Summary Product Characteristics for Pharmaceutical Product

1. Name of the medicinal product

INN Name: Gemcitabine for Injection USP 200 mg

Trade Name: GEMTERO 200 MG

Strength: 200 mg

Pharmaceutical form: Injection, Powder, Lyophilized (for solution)

2.Qualitative and quantitative composition

White to off white lyophilized powder contained in a flint glass vial.

3.Pharmaceutical form

Injection

4.CLINICAL PARTICULARS

4.1 Therapeutic Indications

Ovarian Cancer

Gemcitabine USP in combination with carboplatin is indicated for the treatment of patients with advanced ovarian cancer that has relapsed at least 6 months after completion of platinum-based therapy.

Breast Cancer

Gemcitabine USP in combination with paclitaxel is indicated for the first-line treatment of patients with metastatic breast cancer after failure of prior anthracycline-containing adjuvant chemotherapy, unless anthracyclines were clinically contraindicated.

Non-Small Cell Lung Cancer

Gemcitabine USP in combination with cisplatin is indicated for the first-line treatment of patients with inoperable, locally advanced (Stage IIIA or IIIB) or metastatic (Stage IV) non- small cell lung cancer.

Pancreatic Cancer

Gemcitabine USP is indicated as first-line treatment for patients with locally advanced (nonresectable Stage II or Stage III) or metastatic (Stage IV) adenocarcinoma of the pancreas. Gemcitabine USP is indicated for patients previously treated with fluorouracil.

4.2 Posology and method of administration

Ovarian Cancer

Recommended Dose and Schedule

The recommended dose of Gemcitabine for Injection is 1000 mg/m^2 as an intravenous infusion over 30 minutes on Days 1 and 8 of each 21-day cycle, in combination with carboplatin AUC 4 intravenously after Gemcitabine for Injection administration on Day 1 of each 21-day cycle. Refer to carboplatin prescribing information for additional information.

Dose Modifications

Recommended Gemcitabine for Injection dose modifications for myelosuppression are described in Table 1 and Table 2. Refer to Dosage and Administration (2.5) for recommendations for non-hematologic adverse reactions.

Table 1: Dosage Reduction Guidelines for Gemcitabine for Injection for Myelosuppression on Day of Treatment in Ovarian Cancer

Treatment Day	**Absolute granulocyte count (x 106/L)**		**Platelet count (x 106/L)**	**% of full dose**
Day 1	≥1500 <1500	and or	≥100,000 <100,000	100% Delay Treatment Cycle
Day 8	≥1500 1000-1499 <1000	and or or	≥100,000 75,000-99,999 <75,000	100% 50% Hold

Table 2: Gemcitabine for Injection Dose Modification for Myelosuppression in Previous Cycle in Ovarian Cancer

Occurrence	**Myelosuppression During Treatment Cycle**	**Dose Modification**
Initial Occurrence	Absolute granulocyte count less than 500 x 106/L for more than 5 days Absolute granulocyte count less than 100 x 106/L for more than 3 days Febrile neutropenia Platelets less than 25,000x106/L Cycle delay of more than one week due to toxicity	Permanently reduce Gemcitabine for Injection to 800 mg/ m^2 on Days 1 and 8
Subsequent Occurrence	If any of the above toxicities occur after the initial dose reduction	Permanently reduce Gemcitabine for Injection dose to 800 mg/ m2on Day 1 only

Breast Cancer

Recommended Dose and Schedule

The recommended dose of Gemcitabine for Injection is 1250 mg/ m^2 intravenously over 30 minutes on Days 1 and 8 of each 21-day cycle that includes paclitaxel. Paclitaxel should be administered at 175 mg/ m^2 on Day 1 as a 3 hour intravenous infusion before Gemcitabine for Injection administration.

Dose Modifications

Recommended dose modifications for Gemcitabine for Injection for myelosuppression are described in Table 3 Refer to Dosage and Administration (2.5) for recommendations for non- hematologic adverse reactions

Table 3: Recommended Dose Reductions for Gemcitabine for Injection for Myelosuppression on Day of Treatment in Breast Cancer

Treatment Day	**Absolute granulocyte count (x 106/L)**		**Platelet count (x 106/L)**	**% of full dose**
Day 1	≥1500	and	≥100,000	100%
	less than 1500	or	less than 100,000	Hold
Day 8	≥1200	and	>75,000	100%
	1000-1199	or	50,000-75,000	75%
	700-999	and	≥50,000	50%
	<700	or	<50,000	Hold

Non-Small Cell Lung Cancer

Recommended Dose and
Schedule Every 4-week schedule

The recommended dose of Gemcitabine for Injection is 1000 mg/ m^2 intravenously over 30 minutes on Days 1, 8, and 15 in combination with cisplatin therapy. Administer cisplatin intravenously at 100 mg/ m^2 on Day 1 after the infusion of Gemcitabine for Injection.

Every 3-week schedule

The recommended dose of Gemcitabine for Injection is 1250 mg/ m^2 intravenously over 30 minutes on Days 1 and 8 in combination with cisplatin therapy. Administer cisplatin intravenously at 100 mg/ m^2 on Day 1 after the infusion of Gemcitabine for Injection.

Dose Modifications

Recommended dose modifications for Gemcitabine for Injection

myelosuppression are described in Table 4 Refer to Dosage and Administration (2.5) for Gemcitabine for Injection recommendations for non-hematologic adverse reactions.

Pancreatic Cancer

Recommended Dose and Schedule

The recommended dose of Gemcitabine for Injection is 1000 mg/ m^2 over 30 minutes intravenously. The recommended treatment schedule is as follows: Weeks 1-8: weekly dosing for the first 7 weeks followed by one week rest. After week 8: weekly dosing on Days 1, 8, and 15 of 28-day cycles.

Dose Modifications

Recommended dose modifications for Gemcitabine for Injection for myelosuppression are described in Table 4 Refer to Dosage and Administration (2.5) for recommendations for non- hematologic adverse reactions.

Table 4: Recommended Dose Reductions for Gemcitabine for Injection for Myelosuppression in Pancreatic Cancer and Non-Small Cell Lung Cancer

Absolute granulocyte count (x 106/L)		**Platelet count (x 106/L)**	**% of full dose**
≥1000	And	≥100,000	100%
500-999	Or	50,000-99,999	75%
<500	Or	<50,000	Hold

Dose Modifications for Non-Hematologic Adverse Reactions

Permanently discontinue Gemcitabine for Injection for any of the following: Unexplained dyspnea or other evidence of severe pulmonary toxicity Severe hepatic toxicity

Hemolytic-uremic
syndrome Capillary
leak syndrome
Posterior reversible encephalopathy syndrome

Withhold Gemcitabine for Injection or reduce dose by 50% for other severe (Grade 3 or 4) non-hematological toxicity until resolved. No dose modifications are recommended for alopecia, nausea, or vomiting.

Preparation and Administration Precautions

Exercise caution and wear gloves when preparing Gemcitabine for Injection solutions. Immediately wash the skin thoroughly or rinse the mucosa with copious amounts of water if Gemcitabine for Injection contacts the skin or mucus membranes. Death has occurred in animal studies due to dermal absorption.

Preparation for Intravenous Infusion Administration

Reconstitute the vials with 0.9% Sodium Chloride Injection without preservatives.

Add 5 mL to the 200-mg vial or 25 mL to the 1-g vial. These dilutions each yield a Gemcitabine for Injection concentration of 38 mg/mL. Complete withdrawal of the vial contents will provide 200 mg or 1 g of Gemcitabine for Injection. Prior to administration the appropriate amount of drug must be diluted with 0.9% Sodium Chloride Injection. Final concentrations may be as low as 0.1 mg/mL.

Reconstituted Gemcitabine for Injection is a clear, colorless to light straw-colored solution. Inspect visually prior to administration and discard for particulate matter or discoloration. Gemcitabine for Injection solutions are stable for 24 hours at controlled room temperature of 20° to 25°C (68° to 77°F). Do not refrigerate as crystallization can occur.

No incompatibilities have been observed with infusion bottles or polyvinyl chloride bags and administration sets.

4.3 Contraindications

Gemcitabine for Injection is contraindicated in patients with a known hypersensitivity to gemcitabine. Reactions include anaphylaxis.

4.4 Special warnings and precautions for use Schedule-dependent toxicity:

In clinical trials evaluating the maximum tolerated dose of Gemcitabine USP, 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 USP is influenced by the length of the infusion.

Myelosuppression:

Myelosuppression manifested by neutropenia, thrombocytopenia, and anemia occurs with Gemcitabine USP as a single agent and the risks are increased when Gemcitabine USP is combined with other cytotoxic drugs. In clinical trials, grade 3-4 neutropenia, anemia, and thrombocytopenia occurred in 25%, 8%, and 5%, respectively of the 979 patients who received single agent Gemcitabine USP. The frequencies of grade 3-4 neutropenia, anemia, and thrombocytopenia varied from 48% to 71%, 8% to 28%, and 5% to 55%, respectively, in patients receiving Gemcitabine USP in combination with another drug [see adverse reactions].

Prior to each dose of Gemcitabine USP, obtain a complete blood count (CBC) with a differential and a platelet count. Modify the dosage as recommended.

Pulmonary toxicity and respiratory failure:

Pulmonary toxicity, including interstitial pneumonitis, pulmonary fibrosis, pulmonary edema, 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

Gemcitabine USP [see adverse reactions].

Permanently discontinue Gemcitabine USP in patients who develop unexplained dyspnea, with or without bronchospasm, or evidence of severe pulmonary toxicity.

Hemolytic uremic syndrome:

Hemolytic uremic syndrome (HUS), including fatalities from renal failure or the requirement for dialysis, can occur with Gemcitabine USP. In clinical trials, HUS occurred in 0.25% of 2429 patients. Most fatal cases of renal failure were due to HUS.

Assess renal function prior to initiation of Gemcitabine USP and periodically during treatment. Consider the diagnosis of HUS in patients who develop anemia with evidence of microangiopathic hemolysis; increased bilirubin or LDH; reticulocytosis; severe thrombocytopenia; or renal failure (increased serum creatinine or bun). Permanently discontinue Gemcitabine USP 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 USP alone or with other potentially hepatotoxic drugs [see adverse reactions]. Administration of Gemcitabine USP in patients with concurrent liver metastases or a pre-existing medical history or hepatitis, alcoholism, or liver cirrhosis can lead to exacerbation of the underlying hepatic insufficiency. Assess hepatic function prior to initiation of Gemcitabine USP and periodically during treatment. Permanently discontinue Gemcitabine USP in patients who develop severe hepatic toxicity.

Embryo-fetal toxicity:

Based on animal data and its mechanism of action, Gemcitabine USP can cause fetal harm when administered to a pregnant woman. Gemcitabine was teratogenic, embryo toxic, and fetotoxic in mice and rabbits.

Advise women of the potential risk to a fetus. Advise females of reproductive

potential to use effective contraception during treatment with Gemcitabine USP and for 6 months after the final dose. Advise male patients with female partners of reproductive potential to use effective contraception during treatment with Gemcitabine USP and for 3 months following the final dose.

Exacerbation of radiation therapy toxicity:

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

Concurrent (given together or ≤7 days apart)

Life-threatening mucositis, especially esophagitis and pneumonitis occurred in a trial in which Gemcitabine USP 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 observed when Gemcitabine USP is administered more than 7 days before or after radiation. Radiation recall has been reported in patients who receive Gemcitabine USP after prior radiation.

Capillary leak syndrome:

Capillary leak syndrome (CLS) with severe consequences has been reported in patients receiving Gemcitabine USP as a single agent or in combination with other chemotherapeutic agents. Permanently discontinue Gemcitabine USP if CLS develops during therapy.

Posterior reversible encephalopathy syndrome:

Posterior reversible encephalopathy syndrome (PRES) has been reported in patients receiving Gemcitabine USP as a single agent or in combination with other chemotherapeutic agents. 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 USP if PRES develops during therapy.

4.5 Interaction with other medicinal products and other forms of interaction

No drug interaction studies have been conducted.

4.6 Pregnancy and Lactation

Pregnancy

Pregnancy Category D.

Risk Summary

Gemcitabine for Injection can cause fetal harm when administered to a pregnant woman. Based on its mechanism of action, Gemcitabine for Injection is expected to result in adverse reproductive effects. Gemcitabine was teratogenic, embryotoxic, and fetotoxic in mice and rabbits. If Gemcitabine for Injection is used during pregnancy, or if the patient becomes pregnant while taking Gemcitabine for Injection, the patient should be apprised of the potential hazard to a fetus.

Animal Data

Gemcitabine is embryotoxic causing fetal malformations (cleft palate, incomplete ossification) at doses of 1.5 mg/kg/day in mice (approximately 0.005 times the recommended human dose on a mg/ m^2 basis). Gemcitabine is fetotoxic causing fetal malformations (fused pulmonary artery, absence of gall bladder) at doses of 0.1 mg/kg/day in rabbits (about 0.002 times the recommended human dose on a mg/ m^2 basis). Embryotoxicity was characterized by decreased fetal viability, reduced live litter sizes, and developmental delays.

Nursing Mothers

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from Gemcitabine for Injection, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use

The safety and effectiveness of Gemcitabine for Injection have not been established in pediatric patients. The safety and pharmacokinetics of gemcitabine were evaluated in a trial in pediatric patients with refractory leukemia. 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 for Injection were evaluated in a trial of pediatric patients with relapsed acute lymphoblastic leukemia (22 patients) and acute myelogenous leukemia (10 patients) 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. Toxicities observed included bone marrow suppression, febrile neutropenia, elevation of serum transaminases, nausea, and rash/desquamation. No meaningful clinical activity was observed in this trial.

Geriatric Use

In clinical studies of Gemcitabine for Injection, enrolling 979 patients with various cancers who received Gemcitabine for Injection as a single agent, no overall differences in safety were observed 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 randomized trial in women with ovarian cancer, 175 women received Gemcitabine For Injection plus carboplatin, of which 29% were age 65 years or older. Similar effectiveness was observed between older and younger women. There was significantly higher Grade 3/4 neutropenia in women 65 years of age or older.

Gemcitabine for Injection clearance is affected by age, however there are no recommended dose adjustments based on patients' age

Renal Impairment

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

Hepatic Impairment

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

Gender

Gemcitabine for Injection clearance is affected by gender in single-agent studies of Gemcitabine for Injection, women, especially older women, were more likely not to proceed to a subsequent cycle and to experience Grade 3/4 neutropenia and thrombocytopenia.

4.7 Effects on ability to drive and use machines

No studies have been conducted.

4.8 Undesirable effects

- Hypersensitivity
- Schedule-Dependent Toxicity
- Myelosuppression
- Pulmonary Toxicity and Respiratory Failure
- Hemolytic Uremic Syndrome
- Hepatic Toxicity
- Exacerbation of Radiation Toxicity
- Capillary Leak Syndrome
- Posterior Reversible Encephalopathy

Syndrome Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not

reflect the rates observed in clinical practice.

Single-Agent Use:
The data described below reflect exposure to Gemcitabine for Injection as a single agent administered at doses between 800 mg/m^2 to 1250 mg/m^2 over 30 minutes intravenously, once weekly, in 979 patients with a variety of malignancies. The most common (≥20%) adverse reactions of single-agent Gemcitabine for Injection are nausea/vomiting, anaemia, increased ALT, increased AST, neutropenia, increased alkaline phosphatase, proteinuria, fever, hematuria, rash, thrombocytopenia, dyspnea, and edema. The most common (≥5%) Grade 3 or 4 adverse reactions were neutropenia, nausea/vomiting; increased ALT, increase alkaline phosphatase, anemia, increased AST, and thrombocytopenia. Approximately 10% of the 979 patients discontinued Gemcitabine for Injection due to adverse reactions. Adverse reactions resulting in discontinuation of Gemcitabine for Injection in 2% of 979 patients were cardiovascular adverse events (myocardial infarction, cerebrovascular accident, arrhythmia, and hypertension) and adverse reactions resulting in discontinuation of Gemcitabine for Injection in less than 1% of the 979 patients were anemia, thrombocytopenia, hepatic dysfunction, renal dysfunction, nausea/vomiting, fever, rash, dyspnea, hemorrhage, infection, stomatitis, somnolence, flu-like syndrome, and edema.

Table 5 presents the incidence of adverse reactions reported in 979 patients with various malignancies receiving single-agent Gemcitabine for Injection across 5 clinical trials. Table 5 includes all clinical adverse reactions, reported in at least 10% of patients. A listing of clinically significant adverse reactions is provided following the table.

Table 5: Selected Per-Patient Incidence of Adverse Events in Patients Receiving Single- Agent Gemcitabine for Injection[a]

	All Patients[b]		
	All Grades	**Grade 3**	**Grade 4**
Laboratory[c]			
Hematologic			
Anemia	68	7	1
Neutropenia	63	19	6
Thrombocytopenia	24	4	1
Hepatic			
Increased ALT	68	8	2
Increased AST	67	6	2
Increased Alkaline Phosphatase	55	7	2
Hyperbilirubinemia	13	2	<1
Renal			
Proteinuria	45	<1	0
Hematuria	35	<1	0
Increased BUN	16	0	0
Increased Creatinine	8	<1	0
Non-laboratory[d]			
Nausea and Vomiting	69	13	1
Fever	41	2	0
Rash	30	<1	0
Dyspnea	23	3	<1
Diarrhea	19	1	0
Hemorrhage	17	<1	<1
Infection	16	1	<1
Alopecia	15	<1	0
Stomatitis	11	<1	0
Somnolence	11	<1	<1
Paresthesias	10	<1	0

[a] Grade based on criteria from the World Health Organization (WHO).

[b] N=699-974; all patients with laboratory or non-laboratory data.

[c] Regardless of causality.

[d] For approximately 60% of patients, non-laboratory adverse events were graded only if assessed to be possibly drug-related.

- Transfusion requirements — Red blood cell transfusions (19%); platelet transfusions (<1%)
- Fever — Fever occurred in the absence of clinical infection and frequently in combination with other flu-like symptoms.
- Pulmonary — Dyspnea unrelated to underlying disease and sometimes accompanied by bronchospasm.
- Edema — Edema (13%), peripheral edema (20%), and generalized edema (<1%);
- <1% of patients. discontinued Gemcitabine for Injection due to edema.
- Flu-like Symptoms — Characterized by fever, asthenia, anorexia, headache, cough, chills, myalgia, asthenia insomnia, rhinitis, sweating, and/or malaise (19%); <1% of patients discontinued Gemcitabine for Injection due to flu-like symptoms
- Infection — Sepsis (<1%)
- Extravasation — Injection-site reactions (4%)
- Allergic — Bronchospasm (<2%); anaphylactoid reactions

Non-Small Cell Lung Cancer:

Table 6 presents the incidence of selected adverse reactions, occurring in ≥10% of Gemcitabine for Injection -treated patients and at a higher incidence in the Gemcitabine for Injection plus cisplatin arm, reported in a randomized trial of Gemcitabine for Injection plus cisplatin (n=262) administered in 28-day cycles as compared to cisplatin alone (n=260) in patients receiving first-line treatment for locally advanced or metastatic non-small cell lung cancer (NSCLC)

Patients randomized to Gemcitabine for Injection plus cisplatin received a

median of 4 cycles of treatment and those randomized to cisplatin received a median of 2 cycles of treatment. In this trial, the requirement for dose adjustments (>90% versus 16%), discontinuation of treatment for adverse reactions (15% versus 8%), and the proportion of patients hospitalized (36% versus 23%) were all higher for patients receiving Gemcitabine for Injection plus cisplatin arm compared to those receiving cisplatin alone. The incidence of febrile neutropenia (9/262 versus 2/260), sepsis (4% versus 1%), Grade 3 cardiac dysrhythmias (3% versus <1%) were all higher in the Gemcitabine for Injection plus cisplatin arm compared to the cisplatin alone arm. The two-drug combination was more myelosuppressive with 4 (1.5%) possibly treatment-related deaths, including 3 resulting from myelosuppression with infection and one case of renal failure associated with pancytopenia and infection. No deaths due to treatment were reported on the cisplatin arm.

Table 6: Per-Patient Incidence of Selected Adverse Reactions from Randomized Trial of Gemcitabine for Injection plus Cisplatin versus Single-Agent Cisplatin in Patients with NSCLC Occurring at Higher Incidence in Gemcitabine for Injection -Treated Patients [Between Arm Difference of ≥5% (All Grades) or ≥2% (Grades 3-4)][a]

	Gemcitabine for Injection plus Cisplatin[b]			**Cisplatin[c]**		
	All Grades	**Grade 3**	**Grade 4**	**All Grades**	**Grade 3**	**Grade 4**
Laboratory[d]						
Hematologic						
Anemia	89	22	3	67	6	1
RBC Transfusione	39			13		
Neutropenia	79	22	35	20	3	1
Thrombocytopenia	85	25	25	13	3	1

Platelet Transfusionse	21			<1		
Hepatic						
Increased Transaminases	22	2	1	10	1	0
Increased Alkaline Phosphatase	19	1	0	13	0	0
Renal						
Proteinuria	23	0	0	18	0	0
Hematuria	15	0	0	13	0	0
Elevated creatinine	38	4	<1	31	2	<1
Other Laboratory						
Hyperglycemia	30	4	0	23	3	0
Hypomagnesemia	30	4	3	17	2	0
Hypocalcemia	18	2	0	7	0	<1
Non-laboratory[f]						
Nausea	93	25	2	87	20	<1
Vomiting	78	11	12	71	10	9
Alopecia	53	1	0	33	0	0
Neuro Motor	35	12	0	15	3	0
Diarrhea	24	2	2	13	0	0
Neuro Sensory	23	1	0	18	1	0
Infection	18	3	2	12	1	0
Fever	16	0	0	5	0	0
Neuro Cortical	16	3	1	9	1	0
Neuro Mood	16	1	0	10	1	0
Local	15	0	0	6	0	0
Neuro Headache	14	0	0	7	0	0
Stomatitis	14	1	0	5	0	0
Hemorrhage	14	1	0	4	0	0
Hypotension	12	1	0	7	1	0
Rash	11	0	0	3	0	0

[a] National Cancer Institute Common Toxicity Criteria (CTC) for severity grading.

[b] N=217-253; all Gemcitabine for Injection plus cisplatin patients with laboratory or non- laboratory data Gemcitabine for Injection at 1000 mg/m^2 on Days 1, 8, and 15 and cisplatin at 100 mg/m^2 on Day 1 every 28 days.

[c] N=213-248; all cisplatin patients with laboratory or non-laboratory data. Cisplatin at 100 mg/m^2 on Day 1 every 28 days.

[d] Regardless of causality.

[e] Percent of patients receiving transfusions. Percent transfusions are not CTC-graded events.

[f] Non-laboratory events were graded only if assessed to be possibly drug-related.

Table 7 presents the incidence of selected adverse reactions, occurring in ≥10% of Gemcitabine for Injection -treated patients and at a higher incidence in the Gemcitabine for Injection plus cisplatin arm, reported in a randomized trial of Gemcitabine for Injection plus cisplatin (n=69) administered in 21-day cycles as compared to etoposide plus cisplatin alone (n=66) in patients receiving first-line treatment for locally advanced or metastatic non-small cell lung cancer (NSCLC) A listing of clinically significant adverse reactions is provided following the table.

Patients in the Gemcitabine for Injection cisplatin (GC) arm received a median of 5 cycles and those in the etoposide/cisplatin (EC) arm received a median of 4 cycles. The majority of patients receiving more than one cycle of treatment required dose adjustments; 81% in the (GC) arm and 68% in the (EC) arm. The incidence of hospitalizations for treatment-related adverse events was 22% (GC) and 27% in the (EC) arm. The proportion of discontinuation of treatment for treatment-related adverse reactions was higher for patients in the (GC) arm (14% versus 8%). The proportion of patients hospitalized for febrile neutropenia was lower in the (GC) arm (7% versus 12%). There was one death attributed to treatment, a patient with febrile neutropenia and renal failure, which occurred in the

Gemcitabine for Injection /cisplatin arm.

Table 7: Per-Patient Incidence of Selected Adverse Reactions in Randomized Trial of Gemcitabine for Injection plus Cisplatin versus Etoposide plus Cisplatin in Patients with NSCLC[a]

	Gemcitabine for Injection plus Cisplatin[b]			**Etoposide plus Cisplatin[c]**		
	All Grades	**Grade 3**	**Grade 4**	**All Grades**	**Grade 3**	**Grade 4**
Laboratory[d]						
Hematologic						
Anemia	88	22	0	77	13	2
RBC Transfusions[e]	29	-	-	21	-	-
Neutropenia	88	36	28	87	20	56
Thrombocytopenia	81	39	16	45	8	5
Platelet Transfusionse	3	-	-	8	-	-
Hepatic						
Increased ALT	6	0	0	12	0	0
Increased AST	3	0	0	11	0	0
Increased Alkaline Phosphatase	16	0	0	11	0	0
Bilirubin	0	0	0	0	0	0
Renal						
Proteinuria	12	0	0	5	0	0
Hematuria	22	0	0	10	0	0
BUN	6	0	0	4	0	0
Creatinine	2	0	0	2	0	0
Non-laboratory[f]						
Nausea and Vomiting	96	35	4	86	19	7

Fever	6	0	0	3	0	0
Rash	10	0	0	3	0	0
Dyspnea	1	0	1	3	0	0
Diarrhea	14	1	1	13	0	2
Hemorrhage	9	0	3	3	0	3
Infection	28	3	1	21	8	0
Alopecia	77	13	0	92	51	0
Stomatitis	20	4	0	18	2	0
Somnolence	3	0	0	3	2	0
Paresthesias	38	0	0	16	2	0
Flu-like syndromeg	3	-	-	0	-	-
Edemag	12	-	-	2	-	-

[a] Grade based on criteria from the World Health Organization (WHO).

[b] N=67-69; all Gemcitabine for Injection plus cisplatin patients with laboratory or non- laboratory data. Gemcitabine for Injection at 1250 mg/m^2 on Days 1 and 8 and cisplatin at
100 mg/ m^2 on Day 1 every 21 days.

[c] N=57-63; all cisplatin plus etoposide patients with laboratory or non-laboratory data. Cisplatin at 100 mg/ m^2 on Day 1 and intravenous etoposide at 100 mg/ m^2 on Days 1, 2, and
3 every 21 days.

[d] Regardless of causality.

[e] WHO grading scale not applicable to proportion of patients with transfusions.

[f] Non-laboratory events were graded only if assessed to be possibly drug-related. Pain data were not collected.

[g] Flu-like syndrome and edema were not graded.

Breast Cancer

Table 8 presents the incidence of selected adverse reactions, occurring in ≥10% of Gemcitabine for Injection -treated patients and at a higher incidence in the Gemcitabine for Injection plus paclitaxel arm, reported in a

randomized trial of Gemcitabine for Injection plus paclitaxel (n=262) compared to paclitaxel alone (n=259) for the first-line treatment of metastatic breast cancer (MBC) in women who received anthracycline-containing chemotherapy in the adjuvant/neo-adjuvant setting or for whom anthracyclines were contraindicated.

The requirement for dose reduction of paclitaxel were higher for patients in the Gemcitabine for Injection /paclitaxel arm (5% versus 2%). The number of paclitaxel doses omitted (<1%), the proportion of patients discontinuing treatment for treatment-related adverse reactions (7% versus 5%), and the number of treatment-related deaths (1 patient in each arm) were similar between the two arms.

Table 8: Per-Patient Incidence of Selected Adverse Reactions from Comparative Trial of Gemcitabine for Injection plus Paclitaxel versus Single-Agent Paclitaxel in Breast Cancera Occurring at Higher Incidence in Gemcitabine for Injection -Treated Patients [Between Arm Difference of ≥5% (All Grades) or ≥2% (Grades 3-4)]

	Gemcitabine for Injection plus Paclitaxel (N=262)			**Paclitaxel (N=259)**		
	All Grades	**Grade 3**	**Grade 4**	**All Grades**	**Grade 3**	**Grade 4**
Laboratory[b]						
Hematologic						
Anemia	69	6	1	51	3	<1
Neutropenia	69	31	17	31	4	7
Thrombocytopenia	26	5	<1	7	<1	<1
Hepatobiliary						
Increased ALT	18	5	<1	6	<1	0
Increased AST	16	2	0	5	<1	0

Non-laboratory[c]						
Alopecia	90	14	4	92	19	3
Neuropathy-sensory	64	5	<1	58	3	0
Nausea	50	1	0	31	2	0
Fatigue	40	6	<1	28	1	<1
Vomiting	29	2	0	15	2	0
Diarrhea	20	3	0	13	2	0
Anorexia	17	0	0	12	<1	0
Neuropathy-motor	15	2	<1	10	<1	0
Stomatitis/pharyngitis	13	1	<1	8	<1	0
Fever	13	<1	0	3	0	0
Rash/desquamation	11	<1	<1	5	0	0
Febrile neutropenia	6	5	<1	2	1	0
Laboratoryb						
Hematologic						
Anemia	69	6	1	51	3	<1
Neutropenia	69	31	17	31	4	7
Thrombocytopenia	26	5	<1	7	<1	<1
Hepatobiliary						
Increased ALT	18	5	<1	6	<1	0
Increased AST	16	2	0	5	<1	0
Non-laboratoryc						
Alopecia	90	14	4	92	19	3
Neuropathy-sensory	64	5	<1	58	3	0
Nausea	50	1	0	31	2	0
Fatigue	40	6	<1	28	1	<1
Vomiting	29	2	0	15	2	0
Diarrhea	20	3	0	13	2	0
Anorexia	17	0	0	12	<1	0
Neuropathy-motor	15	2	<1	10	<1	0
Stomatitis/pharyngitis	13	1	<1	8	<1	0
Fever	13	<1	0	3	0	0

Rash/desquamation	11	<1	<1	5	0	0
Febrile neutropenia	6	5	<1	2	1	0

[a] Severity grade based on National Cancer Institute Common Toxicity Criteria (CTC)

Version 2.0.

[b] Regardless of causality.

[c] Non-laboratory events were graded only if assessed to be possibly drug-related.

Clinically relevant Grade 3 or 4 dyspnea occurred with a higher incidence in the Gemcitabine for Injection plus paclitaxel arm compared with the paclitaxel arm (1.9% versus 0).

Ovarian Cancer

Table 9 presents the incidence of selected adverse reactions, occurring in ≥10% of gemcitabine-treated patients and at a higher incidence in the Gemcitabine for Injection plus carboplatin arm, reported in a randomized trial of Gemcitabine for Injection plus carboplatin (n=175) compared to carboplatin alone (n=174) for the second-line treatment of ovarian cancer in women with disease that had relapsed more than 6 months following first-line platinum-based chemotherapy Additional clinically significant adverse reactions, occurring in less than 10% of patients, are provided following Table 9.

The proportion of patients with dose adjustments for carboplatin (1.8% versus 3.8%), doses of carboplatin omitted (0.2% versus 0), and discontinuing treatment for treatment-related adverse reactions (10.9% versus 9.8%), were similar between arms. Dose adjustment for Gemcitabine for Injection occurred in 10.4% of patients and Gemcitabine for Injection dose was omitted in 13.7% of patients in the Gemcitabine for Injection /carboplatin arm.

Table 9: Per-Patient Incidence of Adverse Reactions in Randomized Trial of Gemcitabine for Injection plus Carboplatin versus Carboplatin in Ovarian Cancera Occurring at Higher Incidence in Gemcitabine for Injection -Treated Patients [Between Arm Difference of ≥5% (All Grades) or ≥2% (Grades 3-4)]

	Gemcitabine for Injection plus Carboplatin (N=175)			**Carboplatin (N=174)**		
	All Grades	**Grade 3**	**Grade 4**	**All Grades**	**Grade 3**	**Grade 4**
Laboratory[b]						
Hematologic						
Neutropenia	90	42	29	58	11	1
Anemia	86	22	6	75	9	2
Thrombocytopenia	78	30	5	57	10	1
RBC Transfusionsc	38			15		
Platelet Transfusionsc	9			3		
Non-laboratory[b]						
Nausea	69	6	0	61	3	0
Alopecia	49	0	0	17	0	0

Vomiting	46	6	0	36	2	<1
Constipation	42	6	1	37	3	0
Fatigue	40	3	<1	32	5	0
Diarrhea	25	3	0	14	<1	0
Stomatitis/pharyngitis	22	<1	0	13	0	0
Laboratory[b]						
Hematologic						
Neutropenia	90	42	29	58	11	1
Anemia	86	22	6	75	9	2
Thrombocytopenia	78	30	5	57	10	1
RBC Transfusionsc	38			15		
Platelet Transfusionsc	9			3		
Non-laboratory[b]						
Nausea	69	6	0	61	3	0
Alopecia	49	0	0	17	0	0
Vomiting	46	6	0	36	2	<1

Constipation	42	6	1	37	3	0
Fatigue	40	3	<1	32	5	0
Diarrhea	25	3	0	14	<1	0
Stomatitis/pharyngitis	22	<1	0	13	0	0

[a] Grade based on Common Toxicity Criteria (CTC) Version 2.0.

[b] Regardless of causality.

[c] Percent of patients receiving transfusions. Transfusions are not CTC-graded events. Blood
transfusions included both packed red blood cells and whole blood.

Hematopoietic growth factors were administered more frequently in the Gemcitabine for Injection -containing arm: granulocyte growth factors (23.6% and 10.1%) and erythropoietic agents (7.3% and 3.9%).

The following clinically relevant, Grade 3 and 4 adverse reactions occurred more frequently in the Gemcitabine for Injection plus carboplatin arm: dyspnea (3.4% versus 2.9%), febrile neutropenia (1.1% versus 0), hemorrhagic event (2.3% versus 1.1 %), motor neuropathy
(1.1% versus 0.6%), and rash/desquamation (0.6% versus 0).

Post-Marketing Experience

The following adverse reactions have been identified during post-approval use of Gemcitabine for Injection. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Cardiovascular — Congestive heart failure, myocardial infarction, arrhythmias, supraventricular arrhythmias

Vascular Disorders — Peripheral vasculitis, gangrene, and capillary leak syndrome

Skin — Cellulitis, severe skin reactions, including desquamation and bullous

skin eruptions Hepatic — Hepatic failure, hepatic veno-occlusive disease

Pulmonary — Interstitial pneumonitis, pulmonary fibrosis, pulmonary edema, and adult respiratory distress syndrome (ARDS)

Nervous System — Posterior reversible encephalopathy syndrome (PRES)

Reporting of suspected adverse reactions

Healthcare professionals are requested to report any suspected adverse reactions via pharmacy and poisons board, Pharmacovigilance Electronic Reporting System (PvERS) https://pv.pharmacyboardkenya.org

1. **4.9 OVERDOSE**

Myelosuppression, paresthesias, and severe rash were the principal toxicities seen 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 dose-escalation study.

5.Pharmacological properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antineoplastic

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 Pharmacokinetics

Absorption and Distribution

The pharmacokinetics of gemcitabine were examined in 353 patients, with various solid tumors. Pharmacokinetic parameters were derived using 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 for Injection dose varied from 500 to 3600 mg/ m^2.

The volume of distribution was increased with infusion length. Volume of distribution of gemcitabine was 50 L/m2 following infusions lasting <70 minutes. For long infusions, the volume of distribution rose to 370 L/ m^2.

Gemcitabine pharmacokinetics is linear and is described by a 2-compartment model. Population pharmacokinetic analyses of combined single and multiple dose studies showed that the volume of distribution of gemcitabine was significantly influenced by duration of infusion and gender. Gemcitabine plasma protein binding is negligible.

Metabolism

Gemcitabine disposition was studied in 5 patients who received a single 1000 mg/ m^2/30 minute infusion of radiolabeled drug. Within one (1) week,

92% to 98% of the dose was 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 found in plasma.

The active metabolite, gemcitabine triphosphate, can be extracted from peripheral blood mononuclear cells. The half-life of the terminal phase for gemcitabine triphosphate from mononuclear cells ranges from 1.7 to 19.4 hours.

Elimination

Clearance of gemcitabine was affected by age and gender. The lower clearance in women and the elderly results in 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 10 shows plasma clearance and half-life of gemcitabine following short infusions for typical patients by age and gender.

Table 10: Gemcitabine Clearance and Half-Life for the "Typical" Patient

Age	**Clearance Men (L/hr/ m²)**	**Clearance Women (L/hr/ m²)**	**Half-Lifea Men (min)**	**Half-Lifea Wome n (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 <70 minute infusion.

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

Drug Interactions

When Gemcitabine for Injection (1250 mg/ m^2) on Days 1 and 8) and cisplatin (75 mg/ m^2 on Day 1) were administered in NSCLC patients, the clearance of gemcitabine on Day 1 was 128 L/hr/ m^2 and on Day 8 was 107 L/hr/ m^2. Analysis of data from metastatic breast cancer patients shows that, on average, Gemcitabine for Injection 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. Data from NSCLC patients demonstrate that Gemcitabine for Injection 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.

6.Pharmaceutical particulars

6.1 List of excipients

Mannitol, Sodium acetate trihydrate, Sodium hydroxide, Hydrochloric acid, Water for Injection

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months

6.4 Special precautions for storage

Store below 30°C and protect from light.

6.5 Nature and contents of container

50 ml molded glass vial, type 1 clear, 20 mm neck-US &20 MM Stopper, slotted, gray bromobutyl rubber,(Lyo-wester)-US, 20mm seals flip off, blue,1X10's Vial

6.6 Special precautions for disposal and other handling

No special requirements.

7. MARKETING AUTHORIZATION HOLDER AND MANUFACTURING SITE ADDRESSES

Supplier	Manufacturer
Hetero Labs Limited, Hetero Corporate, 7-2-A2, Industrial Estates, Sanath Nagar, Hyderabad - 500 018 Telangana, INDIA	M/s. Hetero Labs Limited, Unit – VI Sy. No.: 410 - 411, , TSIIC Formulation SEZ, Polepally village, Jadcherla Mandal Mahaboob Nagar, (Dist) – 509301, Telangana, India.

8.MARKETING AUTHORISATION NUMBER(S)

H2014/CTD1289/254

9.RENEWAL OF THE AUTHORISATION

March 26th 2026

10. DATE OF REVISION OF THE TEXT

March 26th, 2026