Applicant: Oethmaan Biosims (Pty) Ltd	**SAHPRA approval date:** 9 December 2024
Product: GEMCITABINE 200 mg OETHMAAN GEMCITABINE 1 g OETHMAAN	**Dosage form and strength:** Each vial contains: Gemcitabine hydrochloride equivalent to 200 mg Gemcitabine free base. Each vial contains: Gemcitabine hydrochloride equivalent to 1 g Gemcitabine free base.

APPROVED PROFESSIONAL INFORMATION

SCHEDULING STATUS:

S4

1. NAME OF THE MEDICINE:

Gemcitabine 200 mg Oethmaan (powder for solution for infusion)

Gemcitabine 1 g Oethmaan (powder for solution for infusion)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION:

Each Gemcitabine 200 mg Oethmaan vial contains: Gemcitabine hydrochloride equivalent to 200 mg Gemcitabine free base. Sugar free.

Each Gemcitabine 1 g Oethmaan vial contains: Gemcitabine hydrochloride equivalent to 1 g Gemcitabine free base. Sugar free.

For full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder for solution for infusion.

Gemcitabine 200 mg Oethmaan and Gemcitabine 1 g Oethmaan powder for solution for infusion is a white to slightly yellowish powder or cake. Reconstitution with 0.9 % sodium chloride results in a clear and colourless solution.

Initial:	09-12-2024

4. CLINICAL PARTICULARS:

4.1 Therapeutic indications

GEMCITABINE OETHMAAN is indicated for treatment in patients:

- with non-small cell lung cancer that is either locally advanced or metastatic.
- with locally advanced (non-resectable Stage II or Stage III) or metastatic (Stage IV) adenocarcinoma of the pancreas.
- with transitional cell bladder cancer.
- with unresectable, locally recurrent or metastatic breast cancer due to relapse following adjuvant/neoadjuvant chemotherapy. Treatment usually in combination with paclitaxel. Prior chemotherapy should have included an anthracycline unless clinically contraindicated.
- alone or in combination, 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 as a 30 minute intravenous infusion. This treatment 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 useful based upon the amount of toxicity experienced by the patient.

GEMCITABINE OETHMAAN may be used concomitantly with cisplatin using either a three or four week schedule. One of the following schedules is suggested:

3 week schedule: 1 250 mg/m^2 **GEMCITABINE OETHMAAN** given as a 30 minute intravenous infusion on the 1st and 8th day of every 21 day cycle and 100 mg/m^2 cisplatin administered on the 1st day. Dosage reduction with each cycle or within a cycle may be useful based upon the amount of toxicity experienced by the patient.

4 week schedule: 1 000 mg/m^2 **GEMCITABINE OETHMAAN** given as a 30 minute intravenous infusion on the 1st, 8th and 15th day of every 28 day cycle and 100 mg/m^2 cisplatin administered on either the 1st, 2nd or 15th day. Dosage reduction with each cycle or within a cycle may be useful based upon the amount of toxicity experienced by the patient.

Pancreatic cancer:

Adults: The recommended dose of **GEMCITABINE OETHMAAN** is 1 000 mg/m^2 given as a 30 minute intravenous infusion. This should be repeated once weekly for up to 7 weeks followed by 1 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 useful based upon the amount of toxicity experienced by the patient.

Bladder cancer:

Adults: The recommended monochemotherapy dosage of **GEMCITABINE OETHMAAN** is 1 250 mg/m^2 given as a 30 minute intravenous infusion. The dose should be given on the 1st, 8th and

15th day of each 28 day cycle. This four week cycle is then repeated. Dosage reduction with each cycle or within a cycle may be useful based upon the amount of toxicity experienced by the patient. **GEMCITABINE OETHMAAN** may be used concomitantly with cisplatin. The recommended dose of **GEMCITABINE OETHMAAN** is 1 000 mg/m^2 given as a 30 minute infusion. The dose should be given on the 1st, 8th and 15th day of each 28 day cycle in combination with cisplatin. Cisplatin is given at a recommended dose of 70 mg/m^2 on the 1st day concomitantly with **GEMCITABINE OETHMAAN** or on the 2nd day of each 28 day cycle. This four week cycle is then repeated. Dosage reduction with each cycle or within a cycle may be useful based upon the amount of toxicity experienced by the patient.

Breast cancer:

Adults: For treatment of breast cancer, recommended treatment is **GEMCITABINE OETHMAAN** in combination with paclitaxel. 175 mg/m^2 paclitaxel administered on the 1st day over approximately 3 hours as a intravenous infusion, followed by 1 250 mg/m^2 **GEMCITABINE OETHMAAN** as a 30 minute intravenous infusion on the 1st and 8th day of the 21 day cycle. Dose reduction with each cycle or within a cycle may be useful 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 **GEMCITABINE OETHMAAN** and paclitaxel combination.

Ovarian Cancer:

Single medicine use:

*Adults***:** The recommended dose of **GEMCITABINE OETHMAAN** 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***: GEMCITABINE OETHMAAN** in combination with carboplatin is recommended using **GEMCITABINE OETHMAAN** 1 000 mg/m^2 administered on days 1 and 8 of each 21 day cycle as a 30 minute intravenous infusion. After **GEMCITABINE OETHMAAN,** 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 **GEMCITABINE OETHMAAN** should be monitored prior to each dose for platelet, leucocyte and granulocyte counts and if necessary, the dose of **GEMCITABINE OETHMAAN** 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 – 1000	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-haematologic toxicity. Dosage reduction with the cycle or within a cycle may be useful 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.

Special Populations

*Patients with hepatic or renal impairment***:**

GEMCITABINE OETHMAAN 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: **GEMCITABINE OETHMAAN** 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 gemcitabine clearance and half-life are affected by age.

Method of administration

GEMCITABINE OETHMAAN is for use as intravenous infusion only.

GEMCITABINE OETHMAAN is well tolerated during infusion, with only a few reported cases of reaction at the injection site. There have been no reports of necrosis at the injection site. **GEMCITABINE OETHMAAN** can be easily administered on an outpatient basis.

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

4.3 Contraindications

GEMCITABINE OETHMAAN is contraindicated in

- patients with known hypersensitivity to gemcitabine or to any of the excipients of **GEMCITABINE OETHMAAN** listed in section 6.1.
- Pregnancy and lactation (see section 4.6). The safety of **GEMCITABINE OETHMAAN** 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

Toxicity has been known to increase should there be prolongation of infusion time and increased dosing frequency.

GEMCITABINE OETHMAAN can suppress bone marrow function as manifested by leucopoenia, thrombocytopenia and anaemia**. GEMCITABINE OETHMAAN** can cause myelosuppression which is usually mild to moderate and is more pronounced in granulocyte count.

Peripheral blood counts may continue to deteriorate after **GEMCITABINE OETHMAAN** 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 **GEMCITABINE OETHMAAN** treatment is given together with other chemotherapy medicines.

Hepatic insufficiency

Administration of **GEMCITABINE OETHMAAN** 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 OETHMAAN 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).

GEMCITABINE OETHMAAN has radiosensitising activity.

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 gemcitabine (see section 4.5).

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 OETHMAAN** 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. **GEMCITABINE OETHMAAN** 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 **GEMCITABINE OETHMAAN** 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. **GEMCITABINE OETHMAAN** should be permanently discontinued and supportive measures implemented, including blood pressure control and antiseizure therapy, if PRES develops during therapy.

Pulmonary toxicity:

Treatment should be stopped if interstitial pneumonitis together with pulmonary infiltrates should occur. Steroids may result in some relief.

Treatment should cease if severe pulmonary effects, such as pulmonary oedema, interstitial pneumonitis and adult respiratory distress syndrome should occur. Early stage supportive treatment may improve the situation.

Renal toxicity:

Haemolytic uraemic syndrome

Use with caution in patients with impaired renal function. Clinical findings consistent with the haemolytic uraemic syndrome (HUS) were rarely reported in patients receiving gemcitabine (see section 4.8).

Discontinue **GEMCITABINE OETHMAAN** at first signs of microangiopathic haemolytic anaemia such as rapidly falling haemoglobin with concomitant thrombocytopenia, elevation of serum bilirubin, serum creatinine, blood urea nitrogen, or LDH. Renal failure may not be reversible even with discontinuation of therapy and dialysis may be required.

General: Patients receiving therapy with **GEMCITABINE OETHMAAN** must be closely monitored. Evaluation of renal and hepatic function as well as medicine toxicity is required.

Carcinogenesis, mutagenesis, impairment of fertility:

Cytogenic damage has been produced by gemcitabine in an *in vivo* assay. Gemcitabine induced forward mutation *in vitro* in a mouse lymphoma assay. The influence of **GEMCITABINE**

OETHMAAN on fertility has not been established in humans. The carcinogenic potential of **GEMCITABINE OETHMAAN** has not been established.

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 3 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 (see section 4.6).

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 OETHMAAN** should be withdrawn immediately.

Sodium

After reconstitution, GEMCITABINE 200 mg OETHMAAN and GEMCITABINE 1 g OETHMAAN contain 17,7 mg and 88,5 mg sodium per vial, equivalent to 0,9 % and 4,43 % of the WHO maximum daily intake (RDI) of 2 g sodium for and adult, respectively.

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 **GEMCITABINE OETHMAAN,** FREQUENCY OF **GEMCITABINE OETHMAAN** 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 **GEMCITABINE OETHMAAN** 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 NONCONCURRENT USE OF **GEMCITABINE OETHMAAN.**

Other:

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

Safety in pregnancy and lactation has not been established.

Women of childbearing age/contraception in men and women

Due to the genotoxic potential of gemcitabine, women of childbearing age must use effective contraception during treatment with gemcitabine and for 6 months after treatment discontinuation. Men must be advised to use effective methods of contraception and not to father a child during treatment with gemcitabine and in the 3 months following its discontinuation.

Breastfeeding:

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.

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 3 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.

4.7 Effects on ability to drive and use machines

GEMCITABINE OETHMAAN can result in mild to moderate somnolence. Use with caution when driving or operating machinery until it is established that the patient does not become somnolent.

4.8 Undesirable effects

a. Summary of the safety profile

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).

b. Tabulated list of adverse reactions

System Organ Class	Adverse reaction	Frequency
Infections and infestations	Infections	Frequent
	Sepsis	Frequency unknown

Blood and lymphatic system disorders	Leucopenia, thrombocytopenia, anaemia. Myelosuppression is usually transient and usually does not result in dose reduction and rarely results in discontinuation. Dosage reduction or omission may be necessary in severe bone marrow depression cases. Febrile neutropenia	Frequent
	Thrombocytosis, Thrombotic microangiopathy	Less frequent
Immune system disorders	Anaphylactoid reaction	Less frequent
Metabolism and nutrition disorders	Anorexia	Frequent
Nervous system disorders	Headache, somnolence, insomnia	Frequent
	Cerebrovascular accident, Posterior reversible encephalopathy syndrome	Less frequent
Cardiac disorders	Myocardial infarct, heart failure, dysrrhythmia (predominantly supraventricular in nature).	Less frequent

Vascular disorders	Clinical signs of peripheral vasculitis, gangrene, hypotension, capillary leak syndrome	Less frequent
Respiratory, thoracic and mediastinal disorders	Dyspnoea Cough and rhinitis	Frequent
	Bronchospasm, pulmonary oedema, interstitial pneumonitis (with associated pulmonary infiltrates), adult respiratory distress syndrome.	Less frequent
Gastrointestinal disorders	Nausea, vomiting Diarrhoea, stomatitis and ulceration of the mouth, constipation.	Frequent
	Ischeamic colitis	Less frequent
Hepatobiliary disorders	Elevation of liver transaminases (AST and ALT) and alkaline phosphatases; Increased bilirubin	Frequent
	Serious hepatotoxicity including liver failure and death, increased gamma-glutamyl transferase (GGT)	Less frequent
Skin and subcutaneous tissue disorders	Allergic skin rash frequently associated with pruritis, alopecia	Frequent

	Severe skin reactions including desquamation and bullous skin eruptions, ulceration, vesicle and sore formation, scaling, toxic epidermal necrolysis, Steven-Johnson syndrome, pseudocellulitis,	Less frequent
	AGEP – acute generalized exanthematous pustulosis (see section 4.4), Lyell's Syndrome	Frequency unknown
Musculoskeletal and connective tissue disorders	Back pain, myalgia	Frequent
Renal and urinary disorders	Haematuria, mild proteinuria	Frequent
	Renal failure, haemolytic uraemic syndrome	Less frequent
General disorders and administration site conditions	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), Oedema/peripheral oedema- including facial oedema. Oedema is	Frequent

	usually reversible after stopping treatment.	
	Fever, asthenia, chills	Frequent
	Injection site reaction mainly mild in nature	Less frequent
Investigations	Elevation of liver transaminase and alkaline phosphatase	Frequent
Injury, poisoning and procedural complications	Radiosensitisation and radiation recall	Less frequent

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

4.9 Overdose:

In the event of an overdose, the patient should be monitored with appropriate blood counts and supportive treatment should be administered, as necessary. There is no known antidote for the overdosage of **GEMCITABINE OETHMAAN**.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacological classification: A 26 Cytostatic agents

Pharmacotherapeutic group: pyrimidine analogues

ATC Code: L01BC05

Gemcitabine exhibits cell phase specificity, primarily killing cells undergoing DNA synthesis (S-phase) and also blocking the progression of cells through the G1/S-phase boundary. Gemcitabine is metabolised intracellularly by nucleoside kinases to the active diphosphate (dFdCDP) and triphosphate (dFdCTP) nucleosides. The cytotoxic effect of gemcitabine is attributed to a combination of two actions of the diphosphate and the triphosphate nuceosides, which leads to inhibition of DNA synthesis.

First, gemcitabine diphosphate inhibits ribonucleotide reductase, which is responsible for catalyzing the reactions that generate the deoxynucleoside triphosphates for DNA synthesis. Inhibition of this enzyme by the diphosphate nucleoside causes a reduction in the concentrations of deoxynucleotides, including dCTP. Second, gemcitabine triphosphate competes with dCTP for incorporation into DNA.

The reduction in the intracellular concentration of dCTP (by the action of the diphosphate) enhances the incorporation of gemcitabine triphosphate into DNA (self potentiation).

After the gemcitabine nucleotide is incorporated into DNA, only one additional nucleotide is added to the growing DNA strands. After this addition, there is inhibition of further DNA synthesis. DNA polymerase epsilon is unable to remove the gemcitabine nucleotide and repair the growing DNA strands (masked chain termination).

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 (interindividual 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

Sodium acetate,

mannitol,

sodium hydroxide,

hydrochloric acid,

water for injection

nitrogen.

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: 2 years

6.4 Special precautions for storage

Before reconstitution: Store below 30 ºC. Protect from moisture, excessive heat and light.

After reconstitution: Store below 30 ºC and should be administered within 24 hours. Discard unused portion. Do not refrigerate as precipitates may occur under these conditions.

6.5 Nature and contents of container

Gemcitabine 200 mg Oethmaan:

10 ml colourless glass vial with a rubber stopper and an aluminium crimp cap with plastic flip off.

Gemcitabine 1 g Oethmaan:

50 ml colourless glass vial with a rubber stopper and an aluminium crimp cap with plastic flip off.

6.6 Special precautions for disposal

Instructions for reconstitution:

GEMCITABINE OETHMAAN should be reconstituted with 0.9 % sodium chloride only. Do not mix any other medicines with **GEMCITABINE OETHMAAN** when reconstituting. Due to solubility of gemcitabine, **GEMCITABINE OETHMAAN** should have a maximum concentration of 40 mg/ml on reconstitution. Reconstitution at concentrations greater than 40 mg/ml may result in incomplete dissolution and therefore should be avoided.

To reconstitute, add at least 5 ml of 0.9 % sodium chloride to the 200 mg vial or at least 25 ml of 0.9 % sodium chloride to the 1 g vial. Shake to dissolve. Administer as is or further dilute to the desired concentration with 0.9 % sodium chloride.

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

Oethmaan Biosims (Pty) Ltd

207A Sherwood House

Greenacres Office Park

c/o Victory and Rustenburg Roads

Victory Park

Johannesburg

2195

Telephone no.: 011 433 0602

8 REGISTRATION NUMBER(S):

Gemcitabine 200 mg Oethmaan: 41/26/0490

Gemcitabine 1 g Oethmaan: 41/26/0489

9 DATE OF FIRST AUTHORISATION

9 October 2009

Initial:	09-12-2024

10 DATE OF REVISION OF THE TEXT

09 December 2024