PACKAGE INSERT FOR ROGEM 200 and 1

SCHEDULING STATUS

S4

PROPRIETARY NAMES AND DOSAGE FORM

ROGEM 200 (powder for injection)

ROGEM 1 (powder for injection)

COMPOSITION

Active ingredient:

ROGEM 200: Each vial contains gemcitabine hydrochloride equivalent to 200 mg of gemcitabine.

ROGEM 1: Each vial contains gemcitabine hydrochloride equivalent to 1 g of gemcitabine.

Inactive ingredients:

Mannitol and sodium acetate (trihydrate).

PHARMACOLOGICAL CLASSIFICATION

A.26 Cytostatic agents

PHARMACOLOGICAL ACTION

Pharmacodynamic properties:

Gemcitabine is an antimetabolite of the pyrimidine analogue type. Influx of gemcitabine through the cell membrane occurs via active nucleoside transporters. Intracellularly, deoxycytidine kinase phosphorylates gemcitabine to produce difluorodeoxycytidine monophosphate, from where it is converted to difluorodeoxycytidine di- and triphosphate (dFdCDP, dFdCTP). The cytotoxicity of gemcitabine is not confined to the S phase of the cell cycle, and the active substance is equally effective against confluent cells and cells in log-phase growth. The cytotoxic activity may be a result of several actions on DNA synthesis:

- dFdCTP competes with dCTP as a weak inhibitor of DNA polymerase.

- dFdCDP is a potent inhibitor of ribonucleotide reductase, resulting in depletion of deoxyribonucleotide pools necessary for DNA synthesis.
- dFdCTP is incorporated into DNA and, after the incorporation of one more nucleotide, leads to DNA strand termination.

Pharmacokinetic properties:

After intravenous doses, gemcitabine is rapidly cleared from the blood and metabolised by cytidine deaminase in the liver, kidney, blood and other tissues. Clearance is approximately 25 % lower in women than in men. Almost the entire dose is excreted in urine as 2'-deoxy-2',2'-difluorouridine (dFdU), only about 1 % being found in the faeces. Intracellular metabolism produces mono-, di-, and triphosphate metabolites, of which the latter two are active. The half-life of gemcitabine ranges from 42 to 94 minutes depending on age and gender.

INDICATIONS

- **ROGEM** is indicated for the treatment of patients with locally advanced or metastatic non-small cell lung cancer.
- **ROGEM** 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.
- **ROGEM** is indicated for patients previously treated with 5-FU.
- **ROGEM** is indicated for treatment of patients with transitional cell bladder cancer.
- **ROGEM**, in combination with paclitaxel, is indicated for the treatment of patients with non-resectable, locally recurrent or metastatic breast cancer, who has relapsed following adjuvant/neoadjuvant chemotherapy. Prior chemotherapy should have included an anthracycline, unless clinically contraindicated.
- **ROGEM**, alone or in combination, is indicated for the treatment of patients with recurrent epithelial ovarian carcinoma who have relapsed following platinum-based chemotherapy.

CONTRAINDICATIONS

Patients with known hypersensitivity to gemcitabine or any of the other ingredients of **ROGEM** (see **COMPOSITION**).

Safety and efficacy in pregnancy and lactation have not been established (see **PREGNANCY AND LACTATION**).

Children, as safety and efficacy have not been established.

WARNINGS AND SPECIAL PRECAUTIONS

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

ROGEM can suppress bone marrow function as manifested by leukopenia, thrombocytopenia and anaemia. Myelosuppression is usually mild to moderate and is more pronounced for the granulocyte count (see **DOSAGE AND DIRECTIONS FOR USE** and **SIDE EFFECTS**).

Caution is advised when starting treatment with **ROGEM** in patients with compromised bone marrow function. The possibility of cumulative bone marrow depression should be considered when using combination or sequential chemotherapy. Peripheral blood counts may continue to fall after **ROGEM** is stopped.

Risk-benefit should be considered when the following medical problems exist:

- Bone marrow depression (see **INTERACTIONS**).
- Existing or recent chickenpox.
- Herpes zoster.

Radiotherapy:

Concurrent (or < 7 days apart): **ROGEM has radiosensitising activity. Administering ROGEM at a dose of 1 000 mg/m^2 concurrently, for up to six consecutive weeks, with therapeutic thoracic radiation to patients with non-small cell lung cancer, can result in significant toxicity in the form of severe and potentially life-threatening mucositis. Especially oesophagitis and pneumonitis have been observed, particularly in patients receiving large volumes of radiotherapy (median treatment volumes 4 795 cm^3). The optimum regimen for safe administration of ROGEM with therapeutic doses of radiation has not yet been determined.**

Close monitoring of all patients on **ROGEM** treatment is of utmost importance. Periodic blood tests will facilitate in determining patient status.

Immunisation should be avoided, unless regarded as imperative by the treating medical practitioner (see **INTERACTIONS**). Contact with persons who have received oral polio vaccination should be avoided.

ROGEM should be administered with caution to patients with impaired renal function and should be discontinued at the first signs of microangiopathic haemolytic anaemia, such as rapidly falling haemoglobin with concomitant thrombocytopenia, elevation of serum bilirubin, serum creatinine, blood urea or lactate dehydrogenase (LDH). Renal failure may not be reversible, even with discontinuation of therapy, and dialysis might be required.

ROGEM should be used with caution in patients with impaired renal function or hepatic insufficiency. No studies have been done in patients with significant renal or hepatic impairment.

ROGEM must be stopped if interstitial pneumonitis and pulmonary infiltrates develop. Steroids may relieve the symptoms in such situations.
In the event of pulmonary oedema and adult respiratory distress syndrome, cessation of **ROGEM** is necessary. Starting supportive treatment at an early stage may improve the situation.

ROGEM contains mannitol, which may have a mild laxative effect.

Effects on the ability to drive and use machines:
ROGEM has been reported to cause mild to moderate somnolence. Patients should be cautioned against driving a vehicle or operating machinery until it is established how **ROGEM** effects them.

INTERACTIONS

Additive bone marrow depression may occur when **ROGEM** is administered with other bone marrow depressants or radiotherapy. Dosage reduction may be required when two or more bone marrow depressants, including radiation, are used concurrently or consecutively (see **WARNINGS AND SPECIAL PRECAUTIONS**).

Concurrent use of **ROGEM** with the following immunosuppressants may increase the risk of infection:

- Azathioprine
- Chlorambucil
- Corticosteroids
- Cyclophosphamide
- Ciclosporin
- Mercaptopurine
- Muromonab CD-3
- Tacrolimus

Due to the suppression of normal defence mechanisms by gemcitabine therapy, concurrent use of **ROGEM** with a live virus vaccine may potentiate the replication of the vaccine virus, increase the side effects of the vaccine virus, and/or decrease the antibody response of the patient to the vaccine (see **WARNINGS AND SPECIAL PRECAUTIONS**).

PREGNANCY AND LACTATION

The safety of **ROGEM** during pregnancy and lactation has not been established (see **CONTRAINDICATIONS**).

DOSAGE AND DIRECTIONS FOR USE

ROGEM is for intravenous use only.

Non-small cell lung cancer:

Adults:

The recommended monochemotherapy dosage is 1 000 mg/m^2, given by 30-minute intravenous infusion. This should be repeated once weekly for three weeks, followed by a one week rest period. This four-week cycle is then repeated. Dosage reduction with each cycle, or within a cycle, may be applied based upon the amount of toxicity experienced by the patient.

ROGEM may be used in combination with cisplatin, using either a three-week or four-week schedule. One of the following regimens is suggested:

3-week schedule:

ROGEM 1 250 mg/m^2, given by 30-minute intravenous infusion on days 1 and 8 of every 21-day 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 amount of toxicity experienced by the patient.

4-week schedule:

ROGEM 1 000 mg/m^2 on days 1, 8 and 15 of every 28-day cycle, and cisplatin 100 mg/m^2 on either day 1, 2 or 15 of therapy. Dose reduction with each cycle, or within a cycle, may be applied based upon the amount of toxicity experienced by the patient.

Pancreatic cancer:

Adults:

The recommended dose of **ROGEM** is 1 000 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. Subsequent cycles should consist of injections once weekly for 3 consecutive weeks out of every 4 weeks. Dosage reduction with each cycle, or within a cycle, may be applied based upon the amount of toxicity experienced by the patient.

Bladder cancer:

Adults:

The recommended monochemotherapy dosage of **ROGEM** 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 four-week

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

ROGEM may be used in combination with cisplatin. The recommended dose of **ROGEM** is 1 000 mg/m^2, given by 30-minute infusion. The dose should be given on days 1, 8 and 15 of each 28-day cycle in combination with cisplatin. Cisplatin is given at a recommended dose of 70 mg/m^2 on day 1 following **ROGEM**, or day 2 of each 28-day cycle. This four week cycle is then repeated. Dosage reduction with each cycle, or within a cycle, may be applied based upon the amount of toxicity experienced by the patient. More myelosuppression may be experienced when cisplatin is used in doses of 100 mg/m^2.

Breast cancer:

Adults:

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

Ovarian cancer:

Single agent use:

Adults:

The recommended dose of **ROGEM** 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 four-week cycle is 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:

ROGEM in combination with carboplatin is recommended using **ROGEM** 1 000 mg/m^2 administered on days 1 and 8 of each 21-day cycle as a 30-minute intravenous infusion. After **ROGEM**, carboplatin will be given on day 1 consistent with a target of 4,0 g/ml/min. Dosage reduction with each cycle, or within a cycle, may be applied based upon the amount of toxicity experienced by the patient.

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

Absolute granulocyte count (x $10^6/\ell$)		**Platelet count (x $10^6/\ell$)**	**% of full dose**
> 1 000	and	> 100 000	100
500 - 1 000	or	50 000 – 100 000	75
< 500	or	< 50 000	hold

Periodic physical examination and checks of renal and hepatic function, should be made to detect non-haematological 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 medical practitioner.

Elderly patients:

ROGEM has been well tolerated in patients over the age of 65 years. There is no evidence to suggest that dose adjustments are necessary in the elderly, although gemcitabine clearance and half-life are affected by age.

Patients with hepatic or renal impairment:

ROGEM should be used with caution in patients with hepatic or renal impairment as there is insufficient information to allow for clear dose recommendations for these patient populations. Mild to moderate renal insufficiency (glomerular filtration rate (GFR) ranging from 30 ml/min to 80 ml/min) has no consistent, significant effect on the pharmacokinetics of **ROGEM**.

Instructions for reconstitution:

The only approved diluent for reconstitution of **ROGEM** is 0,9 % sodium chloride injection without preservatives. It is not recommended that **ROGEM** be mixed with other medicines when reconstituted.

Due to solubility considerations, the maximum concentration for **ROGEM** 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 without preservatives to the 200 mg vial, or at least 25 ml of 0,9 % sodium chloride without preservatives to the 1 g vial. Shake to dissolve. The appropriate amount of medicine may be administered as prepared or further diluted with 0,9 % sodium chloride injection without preservatives.

For in-use storage after reconstitution see **STORAGE INSTRUCTIONS**.

SIDE EFFECTS

Blood and the lymphatic system disorders

Frequent: leukopenia, thrombocytopenia, anaemia, febrile neutropenia

Less frequent: myelosuppression

Immune system disorders

Less frequent: anaphylactoid reaction

Nervous system disorders

Frequent: somnolence, paraesthesia

Cardiac disorders

Less frequent: myocardial infarct, heart failure, dysrhythmia

Vascular disorders

Less frequent: hypotension

Respiratory, thoracic and mediastinal disorders

Frequent: dyspnoea

Less frequent: bronchospasm (usually mild and transient), pulmonary oedema, interstitial pneumonitis (with associated pulmonary infiltrates), adult respiratory distress syndrome (see **WARNINGS AND SPECIAL PRECAUTIONS**)

Gastrointestinal disorders

Frequent: nausea, vomiting, stomatitis, diarrhoea, constipation

Hepatobiliary disorders:

Frequent: elevations of liver transaminases (AST and ALT) and alkaline phosphatase

Less frequent: increased gamma-glutamyl transferase (GGT) and bilirubin

Skin and subcutaneous tissue disorders

Frequent: allergic skin rash (frequently associated with pruritus), alopecia

Less frequent: scaling, vesicle and sore formation, ulceration, severe skin reactions including desquamation and bullous skin eruptions

Renal and urinary disorders

Frequent: haematuria, proteinuria

Frequency unknown: renal failure, haemolytic uraemic syndrome

General disorders and administration site conditions

Frequent: oedema, peripheral oedema, influenza-like symptoms (fever, headache, back pain, shivering, muscle pain, asthenia, cough, rhinitis), fever, asthenia

Less frequent: facial oedema, irritation, pain or redness at the injection site, radio sensitisation and radiation recall

Investigations

Frequent: Elevation of liver transaminases and alkaline phosphatase. **ROGEM** should be used with caution in patients with impaired liver function (see **WARNINGS AND SPECIAL PRECAUTIONS**).

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT

(See **SIDE EFFECTS**.)

There is no specific antidote for a gemcitabine overdosage. In the event of an overdose, treatment is supportive and the patient blood count should be monitored.

IDENTIFICATION

ROGEM 200: A white to off-white lyophilised powder.

ROGEM 1: A white to off-white lyophilised powder.

PRESENTATION

ROGEM 200: Packed in a 10 ml, 20 mm type I clear glass vial and grey bromobutyl slotted rubber stopper, with a 20 mm aluminium seal, with a blue flip off top.

ROGEM 1: Packed in a 50 ml, 20 mm type I clear glass vial and grey bromobutyl slotted rubber stopper, with a 20 mm aluminium seal, with a pink flip off top.

One vial of **ROGEM** will be placed in an outer carton.

STORAGE INSTRUCTIONS

Store at or below 30 °C.

Keep the vial in the outer carton until required for use.

After reconstitution:

Chemical and physical in-use stability has been demonstrated for 24 hours after reconstitution, at or below 30 °C.

From a microbiological point of view, **ROGEM** should be used immediately. If not used immediately, in-use storage times and conditions prior to use, are the responsibility of the user.

Do not refrigerate, crystallisation may occur.

Discard any unused portion.

Reconstituted **ROGEM** should be inspected visually for particulate matter and discolouration, prior to administration.

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

KEEP OUT OF REACH OF CHILDREN.

REGISTRATION NUMBERSs

ROGEM 200: 46/26/0104

ROGEM 1: 46/26/0103

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION

Zydus Healthcare SA (Pty) Ltd.

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