Gemcitabin Ebewe 40 mg/ml concentrate for solution for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1 ml contains 45.6 mg gemcitabine hydrochloride which corresponds to 40 mg of the active ingredient gemcitabine.

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 a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Concentrate for solution for infusion.
Clear, colourless or almost colourless solution.

pH: 2.0 – 2.8
Osmolarity: 270 – 280 mOsmol/kg

4. Clinical particulars

4.1 Therapeutic indications

Gemcitabine is indicated for the treatment of locally advanced or metastatic bladder cancer in combination with cisplatin.
Gemcitabine is indicated for treatment of patients with locally advanced or metastatic adenocarcinoma of the pancreas.
Gemcitabine, in combination with cisplatin is indicated as first line treatment of patients with locally advanced or metastatic non-small cell lung cancer (NSCLC). Gemcitabine monotherapy can be considered in elderly patients or those with performance status 2.
Gemcitabine is indicated for the treatment of patients with locally advanced or metastatic epithelial ovarian carcinoma, in combination with carboplatin, in patients with relapsed disease following a recurrence-free interval of at least 6 months after platinum-based, first-line therapy.
Gemcitabine, 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.

Recommended posology

Bladder cancer

Combination use
The recommended dose for gemcitabine 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 4-week cycle is then repeated. Dosage reduction with each cycle or within a cycle may be applied based upon the grade of toxicity experienced by the patient.

Pancreatic cancer

Monotherapy
The recommended dose of gemcitabine is 1000 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 grade of toxicity experienced by the patient.

Non small Cell lung cancer

Monotherapy
The recommended dose of gemcitabine is 1000 mg/m², 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 grade of toxicity experienced by the patient.

Combination use
The recommended dose for gemcitabine is 1250 mg/m² body surface area given as a 30-minute intravenous infusion on day 1 and 8 of the treatment cycle (21 days) in combination with cisplatin. Cisplatin has been used at doses between 75–100 mg/m² on day 1 following gemcitabine or day 2 once every 3 weeks. Dosage reduction with each cycle or within a cycle may be applied based upon the grade of toxicity experienced by the patient.

Breast cancer

Combination use
Gemcitabine 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 gemcitabine (1250 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 grade of toxicity experienced by the patient. Patients should have an absolute granulocyte count of at least 1,500 (x 10^6/l) prior to initiation of gemcitabine + paclitaxel combination.

Ovarian cancer

Combination use
Gemcitabine in combination with carboplatin is recommended using gemcitabine 1000 mg/m² 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 mg/ml·min. Dosage reduction with each cycle or within a cycle may be applied based upon the grade of toxicity experienced by the patient.

Monitoring for toxicity and dose modification due to toxicity

Dose modification due to non haematological toxicity

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 grade of toxicity experienced by the patient. In general, for severe (Grade 3 or 4) non-haematological toxicity, except nausea/vomiting, therapy with gemcitabine should be withheld or decreased depending on the judgement of the treating physician. Doses should be withheld until toxicity has resolved in the opinion of the physician.
For cisplatin, carboplatin, and paclitaxel dosage adjustment in combination therapy, please refer to the corresponding Summary of Product Characteristics.

Dose modification due to haematological toxicity

Initiation of a cycle
For all indications, the patient must be monitored before each dose for platelet and granulocyte counts. Patients should have an absolute granulocyte count of at least 1,500 (x 10^6/l) and platelet account of 100,000 (x 10^6/l) prior to the initiation of a cycle.

Within a cycle
Dose modifications of gemcitabine within a cycle should be performed according to the following tables:

Dose modification of gemcitabine within a cycle for bladder cancer, NSCLC and pancreatic cancer, given in monotherapy or in combination with cisplatin			
Absolute granulocyte count (x 10^6/l)		Platelet count (x 10^6/l)	Percentage of standard dose of Gemcitabine (%)
> 1,000	and	> 100,000	100
500-1,000	or	50,000-100,000	75
<500	or	< 50,000	Omit dose *

*Treatment omitted will not be re-instated within a cycle before the absolute granulocyte count reaches at least 500 (x10^6/l) and the platelet count reaches 50,000 (x10^6/l).

Dose modification of gemcitabine within a cycle for breast cancer, given in combination with paclitaxel			
Absolute granulocyte count (x 10^6/l)		Platelet count (x 10^6/l)	Percentage of standard dose of Gemcitabine (%)
> 1,200	and	>75,000	100
1,000- <1,200	or	50,000-75,000	75
700- <1,000	and	> 50,000	50
<700	or	<50,000	Omit dose*

*Treatment omitted will not be re-instated within a cycle. Treatment will start on day 1 of the next cycle once the absolute granulocyte count reaches at least 1,500 (x10^6/l) and the platelet count reaches 100,000 (x10^6/l).

Dose modifications due to haematological toxicity in subsequent cycles, for all indications

The gemcitabine dose should be reduced to 75% of the original cycle initiation dose, in the case of the following haematological toxicities:

- Absolute granulocyte count < 500 x 10^6/l for more than 5 days
- Absolute granulocyte count < 100 x 10^6/l for more than 3 days
- Febrile neutropaenia
- Platelets < 25,000 x 10^6/l
- Cycle delay of more than 1 week due to toxicity

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.

National approved name 40 mg/ml 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.

For further instructions on reconstitution, see section 6.6

Special populations

Patients with renal or hepatic impairment

Gemcitabine should be used with caution in patients with hepatic or renal insufficiency 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).

Elderly population(> 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 elderly (see section 5.2).

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

- Hypersensitivity to the active substance or to any of the excipients.
- Breast-feeding (see section 4.6).

4.4 Special warnings and precautions for use

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

National approved name 40 mg/ml concentrate for solution for infusion must be diluted before use (see section 4.2 and 6.6). It is recommended to use large veins for infusion to prevent damage to the vessel and extravasation.

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 short lived and usually does not result in dose reduction and rarely in discontinuation.

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 with other chemotherapy.

Hepatic and/or renal insufficiency

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.

Patients with AST elevations tolerated gemcitabine without increased toxicity, but patients with elevated bilirubin levels (> 1.6 mg/dl) had a significantly increased risk of hepatotoxicity after gemcitabine therapy. A recommendation for dose reduction in the setting of liver dysfunction is promoted.

Patients with renal dysfunction presented with unusual side effects in response to gemcitabine, especially skin toxicity in the form of diffuse erythema and desquamation (see section 4.8).

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

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

Concomitant radiotherapy

Concomitant radiotherapy (given together or ≤7 days apart): Toxicity has been reported (see section 4.5 for details and recommendations for use).

Live vaccinations

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

Cardiovascular

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

Pulmonary

Pulmonary effects, sometimes severe (such as pulmonary oedema, interstitial pneumonitis or adult respiratory distress syndrome (ARDS)) have been reported in association with gemcitabine therapy. The aetiology of these effects is unknown. If such effects develop, consideration should be made to discontinuing gemcitabine therapy. Early use of supportive care measure may help ameliorate the condition.

Renal

Clinical findings consistent with the haemolytic uraemic syndrome (HUS) were rarely reported in patients receiving gemcitabine (see section 4.8). 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 nitrogen, or LDH. Renal failure may not be reversible with discontinuation of therapy and dialysis may be required.

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 (see section 4.6).

4.5 Interaction with other medicinal products and other forms of interaction

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

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 radiosensitising activity. In a single trial, where gemcitabine at a dose of 1,000 mg/m² 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 cm³]. 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/m², four times) and cisplatin (80 mg/m² 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.

Non-concurrent (given >7 days apart)- Analysis of the data does not indicate any enhanced toxicity when gemcitabine is administered more than 7 days before or after radiation, other than radiation recall. Data suggest that gemcitabine can be started after the acute effects of radiation have resolved or at least one week after radiation.

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.

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 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). Based on results from animal studies and the mechanism of action of gemcitabine, this substance should not be used during pregnancy unless clearly necessary. Women should be advised not to become pregnant during treatment with gemcitabine and to warn their attending physician immediately, should this occur after all.

Breast-feeding

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

Fertility

In fertility studies gemcitabine caused hypospermatogenesis in male mice (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

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 (see section 4.4). Dose-limiting adverse reactions are reductions in thrombocyte, leucocyte and granulocyte counts (see section 4.2).

Clinical trial data

Frequencies are defined as: Very common (≥1/10), Common (>1/100 to <1/10), Uncommon (>1/1000 to <1/100), Rare (>1/10,000 to <1/1000), Very Rare (<1/10,000).

The following table of undesirable effects and frequencies is based on data from clinical trials. Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

System Organ Class	Frequency grouping
Blood and lymphatic system disorders	Very common • 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) • Thrombocytopaenia • Anaemia Common • Febrile neutropaenia Very rare • Thrombocytosis
Immune system disorders	Very Rare • Anaphylactoid reaction
Metabolism and nutrition disorders	Common • Anorexia
Nervous system disorders	Common • Headache • Insomnia • Somnolence
Cardiac disorders	Rare • Myocardial infarct • Heart failure • Arrhythmia (mainly supraventricular)
Vascular disorders	Rare • Hypotension Very rare • Clinical signs of peripheral vasculitis
Respiratory, thoracic and mediastinal disorders	Very common • Dyspnoea – usually mild and passes rapidly without treatment • Bronchospasm – usually mild and transient but may require parenteral treatment Common • Cough • Rhinitis Uncommon • Interstitial pneumonitis (see section 4.4) • Lung edema Rare • ARDS (see section 4.4)
Gastrointestinal disorders	Very common • Vomiting • Nausea Common • Diarrhoea • Stomatitis and ulceration of the mouth • Constipation
Hepatobiliary disorders	Very common • Elevation of liver transaminases (AST and ALT) and alkaline phosphatase Common • Increased bilirubin Rare • Increased gamma-glutamyl transferase (GGT)
Skin and subcutaneous tissue disorders	Very common • Allergic skin rash frequently associated with pruritus • Alopecia Common • Itching • Sweating Rare • Ulceration • Vesicle and sore formation • Scaling Very rare • Severe skin reactions, including desquamation and bullous skin eruptions
Musculoskeletal and connective tissue disorders	Common • Back pain • Myalgia
Renal and urinary disorders	Very Common • Haematuria • Mild proteinuria • Increased creatinine Rare • Acute renal failure (see section 4.4) • Hemolytic uremic syndrome (see section 4.4)

System Organ Class	Frequency grouping
General disorders and administration site conditions	Very common • 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 Common • Fever • Asthenia • Chills Rare • Injection site reactions-mainly mild in nature
Injury, poisoning, and procedural Complications	Radiation toxicity (see section 4.5).

Postmarketing experience (spontaneous reports) frequency not known (can't be estimated from the available data)

Nervous system disorders

Cerebrovascular accident

Vascular disorders

Clinical signs of gangrene

Gastrointestinal disorders

Ischaemic colitis

Hepatobiliary disorders

Serious hepatotoxicity, including liver failure and death

Skin and subcutaneous tissue disorders

Lyell's Syndrome, Steven-Johnson Syndrome

Diffuse erythema and desquamation observed in patients with renal dysfunction (see section 4.4)

Injury, poisoning and procedural complications

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.

Grade 3 and 4 Adverse Events Paclitaxel versus gemcitabine plus paclitaxel				
	Number (%) of Patients			
	Paclitaxel arm (N=259)		Gemcitabine plus Paclitaxel arm (N=262)	
	Grade 3	Grade 4	Grade 3	Grade 4
Laboratory				
Anaemia	5 (1.9)	1 (0.4)	15 (5.7)	3 (1.1)
Thrombocytopaenia	0	0	14 (5.3)	1 (0.4)
Neutropaenia	11 (4.2)	17 (6.6)*	82 (31.3)	45 (17.2)*
Non-laboratory				
Febrile neutropaenia	3 (1.2)	0	12 (4.6)	1(0.4)
Fatigue	3 (1.2)	1 (0.4)	15 (5.7)	2 (0.8)
Diarrhoea	5 (1.9)	0	8 (3.1)	0
Motor neuropathy	2(0.8)	0	6(2.3)	1(0.4)
Sensory neuropathy	9(3.5)	0	14(5.3)	1(0.4)

*Grade 4 neutropaenia lasting for more than 7 days occurred in 12.6% of patients in the combination arm and 5.0% of patients in the paclitaxel arm.

Combination use in bladder cancer

Grade 3 and 4 Adverse Events MVAC versus Gemcitabine plus cisplatin				
	Number (%) of Patients			
	MVAC (methotrexate, vinblastine, doxorubicin and cisplatin) arm (N=196)		Gemcitabine plus cisplatin arm (N=200)	
	Grade 3	Grade 4	Grade 3	Grade 4
Laboratory				
Anaemia	30(16)	4(2)	47(24)	7(4)
Thrombocytopaenia	15(8)	25(13)	57(29)	57(29)
Non-laboratory				
Nausea and vomiting	37(19)	3(2)	44(22)	0(0)
Diarrhoea	15(8)	1(1)	6(3)	0(0)
Infection	19(10)	10(5)	4(2)	1(1)
Stomatitis	34(18)	8(4)	2(1)	0(0)

Combination use in non-small-cell lung cancer

Grade 3 and 4 Adverse Events Gemcitabine plus Cisplatin vs Paclitaxel plus Cisplatin				
	% of Patients			
	Gemcitabine plus Cisplatin arm (N=293)		Paclitaxel plus Cisplatin arm (N=300)	
	Grade 3	Grade 4	Grade 3	Grade 4
Hematologic Toxicity				
Neutrophil count	24	39	18	57
Platelet count	22	28	4	2
Anaemia	27	1	12	1
Infection	2	1	4	2
Febrile neutropaenia	1	3	2	14
Non-hematologic Toxicity				
Cardiac toxicity	3	1	0	1
Renal toxicity	2	1	0	0
Nausea	37	0	25	0
Vomiting	7	28	3	21
Diarrhea	2	1	1	6
Hypersensitivity	0	0	2	1
Weakness	17	0	13	1

Neuropathy	9	0	5	0
All toxic effects, highest Grade	21	68 4 Grade 5	19	68 5 Grade 5

Combination use in ovarian cancer

Grade 3 and 4 Adverse Events Carboplatin versus Gemcitabine plus carboplatin				
	Number (%) of Patients			
	Carboplatin arm (N=174)		Gemcitabine plus carboplatin arm (N=175)	
	Grade 3	Grade 4	Grade 3	Grade 4
Laboratory				
Anaemia	10(5.7)	4(2.3)	39(22.3)	9(5.1)
Neutropaenia	19(10.9)	2(1.1)	73(41.7)	50(28.6)
Thrombocytopaenia	18(10.3)	2(1.1)	53(30.3)	8(4.6)
Leucopaenia	11(6.3)	1(0.6)	84(48.0)	9(5.1)
Non-laboratory				
Haemorrhage	0(0.0)	0(0.0)	3(1.8)	(0.0)
Febrile neutropaenia	0(0.0)	0(0.0)	2(1.1)	(0.0)
Infection without neutropaenia	0(0)	0(0.0)	(0.0)	1(0.6)

Sensory neuropathy was also more frequent in the combination arm than with single agent carboplatin

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).

Likewise, 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.

Clinical data

Bladder cancer

A randomised phase III study of 405 patients with advanced or metastatic urothelial transitional cell carcinoma showed no difference between the two treatment arms, gemcitabine/cisplatin versus methotrexate/vinblastine/adriamycin/cisplatin (MVAC), in terms of median survival (12.8 and 14.8 months respectively, p=0.547), time to disease progression (7.4 and 7.6 months respectively, p=0.842) and response rate (49.4% and 45.7% respectively, p=0.512). However, the combination of gemcitabine and cisplatin had a better toxicity profile than MVAC.

Pancreatic cancer

In a randomised phase III study of 126 patients with advanced or metastatic pancreatic cancer, gemcitabine showed a statistically significant higher clinical benefit response rate than 5-fluorouracil (23.8% and 4.8% respectively, p=0.0022). Also, a statistically significant prolongation of the time to progression from 0.9 to 2.3 months (log-rank p<0.0002) and a statistically significant prolongation of median survival from 4.4 to 5.7 months (log-rank p<0.0024) was observed in patients treated with gemcitabine compared to patients treated with 5-fluorouracil.

Non small cell lung cancer

In a randomised phase III study of 522 patients with inoperable, locally advanced or metastatic NSCLC, gemcitabine in combination with cisplatin showed a statistically significant higher response rate than cisplatin alone (31.0% and 12.0%, respectively, p<0.0001). A statistically significant prolongation of the time to progression, from 3.7 to 5.6 months (log-rank p<0.0012) and a statistically significant prolongation of median survival from 7.6 months to 9.1 months (log-rank p<0.004) was observed in patients treated with gemcitabine/cisplatin compared to patients treated with cisplatin.

In another randomised phase III study of 135 patients with stage IIIB or IV NSCLC, a combination of gemcitabine and cisplatin showed a statistically significant higher response rate than a combination of cisplatin and etoposide (40.6% and 21.2%, respectively, p=0.025). A statistically significant prolongation of the time to progression, from 4.3 to 6.9 months (p=0.014) was observed in patients treated with gemcitabine/cisplatin compared to patients treated with etoposide/cisplatin.
In both studies it was found that tolerability was similar in the two treatment arms.

Ovarian carcinoma

In a randomised phase III study, 356 patients with advanced epithelial ovarian carcinoma who had relapsed at least 6 months after completing platinum based therapy were randomised to therapy with gemcitabine and carboplatin (GCb), or carboplatin (Cb). A statistically significant prolongation of the time to progression of disease, from 5.8 to 8.6 months (log-rank p= 0.0038) was observed in the patients treated with GCb compared to patients treated with Cb. Differences in response rate of 47.2% in the GCb arm versus 30.9% in the Cb arm (p=0.0016) and median survival 18 months (GCb) versus 17.3 (Cb) (p=0.73) favoured the GCb arm.

Breast cancer

In a randomised phase III study of 529 patients with inoperable, locally recurrent or metastatic breast cancer with relapse after adjuvant/neoadjuvant chemotherapy, gemcitabine in combination with paclitaxel showed a statistically significant prolongation of time to documented disease progression from 3.98 to 6.14 months (log-rank p=0.0002) in patients treated with gemcitabine/paclitaxel compared to patients treated with paclitaxel. After 377 deaths, the overall survival was 18.6 months versus 15.8 months (log rank p=0.0489, HR 0.82) in patients treated with gemcitabine/paclitaxel compared to patients treated with paclitaxel and the overall response rate was 41.4% and 26.2% respectively (p= 0.0002).

5.2 Pharmacokinetic properties

The pharmacokinetics of gemcitabine have been examined in 353 patients in seven studies. The 121 women and 232 men ranged in age from 29 to 79 years. Of these patients, approximately 45% had non small cell lung cancer and 35% were diagnosed with pancreatic cancer. The following pharmacokinetic parameters were obtained for doses ranging from 500 to 2,592 mg/m² that were infused from 0.4 to 1.2 hours.

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 1,000 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

The volume of distribution of the central compartment was 12.4 l/m² for women and 17.5 l/m²for 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.

Metabolism

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

Excretion

Systemic clearance ranged from 29.2 l/hr/m² to 92.2 /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 - 350 mg/ m²/30 minutes, which give steady state concentrations of 0.4 - 5 µg/ml. At gemcitabine plasma concentrations above 5 µg/ml, dFdCTP levels do not increase, suggesting that the formation is saturable in these cells.
Half life of terminal elimination: 0.7 - 12 hours.

dFdU kinetics

Peak plasma concentrations (3-15 minutes after end of 30 minute infusion, 1000 mg/m²): 28 - 52 µg/ml. Trough concentration following once weekly dosing: 0.07 -1.12 µg/ml, with no apparent accumulation. Triphasic plasma concentration versus time curve, mean half life of terminal phase 65 hours (range 33 - 84 hr).
Formation of dFdU from parent compound: 91% - 98%.
Mean volume of distribution of central compartment: 18 l/m² (range 11 - 22 l/m²).
Mean steady state volume of distribution (Vss): 150 l/m² (range 96 - 228 l/m²).
Tissue distribution: Extensive.
Mean apparent clearance: 2.5 l/hr/m² (range 1 - 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 medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf life

As packaged for sale:
18 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).

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 dilution has taken place in controlled and validated aseptic conditions.

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 dilution has taken place in controlled and validated aseptic conditions.

6.4 Special precautions for storage

As packaged for sale:
Store in a refrigerator (2°C – 8°C). Do not freeze.

For storage condition of the diluted medicinal product, see section 6.3.

6.5 Nature and contents of container

Colourless glass (type I) vials, closed with grey rubber stoppers acc. to Ph.Eur (type I).

Pack sizes:
200 mg/5 ml: 1 vial
1000 mg/25 ml: 1 vial
2000 mg/50 ml: 1 vial

6.6 Special precautions for disposal and other handling

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.

National approved name 40 mg/ml concentrate for solution for infusion must be diluted before use (see section 4.2 and 4.4). It is recommended to use large veins for infusion to prevent damage to the vessel and extravasation.
Transfer the required quantity of solution under aseptic conditions into a suitable infusion bag or bottle. The solution may be administered as prepared or further diluted with 0.9% sodium chloride solution or 5% glucose solution as appropriate. Mix the liquids thoroughly by rotating by hand.

Handling

The normal safety precautions for cytostatic agents must be observed when preparing and disposing of the infusion solution. Handling of the solution for infusion should be done in an isolator or a cytotoxic safety cabinet. Protective clothing should be used as required (protective coat, gloves, mask, protective goggles).
If the preparation comes into contact with the eyes, this may cause serious irritation. The eyes should be rinsed immediately and thoroughly with water. If there is lasting irritation, a doctor should be consulted. If the solution is spilled on the skin, rinse thoroughly with water.

Remnants of the medicinal product as well as all materials that have been used for reconstitution, for dilution and administration must be destroyed according to hospital standard procedures applicable to cytotoxic agents and in accordance with local requirements related to the disposal of hazardous waste.

7. MANUFACTURER

EBEWE Pharma Ges.m.b.H. Nfg.KG
A-4866 Unterach, AUSTRIA

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Ebewe PHARMA