**SCHEDULING STATUS: S4**

## 1. NAME OF MEDICINE

**SPALGEM 200 mg (Powder for Injection)**

**SPALGEM 1000 mg (Powder for Injection)**

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION POSITION

Each **SPALGEM** 200 mg vial contains gemcitabine hydrochloride equivalent to 200 mg of gemcitabine free base.

Each **SPALGEM** 1000 mg vial contains gemcitabine hydrochloride equivalent to 1 g of gemcitabine free base.

**SPALGEM** is sugar free

For the full list of excipients, see section 6.1.

## 3 PHARMACEUTICAL FORM

**SPALGEM 200 mg** is a White to off white coloured lyophilised cake or powder

**SPALGEM 1000 mg** is a White to off white coloured lyophilised cake or powder

## 4 CLINICAL PARTICULARS

### 4.1 Therapeutic indications

**SPALGEM** is indicated for the treatment of patients with locally advanced or metastatic non-small cell lung cancer.

**SPALGEM** 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. **SPALGEM** is indicated for patients previously treated with 5-FU.

**SPALGEM** is indicated for treatment of patients with transitional cell bladder cancer.

**SPALGEM**, 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 contra-indicated.

**SPALGEM**, 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

**Posology**

**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.

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

3 week schedule: **SPALGEM** 1 250 mg/m², given by 30 minute intravenous infusion on days 1 and 8 of every 21 day cycle and cisplatin 100 mg/m² 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: **SPALGEM** 1 000 mg/m$^2$ on days 1, 8 and 15 of every 28 day cycle and cisplatin 100 mg/m2 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 **SPALGEM** 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 **SPALGEM** is 1 250 mg/m², 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.

**SPALGEM** may be used in combination with cisplatin. The recommended dose of **SPALGEM** is 1 000 mg/m², 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/m² on day

1 following **SPALGEM** 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. A clinical trial showed more myelosuppression when cisplatin was used in doses of 100 mg/m².

**Breast cancer:**

**Adults**: **SPALGEM** 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 **SPALGEM** (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 106/L) prior to initiation of **SPALGEM** + paclitaxel combination.

**Ovarian Cancer:**

**Single medicine use:**

**Adults:** The recommended dose of **SPALGEM** is 800 to 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 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**: **SPALGEM** in combination with carboplatin is recommended using **SPALGEM** 1 000 mg/m$^2$ administered on days 1 and 8 of each 21 day cycle as a 30 minute intravenous infusion. After **SPALGEM**, carboplatin will be given on day 1 consistent with a target AUC 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 **SPALGEM** should be monitored prior to each dose for platelet, leucocyte and granulocyte counts and, if necessary, the dose of **SPALGEM** may be either 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)** | **% of full dose** |
|---|---|---|

| | | | |
|---|---|---|---|
| **>1 000** | **and** | **>100 000** | **100** |
| **500 - 1 000** | **or** | **50 000 - 100 000** | **75** |
| **<500** | **or** | **<50 000** | **hold** |

**Special populations**

**Patients with hepatic or renal impairment:**

**SPALGEM** 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 information from clinical studies to allow clear dose recommendation for this patient population.

Periodic physical examination and checks of renal and hepatic function should be made to detect non-haematologic 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: SPALGEM** has been well tolerated in patients over the age of 65. There is no evidence to suggest that dose adjustments are necessary in the elderly, although **SPALGEM** clearance and half-life are affected by age.

**Method of administration**

SPALGEM is for intravenous use only.

**SPALGEM** is well tolerated during the infusion, with only a few cases of injection site reaction reported. **SPALGEM** can be easily administered on an outpatient basis.

Information on instructions for preparation and reconstitution, see section 6.6.

**4.3 Contraindications**

**SPALGEM** is contra-indicated in those patients with a known hypersensitivity to gemcitabine or any of the excipients of **SPALGEM** listed in section 6.1.

**Pregnancy and lactation**: The safety of **SPALGEM** in human pregnancy and lactation has not been established.

**Usage in children**: Safety and effectiveness in children have not been established.

**4.4 Special warnings and precautions for use**

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

**SPALGEM** can suppress bone marrow function as manifested by leucopoenia, thrombocytopenia and anaemia. Myelosuppression is usually mild to moderate and is more pronounced for the granulocyte count.

Peripheral blood counts may continue to deteriorate after **SPALGEM** 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 must be considered when **SPALGEM** treatment is given together with other chemotherapy medicines.

Hepatic insufficiency

Administration of **SPALGEM** 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.

**SPALGEM** should be used with caution in patients with hepatic insufficiency or with impaired renal function as there is insufficient information from clinical studies to allow clear dose recommendation for this patient population (see section 4.2).

Concomitant radiotherapy

Concomitant radiotherapy (given together or ≤7 days apart): Toxicity has been reported (see section 4.5 for details and recommendations for use).

Live vaccinations

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

Cardiovascular

Due to the risk of cardiac and/or vascular disorders with **SPALGEM**, 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 **SPALGEM** as single medicine or in combination with chemotherapeutic medicines. 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, hypoalbuminaemia, severe hypotension, acute renal impairment and pulmonary oedema. **SPALGEM** 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 adult 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 **SPALGEM** as single medicine 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 was typically reversible with appropriate supportive measures. **SPALGEM** 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 oedema, interstitial pneumonitis or adult respiratory distress syndrome (ARDS)) have been reported in association with **SPALGEM** therapy. The aetiology of these effects is unknown. If such effects develop, consideration should be made to discontinuing **SPALGEM** therapy. Early use of supportive care measure may help ameliorate the condition.

Renal

Haemolytic uraemic syndrome

Clinical findings consistent with the haemolytic uraemic syndrome (HUS) were rarely reported in patients receiving gemcitabine (see section 4.8). **SPALGEM** should be discontinued at the first signs of any evidence of microangiopathic

haemolytic anaemia, such as rapidly falling haemoglobin with concomitant thrombocytopaenia, 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.

**4.5 Interaction with other medicines and other forms of interaction**

RADIOTHERAPY:

CONCURRENT (GIVEN TOGETHER OR ≤7 DAYS APART) - TOXICITY ASSOCIATED WITH THIS MULTIMODALITY THERAPY IS DEPENDENT ON MANY DIFFERENT FACTORS, INCLUDING DOSE OF **SPALGEM**, FREQUENCY OF **SPALGEM**

ADMINISTRATION, DOSE OF RADIATION, RADIOTHERAPY PLANNING TECHNIQUE, THE TARGET TISSUE, AND TARGET VOLUME. PRE-CLINICAL AND CLINICAL STUDIES HAVE SHOWN THAT GEMCITABINE HAS RADIOSENSITIZING ACTIVITY. IN A SINGLE TRIAL, WHEN GEMCITABINE AT A DOSE OF 1 000 mg/m$^2$ WAS ADMINISTERED CONCURRENTLY FOR UP TO 6 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 WAS OBSERVED, PARTICULARLY IN PATIENTS RECEIVING LARGE VOLUMES OF RADIOTHERAPY (MEDIAN TREATMENT VOLUMES 4 795 cm$^3$).

THE OPTIMUM REGIMEN FOR SAFE ADMINISTRATION OF **SPALGEM** WITH THERAPEUTIC DOSES OF RADIATION HAS NOT YET 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 **SPALGEM**.

Others

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**

Pregnancy

**SPALGEM** should not be used during pregnancy as safety has not been established (see section 4.3)

There are no adequate data from the use of gemcitabine in pregnant women. Studies in animals have shown reproductive toxicity. Women should be advised not to become pregnant during treatment with **SPALGEM** and to warn their attending medical practitioner immediately, should this occur after all.

Breast-feeding

**SPALGEM** should not be used during breastfeeding as safety has not been established (see section 4.3)

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 **SPALGEM** therapy.

Fertility

In fertility studies 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 **SPALGEM**.

### 4.7 Effects on ability to drive and use machines

**SPALGEM** has been reported to cause mild to moderate somnolence. 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 frequently reported adverse drug reactions associated with Gemcitabine 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% patients; dyspnoea reported in 10-40% of patients (highest incidence in lung cancer patients); allergic skin rashes occur in approximately 25% of patients and are 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 thrombocyte, leucocyte and granulocyte counts (see section 4.2).

The following table of undesirable effects and frequencies is based on data from clinical trials. Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

| System Organ Class | Frequency grouping |
|---|---|

| | |
|---|---|
| Blood and lymphatic system disorders | ***Frequent***<br>Leucopaenia.<br>Neutropaenia.<br>Bone-marrow suppression<br>• Thrombocytopaenia<br>• Anaemia<br>• Febrile neutropaenia<br><br>***Less frequent***<br>• Thrombocytosis<br>• Thrombotic microangiopathy |
| Infections and infestations | ***Frequent***<br>• Infections<br>Frequency unknown<br>• Sepsis |
| Immune system disorders | ***Less frequent***<br>• Anaphylactoid reaction |
| Metabolism and nutrition disorders | ***Frequent***<br>• Anorexia |
| Nervous system disorders | ***Frequent***<br>• Headache<br>• Insomnia<br>• Somnolence<br>***Less frequent***<br>• Posterior reversible encephalopathy syndrome<br>***Frequency unknown***<br>Cerebrovascular accident |
| Cardiac disorders | ***Less frequent***<br>• Myocardial infarct |

| | |
|---|---|
| | ***Frequency unknown***<br>Dysrythmias, predominantly supraventricular in nature<br>Heart failure |
| Vascular disorders | ***Less frequent***<br>• Hypotension<br>• Capillary leak syndrome<br>***Frequency unknown***<br>Clinical signs of peripheral vasculitis and gangrene |
| Respiratory, thoracic and mediastinal disorders | ***Frequent***<br>• Dyspnoea<br>• Cough<br>• Rhinitis<br>***Less frequent***<br>• Interstitial pneumonitis<br>• Bronchospasm<br>Frequency unknown<br>Pulmonary oedema<br>Adult respiratory distress syndrome |
| Gastrointestinal disorders | ***Frequent***<br>• Vomiting<br>• Nausea<br>• Diarrhoea<br>• Stomatitis and ulceration of the mouth<br>• Constipation<br>***Frequency unknown***<br>Ischaemic colitis |
| Hepatobiliary disorders | ***Frequent***<br>• Elevation of liver transaminases (AST and ALT) and alkaline phosphatase<br>• Increased bilirubin<br>***Less frequent***<br>• Increased gamma-glutamyl transferase (GGT)<br>***Frequency unknown*** |

| | |
|---|---|
| | Serious hepatotoxicity, including liver failure and death |
| Skin and subcutaneous tissue disorders | ***Frequent***<br>• Allergic skin rash frequently associated with pruritus<br>• Alopecia<br>• Itching<br>• Sweating<br><br>***Less frequent***<br>• Ulceration<br>• Vesicle and sore formation<br>• Scaling<br>• Severe skin reactions, including desquamation and bullous skin eruptions<br>• Pseudocellulitis<br><br>***Frequency unknown***<br><br>Lyell's Syndrome,<br><br>Steven- Johnson Syndrome |
| Musculoskeletal and connective tissue disorders | ***Frequent***<br>• Back pain<br>• Myalgia |
| Renal and urinary disorders | ***Frequent***<br>• Haematuria<br>• Mild proteinuria<br><br>***Frequency unknown***<br><br>Renal failure<br><br>Haemolytic uraemic syndrome |
| General disorders and Administration site conditions | ***Frequent***<br><br>• Influenza-like symptoms - the most common symptoms are fever, headache, chills, myalgia, asthenia and anorexia. Cough, rhinitis, malaise, perspiration and sleeping difficulties.<br><br>• Oedema/peripheral oedema including facial oedema.<br><br>• Fever<br><br>• Asthenia<br><br>• Chills<br><br>***Less frequent***<br><br>• Injection site reactions-mainly mild in nature |
| Injury, poisoning, and procedural | ***Frequency unknown*** |

| | |
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| Complications | Radiation toxicity<br>Radiation recall |

*Combination use in breast cancer*

The frequency of grade 3 and 4 haematological toxicities, particularly neutropaenia, 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 haemorrhagic events. Fatigue and febrile neutropaenia occur more frequently when gemcitabine is used in combination with paclitaxel. Fatigue, which is not associated with anaemia, usually resolves after the first cycle.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.

Healthcare professionals are asked to report any suspected adverse reactions to SAHPRA via the **"6.04 Adverse Drug Reaction Reporting Form"**, found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8

### 4.9 Overdose

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

## 5 PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties

Pharmacotherapeutic group: pyrimidine analogues ATC code: L01BC05

**Cellular metabolism and mechanism of action:** 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 appears 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 appears to induce the programmed cellular death process known as apoptosis.

**Cytotoxic activity in cell culture models:** Gemcitabine exhibits significant cytotoxicity activity 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 both concentration and time dependent.

**Antitumour activity in preclinical models:** In animal tumour models, the antitumour activity of gemcitabine is schedule dependent. When administered daily, gemcitabine causes death in animals with minimal antitumour activity. However, when an every third or fourth day dosing schedule is used, gemcitabine can be given at non-lethal doses that have excellent antitumour activity against a broad range of mouse tumours.

## 5.2 Pharmacokinetic properties

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

The following pharmacokinetic parameters were obtained for doses ranging from 500 to 2 592 mg/m$^2$ that were infused over 0,4 to 1,2 hours:

*Peak plasma concentrations* (obtained within 5 minutes of end of the infusion): 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 metabolised 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.

Excretion

Systemic clearance ranged from 29.2 l/hr/m$^2$ to 92.2 /hr/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 1000 mg/m$^2$ given as a 30-minute 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/hr/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 faeces.

dFdCTP kinetics

This metabolite can be found in peripheral blood mononuclear cells and the information below refers to these cells.

Intracellular concentrations increase in proportion to gemcitabine doses of 35-350 mg/m$^2$/30-minutes, which give steady state concentrations of 0.4-5 µg/ml. At gemcitabine plasma concentrations above 5 µg/ml, dFdCTP levels do not increase, suggesting that the formation is saturable in these cells.

Half-life of terminal elimination: 0.7-12 hours.

dFdU kinetics

Peak plasma concentrations (3-15 minutes after end of 30-minute infusion, 1000 mg/m$^2$): 28-52 µg/ml.

Trough concentration following once weekly dosing: 0.07-1.12 µg/ml, with no apparent accumulation.

Triphasic plasma concentration versus time curve, mean half-life of terminal phase - 65 hours (range 33-84 hr).

Formation of dFdU from parent compound: 91%-98%.

Mean volume of distribution of central compartment: 18 l/m$^2$ (range 11-22 l/m$^2$).

Mean steady state volume of distribution (Vss): 150 l/m$^2$ (range 96-228 l/m$^2$).

Tissue distribution: Extensive.

Mean apparent clearance: 2.5 l/hr/m$^2$ (range 1-4 l/hr/m$^2$).

Urinary excretion: All.

Gemcitabine and paclitaxel combination therapy

Combination therapy did not alter the pharmacokinetics of either gemcitabine or paclitaxel.

Gemcitabine and carboplatin combination therapy

When given in combination with carboplatin the pharmacokinetics of gemcitabine were not altered

Renal impairment

Mild to moderate renal insufficiency (GFR from 30 ml/min to 80 ml/min) has no consistent, significant effect on gemcitabine pharmacokinetics.

## 6 PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients

mannitol

sodium acetate

sodium hydroxide

water for injection

### 6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 4.2

### 6.3 Shelf life

Unopened vials: 3 years

**Reconstituted solution:**

Chemical and physical in-use stability has been demonstrated for 24 hours at 30°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 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 crystallisation may occur.

### 6.4 Special precautions for storage

Store at or below 30 °C. Protect from light

KEEP OUT OF REACH OF CHILDREN.

### 6.5 Nature and contents of container

**SPALGEM** 200 mg is filled in 10 mL clear tubular vial with 20 mm lyo stopper grey bromobutyl (single slotted) and sealed with 20 mm easy to open C/L alu seals with matt finish plastic german blue botton in mono cartons.

**SPALGEM** 1000 mg is filled in 50 mL clear tubular vial with 20 mm lyo stopper grey bromobutyl (single slotted) and sealed with 20 mm easy to open C/L alu. seals with matt finish plastic german blue button in mono cartons

### 6.6 Special precautions for disposal of a used medicine and other handling

The product should be used immediately after opening.

**Instructions for reconstitution:** The only approved diluent for reconstitution of **SPALGEM** is 0,9% sodium chloride injection without preservatives. It is not recommended that **SPALGEM** be mixed with other medicines when reconstituted. Due to solubility considerations, the maximum concentration for **SPALGEM** 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 injection 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.

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.

Discard after single use.

Discard any unused portion.

## 7 HOLDER OF CERTIFICATE OF REGISTRATION

Ruby Pharmaceuticals (Pty) Ltd

Unit 1, 96 Hartley Road

Durban. 4091

## 8 REGISTRATION NUMBER(S)

Spalgem 200 mg: 55/2.6/0432

Spalgem 1000 mg: 55/2.6/0433

## 9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

## 10 DATE OF REVISION OF THE TEXT