
Professional Information for GEMTAZ 200 mg and GEMTAZ 1 g

SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

GEMTAZ 200 mg injection

GEMTAZ 1 g injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

GEMTAZ 200 mg: Each vial contains gemcitabine hydrochloride equivalent to 200 mg of gemcitabine (40 mg/mL).

GEMTAZ 1 g: Each vial contains gemcitabine hydrochloride equivalent to 1 g of gemcitabine (40 mg/mL).

Contains sugar alcohol:

GEMTAZ 200 mg contains 200 mg mannitol per vial.

GEMTAZ 1 g contains 1 000 mg mannitol per vial.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Injection.

White to off-white lyophilized cake.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

GEMTAZ is indicated for the treatment of patients with locally advanced or metastatic non-small

cell lung cancer.

GEMTAZ is indicated as first-line treatment for patients with locally advanced (non-resectable Stage II of Stage III) or metastatic (Stage IV) adenocarcinoma of the pancreas. GEMTAZ is indicated for patients previously treated with 5-FU.

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

GEMTAZ, 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 contraindicated.

4.2 Posology and method of administration

Posology

Non-small cell lung cancer

Adults: The recommended monotherapy dosage is 1 000 mg/m², 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.

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

3 weeks schedule: GEMTAZ 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 1 000 mg/m² 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 GEMTAZ is 1 000 mg/m², 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 GEMTAZ 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.

GEMTAZ may be used in combination with cisplatin. The recommended dose of GEMTAZ 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 GEMTAZ or day 2 of each 28 day cycle. This four week cycle is then repeated. Dosage reduction with each cycle or within a cycle may be applied based upon the amount of toxicity experienced by the patient. More myelosuppression may be experienced when cisplatin is used in doses of 100 mg/m².

Breast cancer

Adults: GEMTAZ in combination with paclitaxel is recommended using paclitaxel (175 mg/m²) administered on day 1 over approximately 3 hours as an intravenous infusion, followed by

GEMTAZ (1 250 mg/m²) 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 experience by the patient. Patients should have an absolute granulocyte count of at least 1 500 (x 10⁶/L) prior to initiation of GEMTAZ + paclitaxel combination.

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

Absolute granulocyte count (x 10⁶/L)	Platelet count (x 10⁶/L)	% of full dose
> 1 000	and > 100 000	100
500 – 1 000	or 50 000 – 100 000	75
< 500	or < 50 000	hold

Periodic physical examination and checks of renal and hepatic function should be made to detect non-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 physician.

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

Special populations

Elderly patients:

GEMTAZ 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.

Patients with renal or hepatic insufficiency:

The safety of GEMTAZ in patients with renal or hepatic insufficiency has not been established. Caution is advised.

GEMTAZ should be administered with caution to patients with impaired renal function and should be discontinued at the first signs of microangiopathic haemolytic anaemia. Renal failure may not be reversible even with discontinuation of therapy and dialysis might be required.

Method of administration

GEMTAZ is for intravenous use only.

For instructions on infusion, see section 6.6.

4.3 Contraindications

- Patients with a known hypersensitivity to gemcitabine or any of the ingredients of GEMTAZ listed in section 6.1.
- Safety and efficacy in pregnancy and lactation have not been established (see section 4.6).
- Children, as safety and efficacy have not been established.

4.4 Special warnings and precautions for use

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

GEMTAZ can suppress bone marrow function as manifested by leucopenia, thrombocytopenia and anaemia. Myelosuppression is usually mild to moderate and is more pronounced for the

granulocyte count (see section 4.2).

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

- Bone marrow depression (see section 4.5)
- Existing or recent chickenpox
- Herpes zoster

RADIOTHERAPY

Concurrent (or < 7 days apart): GEMTAZ has radiosensitising activity. Administering GEMTAZ at a dose of 1 000 mg/m³ concurrently for up to six consecutive weeks with therapeutic thoracic radiation to patients with non-small cell lung cancer, can result in significant toxicity in the form of severe and potentially life-threatening mucositis. Especially oesophagitis and pneumonitis were observed, particularly in patients receiving large volumes of radiotherapy (median treatment volumes 4 795 cm³). The optimum regimen for safe administration of GEMTAZ with therapeutic doses of radiation has not yet been determined.

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

Avoid any immunisation unless approve by the medical practitioner. Persons who have received oral polio vaccination should be avoided.

Caution is advised when starting treatment of GEMTAZ in patients with compromised bone marrow function. The possibility of cumulative bone marrow depression should be considered when using combination or sequential chemotherapy.

GEMTAZ treatment must be stopped if interstitial pneumonitis and pulmonary infiltrates develops. If

cases of pulmonary oedema, and adult respiratory distress syndrome, cessation of GEMTAZ treatment is necessary.

Risk of 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 should be withdrawn immediately.

4.5 Interaction with other medicines and other forms of interaction

Additive bone marrow depression may occur when administering GEMTAZ with other bone marrow depressants or radiotherapy. Dosage reduction may be required when two or more bone marrow depressants, including radiation, are used concurrently or consecutively (see section 4.4).

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

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

Due to the suppression of normal defence mechanisms by gemcitabine therapy, concurrent use of

GEMTAZ with a live virus vaccine may potentiate the replication of the vaccine virus, increase the side-effects of the vaccine virus, and/or decrease the patient's antibody response to the vaccine.

4.6 Fertility, pregnancy and lactation

Pregnancy

GEMTAZ is contraindicated in pregnancy (see section 4.3).

Females: Because of the potential of genotoxicity, females of reproductive potential should be advised to use effective contraception during treatment with GEMTAZ and for six months after the final dose.

Breastfeeding

GEMTAZ is contraindicated during breastfeeding (see section 4.3).

Fertility

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. Male patients should further seek advice regarding cryoconservation of sperm prior to treatment because of the possibility of infertility due to therapy with GEMTAZ.

4.7 Effects on ability to drive and use machines

GEMTAZ has been reported to cause mild to moderate somnolence. Patients should be cautioned against driving or operating machinery until it is established how GEMTAZ affects them.

4.8 Undesirable effects

Infections and infestations

Less frequent: Febrile neutropenia or other infections; stomatitis.

Blood and lymphatic system disorders

Frequent: Anaemia; leucopenia; neutropenia; thrombocytopenia.

Less frequent: Haemorrhage; haemolytic-uremic syndrome

Immune system disorders

Less frequent: Anaphylactoid reaction

Nervous system disorders

Frequent: Fever.

Less frequent: Paraesthesia; somnolence.

Cardiac disorders

Frequent: Oedema.

Less frequent: Cardiovascular effects (including dysrhythmia); heart failure; cardiac infarction.

Vascular disorders

Less frequent: Hypotension.

Respiratory disorders

Frequent: Dyspnoea.

Less frequent: Bronchospasm; lung toxicity; pulmonary oedema.

Gastrointestinal disorders

Frequent: Constipation; diarrhoea; nausea and vomiting.

Skin and subcutaneous tissue disorders

Frequent: Skin rash (with or without itching); alopecia.

Less frequent: Scaling, vesicle and sore formation; ulceration.

Frequency unknown: acute generalised exanthematous pustulosis.

Renal and urinary disorders

Frequent: Haematuria; proteinuria.

Less frequent: Renal failure.

General disorders and administration site conditions

Frequent: Flu-like syndrome.

Less frequent: Irritation, pain or redness at injection site; radiosensitisation and radiation recall (see section 4.4).

Reporting of suspected adverse reactions:

Reporting suspected adverse reactions after authorisation of GEMTAZ is important. It allows continued monitoring of the benefit/risk balance of GEMTAZ. Health care providers are requested to report any suspected adverse drug reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website.

Suspected adverse reactions can also be reported directly to the Holder of certificate of registration via email or telephonically: pharmacovigilance.africasme@sunpharma.com or Tel: +27(0) 12 6432000

4.9 Overdose

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Category and class: A.26 Cytostatic agents.

Pharmacotherapeutic group: Pyrimidine analogues.

ATC code: L01BC05.

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

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

5.2 Pharmacokinetic properties

After intravenous doses gemcitabine is rapidly cleared from the blood and metabolised by cytidine deaminase in the liver, kidney, blood and other tissues. Clearance is approximately 25 % lower in women than in men. Almost the entire dose is excreted in urine as 2'-deoxy-2',2'-difluorouridine (dFdU), only about 1 % being found in the faeces. Intracellular metabolism produces mono-, di-, and triphosphate metabolites, the latter two active. The half-life of gemcitabine ranges from 42 to 94 minutes depending on age and gender. The intracellular half-life of the triphosphate is stated to range from 0,7 to 12 hours.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Mannitol

Sodium acetate trihydrate

Hydrochloric acid (for pH-adjustment)

Sodium hydroxide (for pH-adjustment).

6.2 Incompatibilities

GEMTAZ should not be mixed with other medicines when reconstituted.

6.3 Shelf life

Unopened vials:

36 months.

After reconstitution:

Reconstituted solution can be stored for 24 hours at or below 25 °C.

6.4 Special precautions for storage

Store at or below 25 °C.

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

Discard any unused portion.

Do not refrigerate.

6.5 Nature and contents of container

GEMTAZ 200 mg is packed into 10 mL colourless type-I tubular glass vials with 20 mm crimp, with 20 mm grey bromobutyl rubber stopper and sealed with green flip-off tear-off aluminium seal.

GEMTAZ 1 g is packed into 50 mL colourless type-I moulded glass vial with 20 mm crimp, with 20 mm grey bromobutyl rubber stopper and sealed with green flip-off tear-off aluminium seal.

6.6 Special precautions for disposal and other handling

Instructions for reconstitution:

The only approved diluent for reconstitution of GEMTAZ is 0,9 % sodium chloride injection without preservative. Due to solubility considerations, the maximum concentration for GEMTAZ upon reconstitution is 40 mg/mL. Reconstitution at concentrations greater than 40 mg/mL may result in incomplete dissolution and should be avoided.

To reconstitute, add at least 5 mL of 0,9 % sodium chloride injection without preservatives to the 200 mg vial or at least 25 mL of 0,9 % sodium chloride without preservatives to the 1 g vial. Shake to dissolve. The appropriate amount of medicine may be administered as prepared or further diluted with 0,9 % sodium chloride injection without preservative.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Ranbaxy Pharmaceuticals (Pty) Ltd

14 Lautre Road

Stormill, Ext. 1

Roodepoort

Johannesburg 1724

8. REGISTRATION NUMBERS

GEMTAZ 200 mg: 41/26/0934

GEMTAZ 1 g: 41/26/0933

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10 June 2009

10. DATE OF REVISION OF THE TEXT

08 April 2024