PROFESSIONAL INFORMATION

SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

GEMTAZ® READY TO USE 10 mg/mL solution for infusion.

GEMTAZ® 1200 mg/120 mL READY TO USE

GEMTAZ® 1300 mg/130 mL READY TO USE

GEMTAZ® 1400 mg/140 mL READY TO USE

GEMTAZ® 1500 mg/150 mL READY TO USE

GEMTAZ® 1600 mg/160 mL READY TO USE

GEMTAZ® 1700 mg/170 mL READY TO USE

GEMTAZ® 1800 mg/180 mL READY TO USE

GEMTAZ® 1900 mg/190 mL READY TO USE

GEMTAZ® 2000 mg/200 mL READY TO USE

GEMTAZ® 2200 mg/220 mL READY TO USE

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each single-dose premixed infusion bag contains gemcitabine (as hydrochloride) 10 mg/mL in 0,9 % sodium chloride

GEMTAZ® 1200 mg/120 mL READY TO USE

GEMTAZ® 1300 mg /130 mL READY TO USE

GEMTAZ® 1400 mg /140 mL READY TO USE

GEMTAZ® 1500 mg/150 mL READY TO USE

GEMTAZ® 1600 mg/160 mL READY TO USE

GEMTAZ® 1700 mg/170 mL READY TO USE

GEMTAZ® 1800 mg/180 mL READY TO USE

GEMTAZ® 1900 mg/190 mL READY TO USE

GEMTAZ® 2000 mg/200 mL READY TO USE

GEMTAZ® 2200 mg/220 mL READY TO USE

For full list of excipients, see section 6.1

Sugar free.

Excipients with known effect

Each mL of **GEMTAZ® READY TO USE** infusion contains 4,575 mg of sodium.

GEMTAZ® 1200 mg/120 mL READY TO USE solution for infusion: Each infusion bag of 120 mL contains 549 mg of Sodium.

GEMTAZ® 1300 mg /130 mL READY TO USE solution for infusion: Each infusion bag of 130 mL contains 594,75 mg of Sodium.

GEMTAZ® 1400 mg /140 mL READY TO USE solution for infusion: Each infusion bag of 140 mL contains 640,5 mg of Sodium.

GEMTAZ® 1500 mg/150 mL READY TO USE solution for infusion: Each infusion bag of 150 mL contains 686,25 mg of Sodium.

GEMTAZ® 1600 mg/160 mL READY TO USE solution for infusion: Each infusion bag of 160 mL contains 732 mg of Sodium.

GEMTAZ® 1700 mg/170 mL READY TO USE solution for infusion: Each infusion bag of 170 mL contains 777,75 mg of Sodium.

GEMTAZ® 1800 mg/180 mL READY TO USE solution for infusion: Each infusion bag of 180 mL contains 823,50 mg of Sodium.

GEMTAZ® 1900 mg/190 mL READY TO USE solution for infusion: Each infusion bag of 190 mL contains 869,25 mg of Sodium.

GEMTAZ® 2000 mg/200 mL READY TO USE solution for infusion: Each infusion bag of 200 mL contains 915 mg of Sodium.

GEMTAZ® 2200 mg/220 mL READY TO USE solution for infusion: Each infusion bag of 220 mL contains 1006,5 mg of Sodium.

3. PHARMACEUTICAL FORM

Solution for infusion, single-dose premixed infusion bag

GEMTAZ® READY TO USE is a “ready-to-infuse” formulation containing gemcitabine 10 mg/mL in 0,9 % sodium chloride**. GEMTAZ® READY TO USE** 10 mg/mL solution for infusion is a clear, colourless solution, free from visible particulate matter in infusion bag with minitulipe stopper.

The PH of **GEMTAZ® READY TO USE** 10 mg/mL solution for infusion is between 6,0 and 8,0.

The osmolality of **GEMTAZ® READY TO USE** 10 mg/mL solution for infusion Between 350 and 450 mOsm/kg.

GEMTAZ® READY TO USE is sugar free.

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

GEMTAZ® READY TO USE is indicated for the treatment of patients with locally advanced or metastatic non-small cell lung cancer.

GEMTAZ® READY TO USE 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.

GEMTAZ® READY TO USE is indicated for patients previously treated with 5-FU.

GEMTAZ® READY TO USE is indicated for treatment of patients with transitional cell bladder cancer.

GEMTAZ® READY TO USE, 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.

GEMTAZ® READY TO USE, 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

Ovarian Cancer

Recommended Dose and Schedule

Single medicine use:

Adults: The recommended dose of **GEMTAZ® READY TO USE** 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.

Combination use:

The recommended dosage of **GEMTAZ® READY TO USE** is 1000 mg/m^2 intravenously over 30 minutes on Days 1 and 8 of each 21-day cycle in combination with carboplatin AUC 4 g/mL/min administered intravenously on Day 1 after **GEMTAZ® READY TO USE** administration.

Select the **GEMTAZ® READY TO USE** premixed bag(s) that allow for a variance of up to 5 % of the BSA-calculated dose as described in table for Infusion Bag Selection and Administration further below.

Refer to carboplatin prescribing information for additional information.

Dosage Modifications

Recommended **GEMTAZ® READY TO USE** dosage modifications for myelosuppression are described in below tables (see section 4.4). Refer to the recommended dosage modifications for non-haematologic adverse reactions.

Table 1: Recommended Dosage Modifications for GEMTAZ® READY TO USE for Myelosuppression on Day of Treatment in Ovarian Cancer

Treatment Day	**Absolute Neutrophil Count (x 10^6/L)**		**Platelet Count (x 10^6/L)**	**Dosage Modification**
Day 1	Greater than or equal to 1500	and	Greater than or equal to 100,000	None
	Less than 1500	or	Less than 100,000	Delay Treatment Cycle
Day 8	Greater than or equal to 1500	and	Greater than or equal to 100,000	None
	1000 to 1499	or	75,000 to 99,999	50 % of full dose
	Less than 1000	or	Less than 75,000	Hold

Breast Cancer

Recommended Dose and Schedule

The recommended dosage of **GEMTAZ® READY TO USE** is 1250 mg/m^2 intravenously over 30 minutes on Days 1 and 8 of each 21-day cycle in combination with paclitaxel 175 mg/m^2 administered as a 3-hour intravenous infusion on Day 1 before **GEMTAZ® READY TO USE** administration. Select the **GEMTAZ® READY TO USE** premixed bag(s) that allow for a variance of up to 5 % of the BSA-calculated dose as described in table under sub-heading "**Infusion Bag Selection and Administration**".

Refer to paclitaxel prescribing information for additional information.

Dosage Modifications

Recommended **GEMTAZ® READY TO USE** dosage modifications for myelosuppression are described in table below (see section 4.4). Refer to the recommended dosage modifications for non-haematologic adverse reactions.

Table 2: Recommended Dosage Modifications for GEMTAZ® READY TO USE for Myelosuppression on Day of Treatment in Breast Cancer

Treatment Day	**Absolute Neutrophil Count (x 10^6/L)**		**Platelet Count (x 10^6/L)**	**Dosage Modification**
Day 1	Greater than or equal to 1500	and	Greater than or equal to 100,000	None
	Less than 1500	or	Less than 100,000	Hold
Day 8	Greater than or equal to 1500	and	Greater than 75,000	None
	1000 to 1199	or	50,000 to 75,000	75 % of full dose
	700 to 999	and	Greater than or equal to 50,000	50 % of full dose
	Less than 700	or	Less than 50,000	Hold

Non-Small Cell Lung Cancer

Recommended Dose and Schedule

28-day schedule

The recommended monochemotherapy dosage of **GEMTAZ® READY TO USE** is 1000 mg/m^2 intravenously over 30 minutes on Days 1, 8, and 15 of each 28-day cycle followed by a one week rest period. This four week cycle is then repeated. **GEMTAZ® READY TO USE** may be used in combination with cisplatin 100 mg/m^2 administered intravenously using either a three week or a four week schedule.

One of the following regimens is suggested:

3 week schedule: GEMTAZ® READY TO USE 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: GEMTAZ® READY TO USE 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.

Select the **GEMTAZ® READY TO USE** premixed bag(s) that allow for a variance of up to 5 % of the BSA-calculated dose as described in Table 4 below.

21-day schedule

The recommended dosage of **GEMTAZ® READY TO USE** is 1250 mg/m^2 intravenously over 30 minutes on Days 1 and 8 of each 21-day cycle in combination with cisplatin 100 mg/m^2 administered intravenously on Day 1 after **GEMTAZ® READY TO USE** administration. Select the **GEMTAZ® READY TO USE** premixed bag(s) that allow for a variance of up to 5 % of the BSA-calculated dose as described in table below.

Refer to cisplatin prescribing information for additional information.

Dosage Modifications

Recommended **GEMTAZ® READY TO USE** dosage modifications for myelosuppression are described in table below (see section 4.4). Refer to the recommended dosage modifications for non- haematologic adverse reactions

Pancreatic Cancer

Recommended Dose and Schedule

The recommended dosage of **GEMTAZ® READY TO USE** is 1000 mg/m^2 intravenously over 30 minutes. The recommended treatment schedule is as follows:

- Weeks 1 to 8: weekly dosing for the first 7 weeks followed by one week rest.
- After week 8: weekly dosing on Days 1, 8, and 15 of each 28-day cycle.

Select the **GEMTAZ® READY TO USE** premixed bag(s) that allow for a variance of up to 5 % of the BSA-calculated dose as described in table below.

Dosage Modifications

Recommended dosage modifications for **GEMTAZ® READY TO USE** for myelosuppression are described in table below (see section 4.4). Refer to the recommended dosage modifications for non-haematologic adverse reactions.

Table 3: Recommended Dosage Modifications for GEMTAZ® READY TO USE for Myelosuppression in Pancreatic Cancer and Non-Small Cell Lung Cancer

Absolute Neutrophil Count ($x 10^6$/L)		**Platelet Count ($x 10^6$/L)**	**Dosage Modification**
Greater than or equal to 1000	and	Greater than or equal to 100,000	None
500 to 999	or	50,000 to 99,999	75 % of full dose
Less than 500	or	Less than 50,000	Hold

Bladder cancer

Adults

The recommended monochemotherapy dosage of **GEMTAZ® READY TO USE** is 1250 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. **GEMTAZ® READY TO USE** may be used in combination with cisplatin. The recommended dose of **GEMTAZ® READY TO USE** is 1000 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 gemcitabine 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.

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 reported more myelosuppression when cisplatin was used in doses of 100 mg/m².

Dosage Modifications for Non-Haematologic Adverse Reactions

Permanently discontinue **GEMTAZ® READY TO USE** for any of the following:

- Unexplained dyspnea or evidence of severe pulmonary toxicity (see section 4.4).
- Haemolytic uremic syndrome (HUS) or severe renal impairment (see section 4.4).
- Severe hepatic toxicity (see section 4.4).
- Capillary leak syndrome (CLS) (see section 4.4).
- Posterior reversible encephalopathy syndrome (PRES) (see section 4.4).

Withhold **GEMTAZ® READY TO USE** or reduce dose by 50 % for other Grade 3 or 4 non-haematological adverse reactions until resolved.

Infusion Bag Selection and Administration

See the **GEMTAZ® READY TO USE** Instructions for use for additional information concerning premixed infusion bag(s) selection and spiking the infusion bag instructions.

Infusion Bag Selection

GEMTAZ® READY TO USE is provided in premixed bags that are ready for infusion and do not require any further preparation prior to use. Do not dilute prior to use. Do not remove or add medication.

Select the **GEMTAZ® READY TO USE** premixed bag(s) for infusion based on the patient's BSA range as outlined below in table below for 1000 mg/m^2 (ovarian cancer, non-small cell lung cancer, and pancreatic cancer) and table below for 1250 mg/m^2 (breast cancer, non-small cell

lung cancer). The **GEMTAZ® READY TO USE** administered dose may vary from the BSA-calculated dose by no more than 5 %.

Use another formulation of gemcitabine ready to use for patients who require a dose that is less than those listed in the tables below (i.e., <1150 mg).

Table 4: GEMTAZ® READY TO USE Infusion Bag(s) Selection for Gemcitabine Doses of 1000 mg/m^2 (Non-Small Cell Lung Cancer, Ovarian Cancer, Pancreatic Cancer)

BSA Range (m^2)	GEMTAZ® READY TO USE Infusion Bag(s)
1,16 to 1,25	1200 mg
1,26 to 1,35	1300 mg
1,36 to 1,45	1400 mg
1,46 to 1,55	1500 mg
1,56 to 1,65	1600 mg
1,66 to 1,75	1700 mg
1,76 to 1,85	1800 mg
1,86 to 1,95	1900 mg
1,96 to 2,10	2000 mg
2,11 to 2,30	2200 mg
2,31 to 2,45	2400 mg (1200 mg and 1200 mg)
2,46 to 2,55	2500 mg (1200 mg and 1300 mg)
2,56 to 2,64	2600 mg (1300 mg and 1300 mg)[a]

[a] Suggested combination. Other possible combinations can be used to reach the appropriate dose.

Table 5: GEMTAZ® READY TO USE Infusion Bag(s) Selection for Gemcitabine Doses of 1250 mg/m^2 (Breast Cancer, Non- Small Cell Lung Cancer)

BSA (m^2)	GEMTAZ® READY TO USE Infusion Bag(s)
1,16 to 1,24	1500 mg
1,25 to 1,32	1600 mg
1,33 to 1,40	1700 mg
1,41 to 1,47	1800 mg
1,48 to 1,56	1900 mg
1,57 to 1,68	2000 mg
1,69 to 1,84	2200 mg
1,85 to 1,96	2400 mg (1200 mg and 1200 mg)
1,97 to 2,04	2500 mg (1300 mg and 1200 mg)
2,05 to 2,12	2600 mg (1300 mg and 1300 mg)[a]
2,13 to 2,20	2700 mg (1200 mg and 1500 mg) [a]
2,21 to 2,28	2800 mg (1400 mg and 1400 mg) [a]
2,29 to 2,36	2900 mg (1200 mg and 1700 mg) [a]
2,37 to 2,44	3000 mg (1500 mg and 1500 mg) [a]
2,45 to 2,52	3100 mg (1200 mg and 1900 mg) [a]
2,53 to 2,60	3200 mg (1600 mg and 1600 mg) [a]
2,61 to 2,64	3300 mg (1600 mg and 1700 mg) [a]

[a] Combinations represented above are suggested combinations. Other possible combinations of bags can be used to reach the appropriate dose.

Special populations

Elderly population

GEMTAZ® READY TO USE 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.

Hepatic or renal impairment

GEMTAZ® READY TO USE should be used with caution in patients with hepatic insufficiency or with impaired renal function as no studies have been reported in patients with significant renal or hepatic impairment. There is insufficient information from reported clinical studies to allow clear dose recommendation for this patient population.

Paediatric population

The safety and effectiveness of **GEMTAZ® READY TO USE** in children aged less than 18 years have not been reported. Gemcitabine should not be used in children under 18 years of age because of safety and efficacy concerns.

Method of administration

Infuse all doses of **GEMTAZ® READY TO USE** over 30 minutes. If two premixed infusion bags are required to achieve the prescribed dose, infuse the total volume of both bags over 30 minutes.

4.3 Contraindications

GEMTAZ® READY TO USE is contraindicated in those patients with a known hypersensitivity to the active substance gemcitabine or to any of the active substances listed in section 6.1.

- Reactions include anaphylaxis (see section 4.8).
- Pregnancy and breast-feeding (see section 4.6).

4.4 Special warnings and precautions for use

Schedule-Dependent Toxicity

In reported clinical trials evaluating the maximum tolerated dose of gemcitabine, prolongation of the infusion time beyond 60 minutes or more frequent than weekly dosing resulted in an increased incidence of clinically significant hypotension, severe flu-like symptoms,

myelosuppression, and asthenia. The half-life of gemcitabine is reported to be influenced by the length of the infusion. Refer to the recommended **GEMTAZ® READY TO USE** dosage (see section 4.2).

Myelosuppression

Myelosuppression manifested by leucopoenia, neutropenia, thrombocytopenia, and anaemia reported with gemcitabine as a single agent and the risks are increased when gemcitabine is combined with other cytotoxic medicines. Myelosuppression is usually mild to moderate and is more pronounced for the granulocyte count (see section 4.2 and 4.8 -Haematological Toxicity).

In clinical trials, Grade 3-4 neutropenia, anaemia, and thrombocytopenia reported in patients who received single agent gemcitabine. The frequencies of Grade 3-4 neutropenia, anaemia, and thrombocytopenia varied in patients receiving gemcitabine in combination with another medicine (see section 4.8).

Prior to each dose of **GEMTAZ® READY TO USE**, obtain a complete blood count (CBC) with a differential and a platelet count. Modify the dosage as recommended (see section 4.2).

Pulmonary Toxicity and Respiratory Failure

Pulmonary toxicity, including interstitial pneumonitis, pulmonary fibrosis, pulmonary oedema, and adult respiratory distress syndrome (ARDS), has been reported. In some cases, these pulmonary events can lead to fatal respiratory failure despite the discontinuation of therapy. The onset of pulmonary symptoms may occur up to 2 weeks after the last dose of **GEMTAZ® READY TO USE** (see section 4.8).

Permanently discontinue **GEMTAZ® READY TO USE** in patients who develop unexplained dyspnoea, with or without bronchospasm, or evidence of severe pulmonary toxicity.

Haemolytic Uremic Syndrome

Haemolytic uremic syndrome (HUS), including fatalities from renal failure or the requirement for dialysis, have been reported with gemcitabine. In clinical trials, HUS was reported in patients. Most fatal cases of renal failure were due to HUS (see section 4.8). Serious cases of thrombotic microangiopathy other than HUS have been reported with gemcitabine (see section 4.8).

Assess renal function prior to initiation of **GEMTAZ® READY TO USE** (and periodically during treatment. Consider the diagnosis of HUS in patients who develop anaemia with evidence of microangiopathic haemolysis; increased bilirubin or LDH; reticulocytosis; severe thrombocytopenia; or renal failure (increased serum creatinine or BUN). Permanently discontinue **GEMTAZ® READY TO USE** (in patients with HUS or severe renal impairment. Renal failure may not be reversible even with the discontinuation of therapy.

Hepatic Toxicity

Drug-induced liver injury, including liver failure and death, has been reported in patients receiving gemcitabine alone or with other potentially hepatotoxic drugs (see section 4.8). Administration of **GEMTAZ® READY TO USE** (in patients with concurrent liver metastases or a pre-existing medical history of hepatitis, alcoholism, or liver cirrhosis can lead to exacerbation of the underlying hepatic insufficiency.

Assess hepatic function prior to initiation of **GEMTAZ® READY TO USE** (and periodically during treatment. Permanently discontinue **GEMTAZ® READY TO USE** (in patients who develop severe hepatic toxicity.

Embryo-Foetal Toxicity

Based on reported animal data and its mechanism of action, gemcitabine can cause foetal harm when administered to a pregnant woman. Gemcitabine was reported to be teratogenic, embryotoxic, and foetotoxic in mice and rabbits. In fertility studies gemcitabine has reportedly caused hypospermatogenesis in male mice.

Advise pregnant women of the potential risk to a foetus. Advise females of reproductive potential to use effective contraception during treatment with **GEMTAZ® READY TO USE** and for 6 months after the final dose.

Advise male patients with female partners of reproductive potential to use effective contraception during treatment with **GEMTAZ® READY TO USE** and for 3 months following the final dose.

Advice males being treated with **GEMTAZ® READY TO USE** 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 **GEMTAZ® READY TO USE.**

Exacerbation of Radiation Therapy Toxicity

Gemcitabine is not recommended for use in combination with radiation therapy.

Concurrent (given together or ≤7 days apart)

Life-threatening mucositis, especially esophagitis and pneumonitis reported in a trial in which gemcitabine was administered at a dose of 1000 mg/m^2 to patients with non-small cell lung cancer for up to 6 consecutive weeks concurrently with thoracic radiation.

Non-concurrent (given >7 days apart)

Excessive toxicity has not been reported when gemcitabine is administered more than 7 days before or after radiation. Radiation recall has been reported in patients who received gemcitabine after prior radiation.

Capillary Leak Syndrome

Capillary leak syndrome (CLS) with severe consequences has been reported in patients receiving gemcitabine as a single agent or in combination with other chemotherapeutic

medicines (see section 4.8).

Although fatal cases have been reported, this condition is usually treatable if recognised early and managed appropriately. 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. Permanently discontinue **GEMTAZ® READY TO USE** if CLS 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

Posterior reversible encephalopathy syndrome (PRES) has been reported in patients receiving gemcitabine as a single agent or in combination with other chemotherapeutic medicines (see section 4.8). PRES can present with headache, seizure, lethargy, hypertension, confusion, blindness, and other visual and neurologic disturbances

Confirm the diagnosis of PRES with magnetic resonance imaging (MRI). Permanently discontinue gemcitabine if PRES develops during therapy.

Severe cutaneous adverse reactions (SCARs)

Severe cutaneous adverse reactions (SCARs) including Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), and acute generalised 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, **GEMTAZ® READY TO USE** should be withdrawn immediately.

Sodium

GEMTAZ® READY TO USE contains sodium. One ml of the solution for infusion contains 4,575 mg sodium.

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

Special Populations

Paediatric Use

The safety and effectiveness of **GEMTAZ® READY TO USE** have not been reported in paediatric patients.

The safety and pharmacokinetics of gemcitabine was reported in paediatric patients with refractory leukaemia. The maximum tolerated dose was 10 mg/m^2/min for 360 minutes weekly for three weeks followed by a one-week rest period. The safety and activity of gemcitabine was reported in paediatric patients with relapsed acute lymphoblastic leukaemia and acute myelogenous leukaemia at a dose of 10 mg/m^2/min administered over 360 minutes weekly for three weeks followed by a one-week rest period. Patients with M1 or M2 bone marrow on Day 28 who did not experience unacceptable toxicity were eligible to receive a maximum of one additional four-week course. Reported toxicities include myelosuppression, febrile neutropenia, increased serum transaminases, nausea, and rash/desquamation. No meaningful clinical activity was reported.

Geriatric Use

In reported clinical studies, where patients with various malignancies received the single agent gemcitabine, no overall differences in safety was reported between patients aged 65 and older and younger patients, with the exception of a higher rate of Grade 3-4 thrombocytopenia in older patients as compared to younger patients.

In a reported randomized trial, women with ovarian cancer received gemcitabine with carboplatin, of which 29 % were age 65 years or older. Similar effectiveness was reported between older and younger women. There was significantly higher Grade 3-4 neutropenia in women 65 years of age or older (see section 4.8).

Gemcitabine clearance is reported to be affected by age; however, there are no recommended dose adjustments based on patients' age.

Gender

Gemcitabine clearance is reported to be decreased in females. In reported studies of gemcitabine, women, especially older women, were more likely not to proceed to a subsequent cycle and to experience Grade 3-4 neutropenia and thrombocytopenia (see section 4.2).

4.5 Interaction with other medicines and other forms of interaction

Cisplatin and carboplatin

When gemcitabine (1250 mg/m^2 on Days 1 and 8) and cisplatin (75 mg/m^2 on Day 1) were administered in patients with NSCLC, the reported clearance of gemcitabine on Day 1 was 128 L/hr/m^2 and on Day 8 was 107 L/hr/m^2. Data from patients with NSCLC reported that gemcitabine and carboplatin given in combination does not alter the pharmacokinetics of gemcitabine or carboplatin compared to administration of either single agent; however, due to wide confidence intervals and small sample size, interpatient variability may be observed.

Paclitaxel

Data from metastatic breast cancer patients reported that gemcitabine has little or no effect on the pharmacokinetics (clearance and half-life) of paclitaxel and paclitaxel has little or no effect on the pharmacokinetics of gemcitabine.

Radiotherapy

Concurrent (given together or ≤7 days apart) - toxicity associated with this multimodality therapy

is dependent on many different factors, including dose of gemcitabine, frequency of gemcitabine administration, dose of radiation, radiotherapy planning technique, the target tissue, and target volume. Reported pre-clinical and clinical studies have shown that gemcitabine has radio sensitising activity. In a reported single trial, when gemcitabine at a dose of 1000 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 reported, particularly in patients receiving large volumes of radiotherapy (median treatment volumes 4 795 cm^3).

It has been reported that studies done subsequently have suggested that it is feasible to administer gemcitabine at lower doses with concurrent radiotherapy with predictable toxicity, such as a phase II study in non-small cell lung cancer, where thoracic radiation doses of 66 Gy were applied concomitantly with an administration with gemcitabine (600 mg/m^2, four times) and cisplatin (80 mg/m^2 twice) during 6 weeks.

The optimum regimen for safe administration of gemcitabine 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 gemcitabine.

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

Risk Summary

Based on reported animal data and its mechanism of action, gemcitabine can cause foetal harm when administered to a pregnant woman. There are no reported data available on the use of gemcitabine in pregnant women. In reported animal reproductive studies, gemcitabine was teratogenic, embryotoxic, and foetotoxic in mice and rabbits (see Data below). Advise pregnant women of the potential risk to a foetus. **GEMTAZ® READY TO USE** should not be used during pregnancy.

Animal Data

Gemcitabine is reported to be embryotoxic in mice. Daily dosing of gemcitabine to pregnant mice increased the reported incidence of foetal malformation (cleft palate, incomplete ossification) at doses of 1,5 mg/kg/day [approximately 0,005 times the 1000 mg/m^2 clinical dose based on body surface area (BSA)]. Gemcitabine was reported to be embryotoxic and foetotoxic in rabbits. Daily dosing of gemcitabine to pregnant rabbits reported for foetotoxicity (decreased foetal viability, reduced litter sizes, and developmental delays) and increased the reported incidence of foetal malformations (fused pulmonary artery, absence of gall bladder) at doses of 0,1 mg/kg/day (approximately 0,002 times the 1000 mg/m^2 clinical dose based on BSA).

Breastfeeding

Risk Summary

There is no reported information regarding the presence of gemcitabine or its metabolites in human milk, or their effects on the breastfed infant or on milk production. Due to the potential for serious adverse reactions in breastfed infants from gemcitabine, advise women not to breastfeed during treatment with gemcitabine and for at least one week following the last dose.

Fertility

Pregnancy Testing

Verify pregnancy status in females of reproductive potential prior to initiating gemcitabine.

Contraception

Gemcitabine can cause foetal harm when administered to a pregnant woman.

Females: Because of the potential for genotoxicity, advise females of reproductive potential to use effective contraception during treatment with gemcitabine and for 6 months after the final dose.

Males: Because of the potential for genotoxicity, advise males with female partners of reproductive potential to use effective contraception during treatment with gemcitabine and for 3 months after the final dose (see section 5.3).

Infertility

Males: Based on reported animal studies, gemcitabine may impair fertility in males of reproductive potential. It is not known whether these effects on fertility are reversible.

4.7 Effects on ability to drive and use machines

Gemcitabine 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

a) Summary of the safety profile

The most commonly reported adverse drug reactions associated with gemcitabine treatment include: nausea with or without vomiting, raised liver transaminases (AST/ALT) and alkaline phosphatase, 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. Dose-limiting adverse reactions are reductions in thrombocyte, leucocyte and granulocyte counts.

The following table of undesirable effects and frequencies is based on reported data from clinical studies and post-marketing reports. Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Table 6 : Tabulated summary of adverse reactions

	Frequency category		
System Organ Class	**Frequent**	**Less frequent**	**Not known**
Infections and infestations	Infections		Sepsis
Blood and lymphatic system disorders	Leucopaenia (Neutropaenia Grade 3 = 19,3 %; Grade 4 = 6 %), bone-marrow suppression (is usually mild to moderate and mostly affects the	Thrombocytosis, thrombotic microangiopathy	

	granulocyte count), thrombo-cytopaenia, anaemia, febrile neutropaenia		
Immune system disorders		Anaphylactoid reaction	
Metabolism and nutrition disorders	Anorexia		
Nervous system disorders	Headache, insomnia, somnolence	Cerebrovascular accident, posterior reversible encephalopathy syndrome	
Cardiac disorders		Arrhythmias, predominantly supra-ventricular in nature, heart failure, myocardial infarct	
Vascular disorders		Clinical signs of peripheral vasculitis and gangrene, hypotension, capillary leak syndrome	
Respiratory,	Dyspnoea -usually mild and passes	Interstitial pneumonitis (with	

thoracic and mediastinal disorders	rapidly without treatment, cough, rhinitis	associated pulmonary infiltrates), bronchospasm - usually mild and transient but may require parenteral treatment, pulmonary oedema, adult respiratory distress syndrome	
Gastrointestinal disorders	Vomiting, nausea, diarrhoea, stomatitis and ulceration of the mouth, constipation	Ischaemic colitis	
Hepatobiliary disorders	Elevation of liver transaminases (AST and ALT) and alkaline phosphatase	Serious hepatotoxicity, including liver failure and death, increased gamma-glutamyl transferase (GGT) and Increased bilirubin.	
Skin and subcutaneous tissue disorders	Allergic skin rash frequently associated with pruritus,	Severe skin reactions, including desquamation and bullous skin eruptions,	Pseudo-Cellulitis, acute generalised

	alopecia, itching, sweating	ulceration, vesicle and sore formation, scaling, Toxic epidermal necrolysis, Stevens-Johnson Syndrome	exanthematous pustulosis
Musculo-skeletal and connective tissue disorders	Back pain, myalgia		
Renal and urinary disorders	Haematuria, mild proteinuria (rarely clinically significant and not usually associated with any change in serum creatinine or blood urea nitrogen).	Haemolytic uraemic syndrome (HUS), renal failure	
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	Injection site reactions-mainly mild in nature	

	sleeping difficulties have also been reported, oedema/ peripheral oedema- including facial oedema. Oedema is usually reversible after stopping treatment. Fever, asthenia, chills		
Injury, poisoning, and procedural complications		Radiation-toxicity (see section 4.5). Radiation recall	

Combination use in breast cancer

Adverse reactions reported with gemcitabine plus paclitaxel include anaemia, thrombocytopaenia, neutropaenia, febrile neutropaenia, fatigue, sensory neuropathy, diarrhoea and motor neuropathy.

Combination use in bladder cancer

Adverse reactions reported with gemcitabine plus cisplatin include anaemia, thrombocytopenia, nausea and vomiting, diarrhoea, infection and stomatitis.

Combination use in ovarian cancer

Adverse reactions reported with gemcitabine plus carboplatin include anaemia, neutropaenia, thrombocytopaenia, leucopaenia and sensory neuropathy, haemorrhage, febrile neutropaenia and infection without neutropaenia.

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 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 overdoses of gemcitabine. Myelosuppression, paresthesias, and severe rash were the principal toxicities reported when a single dose as high as 5700 mg/m^2 was administered by intravenous infusion over 30 minutes every 2 weeks to several patients in a reported dose-escalation study. 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: A.26 Cytostatic agents; ATC code: L01BC05.

Mechanism of Action

Gemcitabine kills cells undergoing DNA synthesis and blocks the progression of cells through the G1/S-phase boundary. Gemcitabine is metabolized by nucleoside kinases to diphosphate (dFdCDP) and triphosphate (dFdCTP) nucleosides. Gemcitabine diphosphate inhibits ribonucleotide reductase, an enzyme responsible for catalyzing the reactions that generate deoxynucleoside triphosphates for DNA synthesis, resulting in reductions in deoxynucleotide

concentrations, including dCTP. 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, which eventually results in the initiation of apoptotic cell death.

5.2 Pharmacokinetic properties

The pharmacokinetics of gemcitabine were reported in patients with various solid tumours. Pharmacokinetic parameters were derived using reported data from patients treated for varying durations of therapy given weekly with periodic rest weeks and using both short infusions (<70 minutes) and long infusions (70 to 285 minutes). The total gemcitabine dose varied from 500 mg/m^2 to 3600 mg/m^2.

Distribution

The volume of distribution was reported to be increased with infusion length. The reported volume of distribution of gemcitabine was 50 L/m^2 following infusions lasting <70 minutes. For long infusions, the reported volume of distribution rose to 370 L/m^2.

Gemcitabine pharmacokinetics are reported to be linear and are described by a 2-compartment model. The volume of distribution of the central compartment was reported as 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.

Population pharmacokinetic analyses of combined single and multiple dose studies reported that the volume of distribution of gemcitabine was significantly influenced by duration of infusion and sex.

Gemcitabine plasma protein binding is 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.

The primary metabolite 2'-deoxy-2',2'-difluorouridine (dFdU) is not active and is found in plasma and urine. Formation of dFdU from parent compound ranges from 91 % to 98 %. Tissue distribution of dFdU is extensive. The active metabolite, gemcitabine triphosphate, reported to be extracted from peripheral blood mononuclear cells. The reported half-life of the terminal phase for gemcitabine triphosphate from mononuclear cells ranges from 1,7 to 19,4 hours.

Excretion

Gemcitabine disposition was reported in patients who received a single 1000 mg/m^2 of radiolabeled drug as a 30-minute infusion. Within one week, 92 % to 98 % of the dose was reported to be recovered, almost entirely in the urine. Gemcitabine (<10 %) and the inactive uracil metabolite, 2´-deoxy-2´,2´-difluorouridine (dFdU) accounted for 99 % of the excreted dose. The metabolite dFdU is also reported in plasma.

Specific Populations

Geriatric Patients

Clearance of gemcitabine was reported to be affected by age. The lower clearance in geriatric patients was reported for higher concentrations of gemcitabine for any given dose. Differences in either clearance or volume of distribution based on patient characteristics or the duration of infusion result in changes in half-life and plasma concentrations. Table below shows plasma

clearance and half-life of gemcitabine following short infusions for typical patients by age and sex.

Table 7: Gemcitabine Clearance and Half-Life for the "Typical" Patient

Age	Clearance Men ($L/hr/m^2$)	Clearance Women ($L/hr/m^2$)	Half-Life[a] Men (min)	Half-Life[a] Women (min)
29	92,2	69,4	42	49
45	75,7	57,0	48	57
65	55,1	41,5	61	73
79	40,7	30,7	79	94

[a] Half-life for patients receiving a <70 minute infusion.

Gemcitabine half-life for short infusions reportedly ranged from 42 to 94 minutes and for long infusions varied from 245 to 638 minutes, depending on age and sex, reflecting a greatly increased volume of distribution with longer infusions.

Male and Female Patients

Clearance of gemcitabine was reported to be affected by gender. Females have been reported for lower clearance (approximately 25 % lower that the values for men) and longer half-lives than male patients as described in table above. 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

Patients with Renal Impairment

No clinical studies have been reported with gemcitabine in patients with decreased renal function.

Patients with Hepatic Impairment

No clinical studies have been reported with gemcitabine in patients with decreased hepatic function.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium chloride, sodium hydroxide, hydrochloric acid, water for injection, nitrogen.

6.2 Incompatibilities

GEMTAZ® READY TO USE is provided in premixed bags that are ready for infusion and do not require any further preparation prior to use. Do not dilute prior to use. Do not remove or add medication (see section 4.2, Infusion bag selection).

6.3. Shelf life

36 Months

6.4 Special precautions for storage

Store at or below 25 °C. Do not freeze as crystallization can occur.

6.5 Nature and contents of container

GEMTAZ® READY TO USE is filled in printed multilayer M312 infusion bag with M916M polyolefin tube and stoppered with polycarbonate minitulipe M95A spike port with chlorobutyl (latex free) 6321 GS joint.

The filled and stoppered infusion bag is packed in preprinted aluminium pouch in such a way that the port of infusion bag will be towards the sealing side.

The sealed pouch is packaged in show box along with package insertand instructions for use.

6.6 Special precautions for disposal and other handling

Handling

- Calculate the dose, and decide which size of the Gemcitabine infusion bags is needed.
- Inspect the product pack for any damage. Do not use if there are signs of tampering.
- Apply patient-specific label on the overwrap.

Removal of infusion bag from overwrap and infusion bag inspection

- Tear overwrap at notch. Do not use if overwrap has been previously opened or damaged.
- Remove infusion bag from overwrap.
- Use only if infusion bag and seal are intact. Prior to administration check for minute leaks by squeezing bag firmly. Ifleaks are found, discard the bag and solution as sterility may be impaired.
- Parenteral medicinal products should be inspected visually for particulate matter and discolouration prior toadministration. If particulate matter is observed, do not administer.

Administration

- Break the Minitulipe stopper seal by applying pressure on one side with hand.
- Using aseptic technique, attach sterile administration set.
- Refer to directions for use accompanying the administration set.

Precautions

- Do not use in series connection.
- Do not introduce additives into the infusion bag.

- The solution for infusion is ready to use and must not be mixed with other medicinal products.

After opening the infusion bag:

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

- Gemcitabine solution for infusion is for single use only.
- Personnel must be provided with appropriate handling materials, notably long sleeved gowns, protection masks, caps,protective goggles, sterile single-use gloves, protective covers for the work area and collection bags for waste.
- Cytotoxic preparations should not be handled by pregnant staff.
- If the product comes into contact with the eyes, severe irritation may result. In such an event, the eyes should be washed thoroughly and immediately. Consult a doctor if irritation persists.
- If the solution should come into contact with skin, rinse the affected area thoroughly with water.
- Excreta and vomit must be handled with care.

Disposal

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

7. HOLDER OF CERTIFICATE OF REGISTRATION

RANBAXY PHARMACEUTICALS (PTY) LTD

14 Lautre Road, Stormill, Ext.1

Roodepoort,

Johannesburg, 1724

8. REGISTRATION NUMBER(S)

GEMTAZ® 1200 mg/120 mL READY TO USE: 54/26/0842

GEMTAZ® 1300 mg/130 mL READY TO USE: 54/26/0843

GEMTAZ® 1400 mg/140 mL READY TO USE: 54/26/0844

GEMTAZ® 1500 mg/150 mL READY TO USE: 54/26/0845

GEMTAZ® 1600 mg/160 mL READY TO USE: 54/26/0846

GEMTAZ® 1700 mg/170 mL READY TO USE: 54/26/0847

GEMTAZ® 1800 mg/180 mL READY TO USE: 54/26/0848

GEMTAZ® 1900 mg/190 mL READY TO USE: 54/26/0849

GEMTAZ® 2000 mg/200 mL READY TO USE: 54/26/0850

GEMTAZ® 2200 mg/220 mL READY TO USE: 54/26/0851

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

30 January 2024

10. DATE OF REVISION OF THE TEXT