PROFFESIONAL INFORMATION

SCHEDULING STATUS: S4

1 NAME OF THE MEDICINE

GEMCITABINE SANDOZ 40 mg/mL (concentrate for solution for infusion)

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 5 mL vial contains 200 mg gemcitabine (as hydrochloride).

Each 25 mL vial contains 1000 mg gemcitabine (as hydrochloride).

Each 50 mL vial contains 2000 mg gemcitabine (as hydrochloride).

For full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Concentrate for solution for infusion.

The pH of the concentrate is 2,0 to 2,8.

Clear, colourless to pale yellow solution.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

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

GEMCITABINE SANDOZ is indicated as first-line treatment for patients with locally advanced (non-resectable stage II or stage III) or metastatic (stage IV) adrenocarcinoma of the pancreas.

GEMCITABINE SANDOZ is indicated for patients previously treated with 5-FU.

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

GEMCITABINE SANDOZ, alone or in combination, is indicated for the treatment of patients with recurrent epithelial ovarian carcinoma who have relapsed following platinum-based chemotherapy.

GEMCITABINE SANDOZ, 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

Gemcitabine should only be prescribed by a physician qualified in the use of anti-cancer chemotherapy.

Posology:

Patients with hepatic or renal impairment:

GEMCITABINE SANDOZ should be used with caution in patients with hepatic insufficiency or with impaired renal function as no studies have been done in patients with significant renal or hepatic impairment, there is insufficient information from clinical studies to allow clear dose recommendation for this patient population.

Bladder cancer:

Adults: The recommended monochemotherapy dosage of GEMCITABINE SANDOZ is 1250 mg/m^2, 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.

GEMCITABINE SANDOZ may be used in combination with cisplatin.

The recommended dose of GEMCITABINE SANDOZ 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/m^2 on day 1 following GEMCITABINE SANDOZ or day 2 of each 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/m^2.

Pancreatic cancer:

Adults: The recommended dose of gemcitabine is 1000 mg/m^2, given by 30-minute intravenous infusion. This should be repeated once weekly for up to 7 weeks followed by a week of rest. Subsequent cycles should consist of injections once weekly for 3 consecutive weeks out of every 4 weeks. Dosage reduction with each cycle or within a cycle may be applied based upon the amount of toxicity experienced by the patient.

Non-small cell lung cancer:

Adults: The recommended monochemotherapy dosage of gemcitabine is 1000 mg/m^2, given by 30-minute intravenous infusion. This should be repeated once weekly for 3 weeks, followed by a 1-week rest period. This 4-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.
GEMCITABINE SANDOZ may be used in combination with cisplatin using either the three or four week schedule.

One of the following schedules is suggested:

3 week schedule: GEMCITABINE SANDOZ 1250 mg/m², given by 30 minutes 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: GEMCITABINE SANDOZ 1000 mg/m² on days 1,8 and 15 of every 28 days 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.

Breast cancer:

Adults: Gemcitabine in combination with paclitaxel is recommended using paclitaxel (175 mg/m^2) administered on Day 1 over approximately 3-hours as an intravenous infusion, followed by gemcitabine (1250 mg/m^2) as a 30-minute intravenous infusion on Days 1 and 8 of each 21-day cycle. Dose reduction with each cycle or within a cycle may be applied based upon the grade of toxicity experienced by the patient. Patients should have an absolute granulocyte count of at least 1500 (x 10^6/L) prior to initiation of gemcitabine + paclitaxel combination.

Ovarian cancer:

Single agent use:

Adults: the recommended dose of GEMCITABINE SANDOZ is 800 to 1250 mg/m², given by a 30 minute intravenous infusion. The dose should be given on day 1,8 and 15 of each 28 day cycle. This four week cycle is the repeated. Dosage reduction with each cycle or within a cycle may be applied based upon the amount of toxicity experienced by the patient.

Combination use:

Adults: Gemcitabine in combination with carboplatin is recommended using gemcitabine 1000 mg/m^2 administered on Days 1 and 8 of each 21-day cycle as a 30-minute intravenous infusion. After gemcitabine, carboplatin will be given on Day 1 consistent with a target Area under curve (AUC) of 4,0 g/mL/min. Dosage reduction with each cycle or within a cycle may be applied based upon the grade of toxicity experienced by the patient.

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

Absolute granulocyte count (x 10^6/L)	***Platelet count (x 10^6/L)***	***Percentage of full dose (%)***
> 1000 and	> 100 000	100
500 to 1000 or	50 000 to 100 000	75
< 500 or	< 50 000	Hold

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

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

Elderly patients: GEMCITABINE SANDOZ has been well tolerated in patient over the age 65. There is no evidence to suggest that dose adjustments are necessary in the elderly, although GEMCITABINE SANDOZ clearance and half-life are affected by age.

Method of administration:

Gemcitabine is tolerated well during infusion and may be administered ambulant. If extravasation occurs, generally the infusion must be stopped immediately and started again in another blood vessel. The patient should be monitored carefully after the administration.

GEMCITABINE SANDOZ concentrate for solution for infusion must be diluted before use (see section 4.4 and 6.6). It is recommended to use large veins for infusion to prevent damage to the vessel and extravasation.

Special populations:

Patients with renal or hepatic impairment:

Gemcitabine should be used with caution in patients with hepatic or renal impairment as there is insufficient information from clinical studies to allow for clear dose recommendations for these patient populations (see sections 4.4, 4.8 and 5.2).

Older people (> 65 years):

Gemcitabine has been well tolerated in patients over the age of 65. There is no evidence to suggest that dose adjustments, other than those already recommended for all patients, are necessary in the older people

Paediatric population (< 18 years):

Gemcitabine is not recommended for use in children under 18 years of age due to insufficient data on safety and efficacy.

4.3 Contraindications

- GEMCITABINE SANDOZ is contraindicated in patients with a known hypersensitivity to gemcitabine or to any of the excipients listed in section 6.1.

- Pregnancy and lactation: The safety of GEMCITABINE SANDOZ in human pregnancy and lactation has not been established (see section 4.6).
- Usage in children: Safety and effectiveness in children have not been established.

4.4 Special warnings and precautions for use

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

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. Pre-clinical and clinical studies have shown that gemcitabine has radio sensitising activity. In a single trial, where 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 oesophagitis, and pneumonitis was observed, particularly in patients receiving large volumes of radiotherapy [median treatment volumes 4,795 cm^3].

Radiation injury has been reported on targeted tissues (e.g. oesophagitis, colitis, and pneumonitis) in association with both concurrent and non-concurrent use of gemcitabine.

Haematological toxicity:

Gemcitabine can suppress bone marrow function as manifested by leucopaenia, thrombocytopaenia and anaemia.

Patients receiving gemcitabine should be monitored prior to each dose for platelet,

leucocyte and granulocyte counts. Suspension or modification of therapy should be considered when drug-induced bone marrow depression is detected (see section 4.2). However, myelosuppression is mild to moderate and is pronounced for the granulocyte count (see section 4.2).

Peripheral blood counts may continue to deteriorate after gemcitabine administration has been stopped. In patients with impaired bone marrow function, the treatment should be started with caution. As with other cytotoxic treatments, the risk of cumulative bone-marrow suppression must be considered when gemcitabine treatment is given together or sequentially with other chemotherapy.

Hepatic and renal impairment:

Administration of gemcitabine in patients with concurrent liver metastases or a pre-existing medical history of hepatitis, alcoholism or liver cirrhosis may lead to exacerbation of the underlying hepatic insufficiency.

Laboratory evaluation of renal and hepatic function (including virological tests) should be performed periodically.

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

Live vaccinations:

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

Posterior reversible encephalopathy syndrome:

Reports of posterior reversible encephalopathy syndrome (PRES) with potentially severe consequences have been reported in patients receiving gemcitabine as single medicine or in combination with other chemotherapeutic medicines.

Acute hypertension and seizure activity were reported in most gemcitabine patients experiencing PRES, but other symptoms such as headache, lethargy, confusion and blindness could also be present. Diagnosis is optimally confirmed by magnetic resonance imaging (MRI). PRES was typically reversible with appropriate supportive measures. Gemcitabine should be permanently discontinued and supportive measures implemented, including blood pressure control and anti-seizure therapy, if PRES develops during therapy.

Cardiovascular:

Due to the risk of cardiac and/or vascular disorders with gemcitabine, particular caution must be exercised with patients presenting a history of cardiovascular events.

Capillary leak syndrome:

Capillary leak syndrome has been reported in patients receiving gemcitabine as single medicine or in combination with other chemotherapeutic medicines (see section 4.8). The condition is usually treatable if recognised early and managed appropriately, but fatal cases have been reported. The condition involves systemic capillary hyperpermeability during which fluid and proteins from the intravascular space leak into the interstitium. The clinical features include generalised oedema, weight gain, hypoalbuminaemia, severe hypotension, acute renal impairment and pulmonary oedema. Gemcitabine should be discontinued and supportive measures implemented if capillary leak syndrome develops during therapy. Capillary leak syndrome can occur in later cycles and has been associated in the literature with adult respiratory distress syndrome.

Pulmonary toxicity:

Interstitial pneumonitis together with pulmonary infiltrates has been seen in less than 1 % of patients. In such cases, GEMCITABINE SANDOZ must be stopped. Steroids may relieve the symptoms in such situations. Severe rarely fatal pulmonary effects, such as pulmonary oedema, interstitial pneumonitis and ARDS have been reported as less common or rare. In such cases, cessation of GEMCITABINE SANDOZ is necessary. Starting supportive treatment at an early stage may improve the situation.

Haemolytic uraemic syndrome:

Clinical findings consistent with the haemolytic uraemic syndrome (HUS) were rarely reported (post- marketing data) in patients receiving gemcitabine (see section 4.8). HUS is a potentially life-threatening disorder. Gemcitabine should be discontinued at the first signs of any evidence of microangiopathic haemolytic anaemia, such as rapidly falling haemoglobin with concomitant thrombocytopaenia, elevation of serum bilirubin, serum creatinine, blood urea, or LDH. Renal failure may not be reversible with discontinuation of therapy and dialysis may be required.

Severe cutaneous adverse reactions (SCARs) including Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), and acute generalized exanthematous pustulosis (AGEP), which can be life-threatening or fatal, have been reported in association with gemcitabine treatment. Patients should be advised of the signs and symptoms and monitored closely for skin reactions. If signs and symptoms suggestive of these reactions appear, gemcitabine should be withdrawn immediately.

4.5 Interaction with other medicines and other forms of interaction

No specific interaction studies have been performed (see section 5.2).

Concomitant radiotherapy:

Concomitant radiotherapy (given together or ≤ 7 days apart): Toxicity has been reported (see section 4.4 for details).

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

GEMCITABINE SANDOZ is contraindicated during pregnancy and lactation.

Pregnancy:

There are no adequate data from the use of gemcitabine in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3). Women should be advised not to become pregnant during treatment with gemcitabine and to warn their attending physician immediately, should this occur after all.

Breastfeeding:

It is not known whether gemcitabine is excreted in human milk and adverse effects on the suckling child cannot be excluded. Breastfeeding must be discontinued during gemcitabine therapy.

Fertility:

In fertility studies gemcitabine caused hypospermatogenesis in male mice (see section 5.3). Therefore, men being treated with gemcitabine are advised not to father a child during and up to 6 months after treatment and to seek further advice regarding cryoconservation of sperm prior to treatment because of the possibility of infertility due to therapy with gemcitabine.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. However, gemcitabine has been reported to cause mild to moderate somnolence, especially in combination with alcohol consumption. Patients should be cautioned against driving or operating machinery until it is established that they do not become somnolent.

4.8 Undesirable effects

System Organ Class	Frequency grouping
Infections and infestations	***Frequent:*** Infections ***Frequency unknown:*** Sepsis
Blood and lymphatic system disorders	***Frequent:*** Leucopaenia (Neutropaenia Grade 3 = 19,3 %; Grade 4 = 6 %). Bone-marrow suppression is usually mild to moderate and mostly affects the granulocyte count (see section 4.2 and 4.4),

System Organ Class	Frequency grouping
	thrombocytopaenia, anaemia febrile, neutropaenia ***Less frequent:*** Thrombocytosis, thrombotic microangiopathy
Immune system disorders	***Less frequent:*** Anaphylactoid reaction
Metabolism and nutrition disorders	***Frequent:*** Anorexia
Nervous system disorders	***Frequent:*** Headache, insomnia, somnolence ***Less frequent:*** Cerebrovascular accident, posterior reversible encephalopathy syndrome (PRES) (see section 4.4)
Cardiac disorders	***Less frequent:*** Dysrhythmias, predominantly supraventricular in nature, heart failure, myocardial infarct
Vascular disorders	***Less frequent:*** Hypotension, clinical signs of peripheral vasculitis and gangrene, capillary leak syndrome (see section 4.4)

System Organ Class	Frequency grouping
Respiratory, thoracic and mediastinal disorders	***Frequent:*** Dyspnoea – usually mild and passes rapidly without treatment, cough, rhinitis ***Less frequent:*** Interstitial pneumonitis (see section 4.4), bronchospasm – usually mild and transient but may require parenteral treatment, pulmonary oedema, adult respiratory distress syndrome (see section 4.4)
Gastrointestinal disorders	***Frequent:*** Vomiting, nausea, diarrhoea, stomatitis and ulceration of the mouth, constipation ***Less frequent:*** Ischaemic colitis
Hepatobiliary disorders	***Frequent:*** Elevation of liver transaminases (AST and ALT) and alkaline phosphatase, increased bilirubin ***Less frequent:*** Serious hepatotoxicity, including liver failure and death, increased glutamyl-glutamyl transferase (GGT)

System Organ Class	Frequency grouping
Skin and subcutaneous tissue disorders	***Frequent***: Allergic skin rash frequently associated with pruritus, alopecia, itching, sweating ***Less frequent:*** Severe skin reactions, including desquamation and bullous skin eruptions, ulceration, vesicle and sore formation, scaling, toxic epidermal necrolysis, Stevens-Johnson Syndrome ***Frequency unknown:*** Pseudocellulitis, acute generalised exanthematous pustulosis
Musculoskeletal and connective tissue disorders	***Frequent***: Back pain, myalgia
Renal and urinary disorders	***Frequent***: Haematuria, mild proteinuria ***Less frequent:*** Renal failure (see section 4.4), hemolytic uremic syndrome (see section 4.4)

System Organ Class	Frequency grouping
General disorders and administration site conditions	***Frequent***: Influenza-like symptoms - the most common symptoms are fever, headache, chills, myalgia, asthenia and anorexia. Cough, rhinitis, malaise, perspiration and sleeping difficulties have also been reported, oedema/peripheral oedema- including facial oedema, oedema is usually reversible after stopping treatment, fever, asthenia, chills ***Less frequent:*** Injection site reactions- mainly mild in nature
Injury, poisoning, and procedural complications	***Less frequent:*** Radiation toxicity (see section 4.5), radiation recall

Combination use in breast cancer:

The frequency of grade 3 and 4 haematological toxicities, particularly neutropaenia, increases when gemcitabine is used in combination with paclitaxel. However, the increase in these adverse reactions is not associated with an increased incidence of infections or haemorrhagic events. Fatigue and febrile neutropaenia occur more frequently when gemcitabine is used in combination with paclitaxel. Fatigue, which is not associated with anaemia, usually resolves after the first cycle.

Reporting of suspected adverse reactions

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

Suspected adverse reactions can also be reported directly to the HCR via https://pvi1j.solutions.iqvia.com or the e-mail address: adverse.event.sac@sandoz.com.

4.9 Overdose

There is no known antidote for overdose of gemcitabine. Doses as high as 5700 mg/m² have been administered by intravenous infusion over 30 minutes every 2 weeks with clinically acceptable toxicity. In the event of suspected overdose, the patient should be monitored with appropriate blood counts and receive supportive therapy, as necessary.

5.PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: pyrimidine analogues

ATC code**:** L01BC05

Cytotoxic activity in cell cultures:

Gemcitabine shows significant cytotoxic effects against a variety of cultured murine and human tumour cells. Its action is phase-specific such that gemcitabine primarily kills cells that are undergoing DNA synthesis (S phase) and, under certain circumstances, blocks the progression of cells at the junction of the G1/S phase boundary. *In vitro*, the cytotoxic effect of

gemcitabine is dependent on both concentration and time.

Antitumoral activity in preclinical models:

In animal tumour models, antitumoural activity of gemcitabine is schedule-dependent. When gemcitabine is administered daily, high mortality among the animals but minimal antitumoural activity is observed. If, however, gemcitabine is given every third or fourth day, it can be administered in non-lethal doses with substantial antitumoural activity against a broad spectrum of mouse tumours.

Mechanism of action:

Cellular metabolism and mechanism of action: Gemcitabine (dFdC), which is a pyrimidine antimetabolite, is metabolised intracellularly by nucleoside kinase to the active diphosphate (dFdCDP) and triphosphate (dFdCTP) nucleosides. The cytotoxic effect of gemcitabine is due to inhibition of DNA synthesis by two mechanisms of action by dFdCDP and dFdCTP. First, dFdCDP inhibits ribonucleotide reductase, which is uniquely responsible for catalysing the reactions that produce deoxynucleoside triphosphates (dCTP) for DNA synthesis. Inhibition of this enzyme by dFdCDP reduces the concentration of deoxynucleosides in general and, in particular, dCTP. Second, dFdCTP competes with dCTP for incorporation into DNA (self-potentiation).

A small amount of gemcitabine may also be incorporated into RNA. Thus, the reduced intracellular concentration of dCTP potentiates the incorporation of dFdCTP into DNA. DNA polymerase epsilon lacks the ability to eliminate gemcitabine and to repair the growing DNA strands. After gemcitabine is incorporated into DNA, one additional nucleotide is added to the growing DNA strands. After this addition there is essentially a complete inhibition in further DNA synthesis (masked chain termination). After incorporation into DNA, gemcitabine

appears to induce the programmed cell death process known as apoptosis.

5.2 Pharmacokinetic properties

The following pharmacokinetic parameters were obtained for doses ranging from 500 to 2592 mg/m² that were infused from 0,4 to 1,2 hours.

Absorption:

Peak plasma concentrations (obtained within 5 minutes of the end of the infusion) were 3,2 to 45,5 µg/mL. Plasma concentrations of the parent compound following a dose of 1000 mg/m²/30 minutes are greater than 5 µg/mL for approximately 30 minutes after the end of the infusion, and greater than 0,4 µg/mL for an additional hour.

Distribution:

The volume of distribution of the central compartment was 12,4 L/m² for women and 17,5 L/m² for men (inter individual variability was 91,9 %). The volume of distribution of the peripheral compartment was 47,4 L/m². The volume of the peripheral compartment was not sensitive to gender. The plasma protein binding was considered to be negligible.

Half life: This ranged from 42 to 94 minutes depending on age and gender. For the recommended dosing schedule, gemcitabine elimination should be virtually complete within 5 to 11 hours of the start of the infusion. Gemcitabine does not accumulate when administered once weekly.

Biotransformation:

Gemcitabine is rapidly metabolised by cytidine deaminase in the liver, kidney, blood and other tissues. Intracellular metabolism of gemcitabine produces the gemcitabine mono, di and triphosphates (dFdCMP, dFdCDP and dFdCTP) of which dFdCDP and dFdCTP are considered active. These intracellular metabolites have not been detected in plasma or urine. The primary metabolite, 2' deoxy 2', 2' difluorouridine (dFdU), is not active and is found in plasma and urine.

Elimination:

Systemic clearance ranged from 29,2 L/hr/m² to 92,2 L/hr/m² depending on gender and age (inter individual variability was 52,2 %). Clearance for women is approximately 25 % lower than the values for men.

Although rapid, clearance for both men and women appears to decrease with age. For the recommended gemcitabine dose of 1000 mg/m² given as a 30 minute infusion, lower clearance values for women and men should not necessitate a decrease in the gemcitabine dose.

Urinary excretion: Less than 10 % is excreted as unchanged drug. Renal clearance was 2 to 7 L/hr/m².

During the week following administration, 92 to 98 % of the dose of gemcitabine administered is recovered, 99 % in the urine, mainly in the form of dFdU and 1 % of the dose is excreted in faeces.

dFdCTP kinetics:

This metabolite can be found in peripheral blood mononuclear cells and the information below refers to these cells. Intracellular concentrations increase in proportion to gemcitabine doses of 35 to 350 mg/ m²/30 minutes, which give steady state concentrations of 0,4 to 5 µg/mL. At

gemcitabine plasma concentrations above 5 µg/mL, dFdCTP levels do not increase, suggesting that the formation is saturable in these cells.

Half life of terminal elimination: 0,7 to 12 hours.

dFdU kinetics:

Peak plasma concentrations (3 to 15 minutes after end of 30 minute infusion, 1000 mg/m²): 28 to 52 µg/mL. Trough concentration following once weekly dosing: 0,07 to 1,12 µg/mL, with no apparent accumulation. Triphasic plasma concentration versus time curve, mean half life of terminal phase 65 hours (range 33 to 84 hours).

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

Mean volume of distribution of central compartment: 18 L/m² (range 11 to 22 L/m²). Mean steady state volume of distribution (Vss): 150 L/m² (range 96 to 228 L/m²).

Tissue distribution: Extensive.

Mean apparent clearance: 2,5 L/hr/m² (range 1 to 4 L/hr/m²).

Urinary excretion: All.

Gemcitabine and paclitaxel combination therapy:

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

Gemcitabine and carboplatin combination therapy:

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

Renal impairment:

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

5.3 Preclinical safety data

In repeat-dose studies of up to 6 months in duration in mice and dogs, the principal finding was schedule and dose-dependent haematopoietic suppression which was reversible.

Gemcitabine is mutagenic in an *in vitro* mutation test and an *in vivo* bone marrow micronucleus test. Long term animal studies evaluating the carcinogenic potential have not been performed.

In fertility studies, gemcitabine caused reversible hypospermatogenesis in male mice. No effect on the fertility of females has been detected.

Evaluation of experimental animal studies has shown reproductive toxicity e.g. birth defects and other effects on the development of the embryo or foetus, the course of gestation or peri- and postnatal development.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

- Water for injections
- Diluted hydrochloric acid (for pH adjustment)

6.2 Incompatibilities

This medicine must not be mixed with other medicines except those mentioned in section 6.6.

6.3 Shelf life

Unopened Vials: 24 months

Stability after first opening:

Chemical and physical stability has been demonstrated for 28 days at 2°C – 8°C and at room temperature (15°C – 25°C).

Shelf life after dilution:

Chemical and physical in-use stability has been demonstrated for 28 days at 2°C – 8°C and at room temperature in glucose 5 % or sodium chloride 0.9 % (1.0 mg/ml, 7.0 mg/ml and 25 mg/ml).

From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2°C – 8°C, unless opening or dilution has taken place in controlled and validated aseptic conditions.

6.4 Special precautions for storage

Unopened Vials: Store in a refrigerator (2 °C to 8 °C). Do not freeze.

If the solution appears discoloured or contains visible particles, it should be discarded. For storage conditions after dilution of the medicine, see section 6.3.

6.5 Nature and contents of container

The container closure system for Gemcitabine 40 mg/mL consists of colourless glass vials of glass type I according to Ph. Eur. with a nominal capacity of 5 mL and 50 mL with dimensions according to DIN ISO 8362.

The vials are closed with rubber stoppers according to Ph. Eur. and to DIN ISO 8362 with an aluminium crimp cap. All type of vials use stopper of the same quality and size.

Pack sizes:

5 mL vial: 1 vial, 5 vials, 10 vials

25 mL vial: 1 vial

50 mL vial: 1 vial

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

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

Parenteral drugs should be inspected visually for particulate matter and discolouration, prior to administration, whenever solution and container permit.

If the solution appears discoloured or contains visible particles, it should be discarded.

Gemcitabine Sandoz concentrate for solution for infusion must be diluted before use (see section 4.2 and 4.4)

Transfer the required quantity of solution under aseptic conditions into a suitable infusion bag or bottle. The solution must be diluted with 0.9% sodium chloride solution or 5% glucose solution as appropriate. Mix the liquids thoroughly by rotating by hand.

7. HOLDER OF THE CERTIFICATE OF REGISTRATION

Sandoz SA (Pty) Ltd[1]

Waterfall 5-Ir

Magwa Crescent West

Waterfall City

Jukskei View

2090

8. REGISTRATION NUMBER

45/26/1159

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date on registration certificate: 10 November 2020

10. DATE OF REVISION OF THE TEXT

20 December 2024

[1]Company Reg. No.: 1990/001979/07