **GEMCITABINE FRESENIUS RTU** is 1 000 mg/m^2, given by 30-minute intravenous infusion. The dose should be given at a recommended dose of 70 mg/m^2 on day 1 following **GEMCITABINE FRESENIUS RTU**, 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 grade of toxicity experienced by the patient. More myelosuppression occurred when cisplatin was used in doses of 100 mg/m^2.

Breast cancer

Adults: **GEMCITABINE FRESENIUS RTU** 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-minute intravenous infusion on day 1 and 8 of each 21-day 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 FRESENIUS RTU** + paclitaxel combination.

Ovarian cancer

Monotherapy:

Adults: The recommended dose of **GEMCITABINE FRESENIUS RTU** is 800 - 1 250 mg/m^2, given by a 30-minute intravenous infusion. The dose should be given on days 1, 8 and 15 of each 28-day cycle. This 4-week cycle is then

repeated. Dosage reduction with each cycle or within a cycle may be applied based upon the amount of toxicity experienced by the patient.

Combination use:

Adults: **GEMCITABINE FRESENIUS RTU** in combination with carboplatin is recommended, using **GEMCITABINE FRESENIUS RTU** 1 000 mg/m^2 administered on days 1 and 8 of each 21-day cycle as a 30-minute intravenous infusion. After **GEMCITABINE FRESENIUS RTU**, carboplatin will be given on day 1 consistent with a target AUC of 4,0 mg/ml/min. Dose reduction with each cycle may be applied upon the grade of toxicity experienced by the patient.

Patients receiving **GEMCITABINE FRESENIUS RTU** should be monitored prior to each dose for platelet, leucocyte and granulocyte counts and, if necessary, the dose of **GEMCITABINE FRESENIUS RTU** may be reduced or withheld in the presence of haematological toxicity, according to the following scale:

Absolute granulocyte count (x 10^6/L)	**Platelet count (x 10^6/L)**	**Percentage of full dose**
> 1 000 and	> 100 000	100
500-1 000 or	50 000-100 000	75
< 500 or	< 50 000	withhold

Periodic physical examination and checks of renal and hepatic function should be made to detect non-haematologic toxicity. Dosage reduction with each 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 doctor.

GEMCITABINE FRESENIUS RTU can be administrated on an outpatient basis.

Special populations

Patients with hepatic or renal impairment

GEMCITABINE FRESENIUS RTU should be used with caution in patients with hepatic insufficiency or with impaired renal function as no studies have been done in patients with significant renal or hepatic impairment. There is insufficient data to allow clear dose recommendation for this patient population.

Elderly patients:

GEMCITABINE FRESENIUS RTU has been widely used in patients over the age of 65. There is no evidence to suggest that dose adjustments are necessary in the elderly, although gemcitabine clearance and half-life are affected by age.

Paediatric population

The safety and efficacy of **GEMCITABINE FRESENIUS RTU** in children have not been established (see section 4.3).

Method of administration

For IV administration only.

GEMCITABINE FRESENIUS RTU is administered as a 30-minute intravenous infusion. The only approved diluent for **GEMCITABINE FRESENIUS RTU** is 0,9 % sodium chloride. It is not recommended that **GEMCITABINE FRESENIUS RTU** be mixed with other medicines when diluted.

For instructions for reconstitution, see section 6.6.

4.3 Contraindications

- Hypersensitivity to gemcitabine or to any of the excipients of **GEMCITABINE FRESENIUS RTU.**
- Pregnancy and breastfeeding: the safety of **GEMCITABINE FRESENIUS RTU** in human pregnancy and lactation has not been established (see section 4.6).
- Usage in children: safety and efficacy in children have not been established.

4.4 Special warnings and precautions for use

Patients receiving therapy with **GEMCITABINE FRESENIUS RTU** should be monitored closely by experienced staff in specialised centres.

Treatment for a patient compromised by medicine toxicity may be required. Prolongation of the infusion time and increased dosing frequency have been shown to increase toxicity.

Laboratory facilities should be available to monitor patient status.

Haematological toxicity

GEMCITABINE FRESENIUS RTU may suppress bone marrow function as manifested by leucopoenia, thrombocytopenia and anaemia.

Patients receiving **GEMCITABINE FRESENIUS RTU** should be monitored prior to each dose for platelet, leucocyte and granulocyte counts. The possibility of cumulative bone marrow suppression when using combination or

sequential chemotherapy should be considered. Suspension or modification of therapy should be considered when medicine-induced bone marrow depression is detected (see section 4.2).

Peripheral blood counts may continue to deteriorate after **GEMCITABINE FRESENIUS RTU** administration has been stopped. In patients with impaired bone marrow function, the treatment should be started with caution. The risk of cumulative bone marrow suppression should be considered when **GEMCITABINE FRESENIUS RTU** treatment is given together with other chemotherapy.

Hepatic and renal impairment

GEMCITABINE FRESENIUS RTU should be used with caution in patients with hepatic or renal function impairment as there is insufficient information to allow clear dose recommendation for this patient population (see section 4.2).

Administration of **GEMCITABINE FRESENIUS RTU** 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 impairment.

Laboratory evaluation of renal and hepatic function (including virologic tests) should be performed periodically.

Live vaccinations

Yellow fever vaccine and other live attenuated vaccines are not recommended in patients treated with **GEMCITABINE FRESENIUS RTU** (see section 4.5).

Nervous system

Posterior reversible encephalopathy syndrome

Reports of posterior reversible encephalopathy syndrome (PRES) with potentially severe consequences have been reported in patients receiving gemcitabine (as in **GEMCITABINE FRESENIUS RTU**) as single therapy or in combination with other chemotherapeutic medicines. 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 is typically reversible with appropriate supportive measures.

GEMCITABINE FRESENIUS RTU should be permanently discontinued, and supportive measures implemented, including blood pressure control and anti-seizure therapy, if PRES develops during therapy.

Cardiovascular

Due to the risk of cardiac and/or vascular disorders with **GEMCITABINE FRESENIUS RTU**, particular caution should be exercised with patients with a history of cardiovascular events.

Capillary leak syndrome

Capillary leak syndrome has been reported in patients receiving gemcitabine (as in **GEMCITABINE FRESENIUS RTU**) as single therapy, or in combination with other chemotherapeutic medicines (see section 4.8). The condition is usually treatable if recognised early and managed appropriately, but fatal cases have been reported. The condition involves systemic capillary hyperpermeability during which fluid and proteins from the intravascular space leak into the interstitium. The clinical features include generalised oedema, weight gain, hypoalbuminemia, severe hypotension, acute renal impairment and pulmonary oedema. **GEMCITABINE FRESENIUS RTU** should be discontinued, and supportive measures implemented if capillary leak syndrome develops during therapy. Capillary leak syndrome may occur in later cycles and has been associated in the literature with adult respiratory distress syndrome.

Pulmonary toxicity

Pulmonary effects, sometimes severe (such as pulmonary oedema, interstitial pneumonitis or adult respiratory distress syndrome (ARDS)) have been reported in association with gemcitabine (as in **GEMCITABINE FRESENIUS RTU**) therapy. If such effects develop, consideration should be made to discontinuing **GEMCITABINE FRESENIUS RTU** therapy. Early use of supportive care measure may help ameliorate the condition.

Renal toxicity

Renal failure and the haemolytic uremic syndrome (HUS) have been reported less frequently with gemcitabine use. **GEMCITABINE FRESENIUS RTU** should be administered with caution to patients with impaired renal function.

Haemolytic uremic syndrome (HUS)

Clinical findings consistent with HUS were reported in patients receiving gemcitabine (as in **GEMCITABINE FRESENIUS RTU**; see section 4.8). HUS is a potentially life-threatening disorder. **GEMCITABINE FRESENIUS RTU** 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, or LDH. Renal failure may not be reversible with discontinuation of therapy and dialysis may be required.

Carcinogenesis, mutagenesis, impairment of fertility

The carcinogenic potential of gemcitabine has not been established. Cytogenic damage has been produced by gemcitabine in an in vivo assay. It induced forward mutation in vitro in a mouse lymphoma assay.

Severe cutaneous adverse reactions (SCARs)

Severe cutaneous adverse reactions (SCARs) including Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), and acute generalized exanthematous pustulosis (AGEP), which can be life-threatening or fatal, have been reported in association with gemcitabine treatment. Patients should be advised of the signs and

symptoms and monitored closely for skin reactions. If signs and symptoms suggestive of these reactions appear, gemcitabine should be withdrawn immediately.

Fertility

The influence of gemcitabine on fertility has not been established in humans (see section 4.6).

Concomitant radiotherapy

Toxicity is associated with concurrent administration with **GEMCITABINE FRESENIUS RTU** (given together, or ≤ 7 days apart). See section 4.5 for details and recommendations for use.

Sodium

GEMCITABINE FRESENIUS RTU 200 mg contains a maximum of 2,4 mg (<1 mmol) sodium per vial.

GEMCITABINE FRESENIUS RTU 1 g contains a maximum of 12,1 mg (<1 mmol) sodium per vial.

GEMCITABINE FRESENIUS RTU 2 g contains a maximum of 24,2 mg sodium per vial.

This should be taken into consideration for patients on a sodium-controlled diet.

4.5 Interaction with other medicines and other forms of interaction

No specific interaction studies have been performed.

Radiotherapy

Concurrent radiotherapy (given together, or ≤ 7 days apart) - toxicity associated with this multimodality therapy is dependent on many different factors, including dose of **GEMCITABINE FRESENIUS RTU**, frequency of **GEMCITABINE FRESENIUS RTU** administration, dose of radiation, radiotherapy planning technique, the target tissue, and target volume.

Studies indicated that gemcitabine (as in **GEMCITABINE FRESENIUS RTU**) has radiosensitising activity when **GEMCITABINE FRESENIUS RTU** at a dose of 1 000 mg/m^2 is administered concurrently for up to six 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 esophagitis, and pneumonitis is observed, particularly in patients receiving large volumes of radiotherapy (median treatment volumes 4 795 cm^3).

The optimum regimen for safe administration of gemcitabine (as in **GEMCITABINE FRESENIUS RTU**) with therapeutic doses of radiation has not been determined in all tumour types.

Radiation injury has been reported on targeted tissues (e.g. esophagitis, colitis, and pneumonitis) in association with both concurrent and non-concurrent use of **GEMCITABINE FRESENIUS RTU.**

Live vaccines

Yellow fever and other live attenuated vaccines are not recommended due to the risk of systemic, possibly fatal, disease, particularly in immunosuppressed patients.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential

Women should be advised not to become pregnant during treatment with **GEMCITABINE FRESENIUS RTU** and to inform their attending doctor immediately, should this occur.

The duration of contraception for women following the end of treatment with GEMCITABINE FRESENIUS RTU is 6 months.

Pregnancy

The safety of **GEMCITABINE FRESENIUS RTU** in human pregnancy has not been established (see section 4.3).

Studies in animals have shown reproductive toxicity.

Breastfeeding

It is not known whether gemcitabine is excreted in human milk (see section 4.3), and adverse effects on the suckling child cannot be excluded. Breastfeeding should be discontinued during therapy with **GEMCITABINE FRESENIUS RTU** (see section 4.3).

Fertility

Fertility studies showed that gemcitabine causes hypospermatogenesis in male mice. Therefore, men being treated with **GEMCITABINE FRESENIUS RTU** are advised not to father a child during and up to 6 months after treatment. Men should seek further advice regarding cryoconservation of sperm prior to treatment because of the possibility of infertility due to therapy with **GEMCITABINE FRESENIUS RTU**.

4.7 Effects on ability to drive and use machines

GEMCITABINE FRESENIUS RTU may cause mild to moderate somnolence. Patients should be cautioned against driving or operating machinery until it is established that they do not become drowsy.

4.8 Undesirable effects

a. Summary of the safety profile

The most commonly reported adverse reactions associated with gemcitabine (contained in **GEMCITABINE FRESENIUS RTU**) treatment include nausea with or without vomiting, raised liver transaminases (AST/ALT) and

alkaline phosphatase, reported in approximately 60 % of patients; proteinuria and haematuria reported in approximately 50 % of patients; dyspnoea reported in 10-40 % of patients (highest incidence in lung cancer patients) and allergic skin rashes occurring in approximately 25 % of patients and associated with itching in 10 % of patients.

The frequency and severity of the adverse reactions are affected by the dose, infusion rate and intervals between doses (see section 4.4). Dose-limiting adverse reactions are reductions in platelet, leucocyte and granulocyte counts (see section 4.2).

b. Tabulated list of adverse reactions

System organ class	
Frequency grouping	***Adverse events***
Infections and infestations	
Frequent	Infections
Frequency unknown	Sepsis
Blood and the lymphatic system disorders	
Frequent	Leucopoenia, neutropenia, thrombocytopenia, anaemia, febrile neutropenia (see section 4.2 and 4.4)
Less frequent	Thrombocytosis, thrombotic microangiopathy
Immune system disorders	
Less frequent	Anaphylactoid reaction
Metabolism and nutrition disorders	
Frequent	Anorexia
Psychiatric disorders	
Frequent	Insomnia
Less frequent	Somnolence
Nervous system disorders	
Frequent	Headache
Less frequent	Posterior reversible encephalopathy syndrome (see section 4.4)
Frequency unknown:	Cerebrovascular accident
Cardiac disorders	

Less frequent	Dysrhythmias - predominantly supraventricular in nature, heart failure, myocardial infarction
Vascular disorders	
Less frequent	Clinical signs of peripheral vasculitis and gangrene, hypotension, capillary leak syndrome (see section 4.4)
Respiratory, thoracic and mediastinal disorders	
Frequent	Dyspnoea – usually mild and passes without treatment, cough, rhinitis
Less frequent	Interstitial pneumonitis (see section 4.4), bronchospasm – usually mild and transient but may require parenteral treatment, pulmonary oedema, adult respiratory distress syndrome (see section 4.4)
Frequency unknown	Pulmonary eosinophilia
Gastrointestinal disorders	
Frequent	Vomiting, nausea, diarrhoea, stomatitis and ulceration of the mouth, constipation
Frequency unknown	Ischaemic colitis
Hepatobiliary disorders	
Frequent	Elevation of liver transaminases (AST and ALT) and alkaline phosphatase, increased bilirubin
Less frequent	Serious hepatotoxicity (including liver failure and death), increased gamma-glutamyl transferase (GGT).
Skin and subcutaneous tissue disorders	
Frequent	Allergic skin rash frequently associated with pruritus, alopecia, itching, sweating
Less frequent	Severe skin reactions, including desquamation and bullous skin eruptions, ulceration, vesicle and sore formation, scaling, toxic epidermal necrolysis, Stevens-Johnson syndrome, pseudocellulitis
Frequency unknown	Acute generalised exanthematous pustulosis
Musculoskeletal and connective tissue disorders	
Frequent	Back pain, myalgia
Renal and urinary disorders	
Frequent	Haematuria, proteinuria

Less frequent	Renal failure (see section 4.4), haemolytic uremic syndrome (see section 4.4)
General disorders and administration site conditions	
Frequent	Influenza-like symptoms [(1)], oedema, peripheral oedema, including facial oedema, fever, asthenia, chills
Less frequent	Injection site reactions
Injury, poisoning, and procedural complications	
Less frequent	Radiation toxicity (see section 4.5), radiation recall

[1.] Influenza-like symptoms may include fever, headache, chills, myalgia, asthenia and anorexia. Cough, rhinitis, malaise, perspiration and sleeping difficulties have also been reported.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the "**6.04 Adverse Drug Reactions Reporting Form**", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8

Healthcare providers should also report adverse reactions to the Holder of Certificate of Registration, Fresenius Kabi South Africa (Pty) Limited

The contact details for our national reporting system are:

Email: safety.fksa@fresenius-kabi.com

Tel: +27 11 545 0000

Emergency: 0860 203 900

4.9 Overdose

Symptoms

In overdose, side effects can be precipitated and/or be of increased severity (see section 4.8).

Management

There is no antidote for overdosage of **GEMCITABINE FRESENIUS RTU.** In the event of a suspected overdose, the patient should be monitored with appropriate blood counts and receive supportive therapy, as necessary.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Category A 26 Cytostatic agents

Gemcitabine (dFdC) is metabolised intracellularly by nucleoside kinases to mono-, di- and triphosphates (dFdCMP, dFdCDP and dFdCTP) of which dFdCDP and dFdCTP are active.

The cytotoxic action of gemcitabine seems to be due to inhibition of DNA synthesis by two actions of dFdCDP and dFdCTP.

Firstly, dFdCDP inhibits ribonucleotide reductase which is uniquely responsible for catalysing the reactions that generate the deoxynucleoside triphosphates for DNA synthesis. Inhibition of this enzyme by dFdCDP causes a reduction in the concentrations of deoxynucleosides in general, and especially in that of dCTP.

Secondly, dFdCTP competes with dCTP for incorporation into DNA. Likewise, a small amount of gemcitabine may also be incorporated into RNA. Thus, the reduction in the intracellular concentration of dCTP potentiates the incorporation of dFdCTP into DNA (self-potentiation). DNA polymerase epsilon is essentially unable to remove gemcitabine and repair the growing DNA strands. After gemcitabine Is incorporated into DNA, one additional nucleotide is added to the growing DNA strands. After this addition there is essentially a complete inhibition in further DNA synthesis (masked chain termination). After incorporation into DNA, gemcitabine also appears to induce apoptosis.

Cytotoxic activity in cell cultures

Gemcitabine shows significant cytotoxic effects 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 dependent on both concentration and time.

5.2 Pharmacokinetic properties

Gemcitabine is administered as an intravenous infusion.

The pharmacokinetics of gemcitabine appear to be linear over the doses examined.

The following pharmacokinetic parameters have been reported for doses ranging from 500 to 2,592 mg/m^2 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 µg/ml.

Half-life: 42 – 94 minutes, depending on age and gender. At the recommended dosage, gemcitabine elimination should be virtually complete within 5 – 11 hours of the start of infusion. Gemcitabine does not accumulate when

administered once weekly.

Distribution

Volume of distribution of the central compartment (Vc): 12,4 L/m^2 for women and 17,5 L/m^2 for men (inter-individual variability was 91,9 %).

Volume of distribution of the peripheral compartment (Vp): 47,4 L/m^2.

The volume of the peripheral compartment was not sensitive to gender.

Plasma protein binding: Negligible.

Metabolism

Gemcitabine is rapidly metabolised by cytidine deaminase in the liver, kidney, blood and other tissues.

The primary metabolite, 2'-deoxy-2',2'-diflourouridine (dFdU), is not active and found in plasma and urine.

Formation of dFdU from parent compound ranges from 91 % to 98 %. Tissue distribution of dFdU is extensive.

Elimination

Systemic clearance: 29,2 L/h/m^2 to 92,2 L/h/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-minute infusion, lower clearance for women or the elderly should not necessitate a decrease in the gemcitabine dose.

Urinary excretion: Less than 10 % is excreted unchanged.

Mean renal clearance: 2 to 7 L/hr/m^2

Overall elimination: One week following a single 30-minute infusion of 1 000 mg/m^2, 92 – 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 faeces.

5.3 Preclinical safety data

Not Applicable

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Propylene glycol (E490), macrogol 400, sodium hydroxide (E524) (for pH adjustment), hydrochloric acid (E507) (for pH adjustment), water for injection.

6.2 Incompatibilities

GEMCITABINE FRESENIUS RTU must not be mixed with other medicines, except those mentioned in section 6.6.

6.3 Shelf life

Unopened vial

24 months, below 25 °C. Do not refrigerate or freeze.

In-use: further dilution

Proposed shelf life of the diluted injection:

Chemical and physical in-use stability after dilution in 0,9 % m/v sodium chloride solution at a concentration of 0,1 mg/ml and 5 mg/ml has been demonstrated for 7 days at 2 °C to 8 °C or at 25 °C.

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 2 °C to 8 °C, unless dilution has taken place in controlled and validated aseptic conditions.

Discard unused portion.

6.4 Special precautions for storage

Store below 25 °C.

Do not refrigerate or freeze.

For storage conditions after dilution of the medicine, see section 6.3.

6.5 Nature and contents of container

200 mg/5,26 mL presentation

A 6 ml, Ph Eur Type I clear colourless tubular glass vial with a 20 mm neck diameter; stoppered with a 20 mm grey chlorobutyl Flurotec coated rubber closure with an aluminium flip-off overseal with a green polypropylene flip.

Each vial may be shrink wrapped along with a plastic bottom and packaged in a mono-carton.

Each pack contains one vial and one PIL.

1 g/26,3 mL presentation

A 30 ml, Ph Eur Type I clear colourless tubular glass vial with a 20 mm neck diameter; stoppered with a 20 mm grey chlorobutyl Flurotec coated closure with an aluminium flip-off overseal with a blue polypropylene flip.

Each vial may be shrink wrapped along with a plastic bottom and packaged in a mono-carton.

Each pack contains one vial and one PIL.

2 g/52,6 mL presentation

A 100 ml, Ph Eur Type I clear, colourless, moulded glass vial with 20 mm neck diameter, stoppered with a grey Flurotec coated chlorobutyl with an aluminium flip-off overseal with a yellow polypropylene flip.

Each vial may be shrink wrapped along with a plastic bottom and packaged in a mono-carton.Each pack contains one vial and one PIL.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal <and other handling>

Handling

The normal safety precautions for cytostatic medicines must be observed when preparing and disposing of the infusion solution.

- Personnel should be trained to dilute **GEMCITABINE FRESENIUS RTU.**
- Pregnant staff should be excluded from working with this medicinal product.
- Personnel performing this procedure should wear protective clothing including mask, goggles and gloves.
- All items for administration or cleaning, including gloves, should be placed in high-risk, waste disposal bags for high-temperature incineration.
- Accidental contact with the skin or eyes should be treated immediately with copious amounts of water. If there is lasting irritation, a doctor should be consulted.
- Liquid waste may be flushed with large amounts of water.

Instructions on dilution

GEMCITABINE FRESENIUS RTU contains 38 mg gemcitabine per mL concentrated solution. The required volume of the **GEMCITABINE FRESENIUS RTU** is administered after diluting it with 0,9 % m/v sodium chloride intravenous infusion.

- Use aseptic techniques for the preparation of **GEMCITABINE FRESENIUS RTU** for intravenous infusion administration.
- Parenteral products should be visually inspected for particulate matter and discolouration prior to administration. The concentrated solution is clear, colourless or light straw-coloured. If visible particles are observed, **GEMCITABINE FRESENIUS RTU** should not be administered.

- **GEMCITABINE FRESENIUS RTU** is for single use only. Any unused product or waste material should be disposed of in accordance with local requirements.
- Chemical and physical in-use stability after dilution in 0,9 % m/v sodium chloride solution at a concentration of 0,1 mg/ml and 5 mg/ml have been demonstrated for 7 days at 2 - 8 °C and also at 25 °C.

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 2 - 8 °C, unless dilution has taken place in controlled and validated aseptic conditions.

7 HOLDER OF CERTIFICATE OF REGISTRATION

Fresenius Kabi South Africa (Pty) Limited

Stand 7 Growthpoint Park

162 Tonetti Street

Midrand, South Africa

8 REGISTRATION NUMBER(S)

GEMCITABINE 200 mg RTU FRESENIUS: 50/26/0871

GEMCITABINE 1 g RTU FRESENIUS: 50/26/0872

GEMCITABINE 2 g RTU FRESENIUS: 50/26/0874

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

21 January 2021

10 DATE OF REVISION OF THE TEXT

30 August 2024