Agenzia Italiana del Farmaco

AIFA

Public Assessment Report

Scientific discussion

GEMCITABINA HIKMA

Gemcitabine hydrochloride

2g powder for solution for infusion

IT/H/167/03/DC

HIKMA Farmaceutica (Portugal), S.A.

IT Marketing Authorisation Number: 039727

TABLE OF CONTENTS

Module 1

Information about the Initial Procedure

ADMINISTRATIVE INFORMATION

Product Name	**GEMCITABINA HIKMA**
Active Substance	**Gemcitabine hydrochloride**
Form	Powder for solution for infusion
Strength(s):	2000 mg
Procedure number	IT/H/167/03/DC
MA Holder	Hikma Farmacêutica, S.A. Estrada do Rio da Mó, nº8, 8A e 8B, Fervença, 2705-906 Terrugem SNT Portugal
Reference Member State:	ITALY
Concerned Member States:	DE
Timetable	End of procedure: Day 210- 07/01/2014

Module 2

Summary of Product Characteristics

In accordance with Directive 2010/84/EU, the Italian version of the file Summaries of Product Characteristics (SmPCs) for products granted Marketing Authorisations at a national level will be available on the AIFA website once the Marketing Authorization will be granted.
The English version of the SmPC approved at European level.

1. NAME OF THE MEDICINAL PRODUCT

<Product Name> 2 g powder for solution for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One vial contains:
2280 mg gemcitabine hydrochloride equivalent to 2 g gemcitabine.

After reconstitution, the solution contains 38mg/ml of gemcitabine

Excipients

Each 2 g vial contains 35 mg (1.52 mmol) sodium.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder for solution for infusion
A white to off-white powder.

4. CLINICAL PARTICULARS

4.1Therapeutic indications

Gemcitabine is indicated for the treatment of locally advanced or metastatic bladder cancer in combination with cisplatin.

Gemcitabine is indicated for the 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/m^2 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 amount of toxicity experienced by the patient.

Pancreatic cancer
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 grade of toxicity experienced by the patient.

Non small Cell lung cancer
Monotherapy
The recommended dose 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 grade of toxicity experienced by the patient.

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

Breast cancer
Combination use
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 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/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 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) nonhaematological 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 <Product name> (%)
> 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 <Product name> (%)
≥ 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 modification of gemcitabine within a cycle for ovarian cancer, given in combination with carboplatin		
Absolute granulocyte count (x 10^6/l)	**Platelet count (x 10^6/l)**	Percentage of standard dose of <Product name> (%)
> 1,500 and	> 100,000	100
1000-1,500 or	75,000-100,000	50
<1000 or	< 75,000	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

<Product name> 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.

For 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 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.

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 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.

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).

Sodium
<Product name> 2 g contains 35 mg (1.52 mmol) sodium per vial. This should be taken into consideration by patients on a controlled sodium diet.

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 radiotherapy (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 radiosensitizing 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 esophagitis, 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, were thoracic radiation doses of 66 Gy were applied concomitantly with an administration with gemcitabine (600mg/m^2, four times) and cisplatin (80mg/m^2 twice) during 6 weeks. The optimum regimen for safe administration of gemcitabine with therapeutic doses of radiation has not yet been determined in all tumour types.

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. esophagitis, colitis, and pneumonitis) in association with both concurrent and non-concurrent use of gemcitabine.

Others
Yellow fever and other live attenuated vaccines are not recommended due to the risk of systemic, possibly fatal, disease, particularly in immunosuppressed patients.

4.6 Fertility, pregnancy and lactation

Pregnancy
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 disorder	Rare • Myocardial infarct
Vascular disorder	Rare • Hypotension
Respiratory, thoracic and mediastinal disorders	Very common • Dyspnoea – usually mild and passes rapidly without treatment Common • Cough • Rhinitis

	Uncommon • Interstitial pneumonitis (see section 4.4) • Bronchospasm – usually mild and transient but may require parenteral treatment
Gastrointestinal disorders	Very common • Vomiting • Nausea Common • Diarrhoea • Stomatitis and ulceration of the mouth • Constipation
Hepatobiliary disorders	Very common • Elevation of the 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
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)

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

Nervous system disorders
Cerebrovascular accident

Cardiac disorders
Arrhythmias, predominantly supraventricular in nature
Heart failure

Vascular disorders
Clinical signs of peripheral vasculitis and gangrene

Respiratory, thoracic and mediastinal disorders
Pulmonary oedema Adult respiratory distress syndrome (see section 4.4)

Gastrointestinal disorders
Ischemic colitis

Hepatobiliary disorders
Serious hepatotoxicity, including liver failure and death

Skin and subcutaneous tissue disorders
Severe skin reactions, including desquamation and bullous skin eruptions, Lyell's Syndrome, Steven-Johnson Syndrome.

Renal and urinary disorders
Renal failure (see section 4.4)
Haemolytic uraemic syndrome (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)
Thrombocytopenia	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)
Thrombocytopenia	15 (8)	25 (13)	57 (29)	57 (29)
Non-laboratory				
Nausea & 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 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)
Thrombocytopenia	18 (10.3)	2 (1.1)	53 (30.3)	8 (4.6)
Leucopenia	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

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via national reporting system.

4.9 Overdose

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: pyrimidine analogue ATC code: L01BC05

Cytotoxic activity in cell cultures:
Gemcitabine shows significant cytotoxic effects against a variety of 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 G_1/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, antitumoral activity of gemcitabine is schedule-dependent. When gemcitabine is administered daily, high mortality among the animals but minimal antitumoral activity is observed. If, however, gemcitabine is given every third or fourth day, it can be administered in non-lethal doses with substantial antitumoral 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 the 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 of 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/m^2 that were infused from 0.4 to 1.2 hours.

Peak plasma concentrations (obtained within 5 minutes of the end of infusion) were 3.2 to 45.5 μg/ml. Plasma concentrations of the parent compound following a dose of 1,000 mg/ml^2/30 minutes are greater than 5μg/ml for approximately 30-minutes after the end of the infusion, and greater than 0.4μg/ml for an additional hour.

Distribution

The volume of distribution of the central compartment was 12.4 l/m^2 for women and 17.5 l/m^2 for men. (interindividual variability was 91.9%).
The volume of distribution of the peripheralcompartment was 47.4 l/m^2. 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/hour/m^2 to 92.2 l/hour/m^2 depending on gender and age (interindividual variability was 52.2%). Clearance for women was 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/m^2 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/m^2.

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/m^2/30 minutes, which give steady-state concentrations of 0.4 - 5 μg/ml. At gemcitabine plasma concentrations above 5 μg/ml, the 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/m^2): 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/m^2 (range 11-22 l/m^2).
Mean steady state volume of distribution (Vss): 150 l/m^2 (range 96-228 l/m^2).
Tissue distribution: Extensive.
Mean apparent clearance: 2.5 l/hr/m^2 (range 1-4 l/hr/m^2).
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

<Product Name> 2g contains:
Mannitol
Sodium acetate trihydrate
Hydrochloric acid (pH adjustment)
Sodium hydroxide (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

Unopened vials: 36 months.

Reconstituted solution:
Chemical and physical in-use stability has been demonstrated for 24 hours at 20-25°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 20-25°C, unless reconstitution has taken place in controlled and validated aseptic conditions.

Solutions of reconstituted gemcitabine should not be refrigerated, as crystallisation may occur.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions

For storage conditions of the reconstituted medicinal product see section 6.3.

6.5 Nature and contents of container

The product is packed in Type I clear glass vials with grey bromobutyl stoppers and aluminium flip-off caps with light grey coloured polypropylene disks.

Pack sizes:
1 vial /carton

6.6 Special precautions for disposal and other handling

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 a safety box and protective coats and gloves should be used. If no safety box is available, the equipment should be supplemented with a mask and protective glasses.
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.

Reconstitution perspectives.

To reconstitute, add 50 mL of 0.9% Sodium Chloride Injection to the 2g vial. Shake to dissolve. The obtained solution contains 38mg/ml of active ingredient. Complete withdrawal of the vial contents will provide 2000 mg(2 g) of gemcitabine, . The appropriate amount of drug may be administered as prepared or further diluted with 0.9% Sodium Chloride Injection to concentrations as low as 0.1 mg/ml

Reconstituted Gemcitabine Solution is a clear, colorless to light straw-colored solution. After reconstitution with 0.9% Sodium Chloride Injection, the pH of the resulting solution lies in the range of 2.7 to 3.3. The solution should be inspected visually for particulate matter and discoloration, prior to administration, whenever solution or container permits. If particulate matter or discoloration is found, do not administer.

When prepared as directed, Gemcitabine solutions are stable for 24 hours at controlled room temperature 20° to 25°C. Discard unused portion. Solutions of reconstituted Gemcitabine should not be refrigerated, as crystallization may occur.

7: MARKETING AUTHORISATION HOLDER:

<To be completed nationally>

8. MARKETING AUTHORISATION NUMBER(S)

<To be completed nationally>

9: DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

<To be completed nationally>

10: DATE OF REVISION OF THE TEXT

Module 3

Package Leaflets

In accordance with Directive 2010/84/EU, Italian version of the file of the package leaflets for products granted Marketing Authorisations at a national level will be available on the AIFA website once the Marketing Authorization will be granted.
Here the English version of the Pil approved at European level.

PACKAGE LEAFLET: INFORMATION FOR THE USER

<Product Name> 2g powder for solution for infusion
gemcitabine

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

What is in this leaflet:

1.What<product name> is and what it is used for

<Product name> belongs to a group of medicines called “cytotoxics”. These medicines kill dividing cells, including cancer cells.

<Product name> may be given alone or in combination with other anti-cancer medicines, depending on the type of cancer.

<Product name> is used in the treatment of the following types of cancer:
- non-small cell lung cancer (NSCLC), alone or together with cisplatin
- pancreatic cancer.
- breast cancer, together with paclitaxel.
- ovarian cancer, together with carboplatin.
- bladder cancer, together with cisplatin.

2. What you need to know before you use <product name>

Do not use <Product Name>
- if you are allergic (hypersensitive) to gemcitabine or any of the other ingredients of this medicine (listed in section 6)
- if you are breast-feeding

Warnings and precautions
Before the first infusion you will have samples of your blood taken to evaluate if you have sufficient kidney and liver function. Before each infusion you will have samples of your blood taken to evaluate if you have enough blood cells to receive <Product name>. Your doctor may decide to change the dose or delay treating you depending on your general condition and if your blood cell counts are too low.
Periodically you will have samples of your blood taken to evaluate your kidney and liver function.
Please tell your doctor if:

- you have, or have previously had liver disease, heart disease or vascular disease.
- you have recently had, or are going to have radiotherapy,
- you have been vaccinated recently
- you develop breathing difficulties or feel very weak and are very pale (may be a sign of kidney failure).

Men are advised not to father a child during and up to 6 months following treatment with <Product name>. If you would like to father a child during the treatment or in the 6 months following treatment, seek advice from your doctor or pharmacist. You may want to seek counselling on sperm storage before starting your therapy.

Other medicines and <product name>

Please tell your doctor or hospital pharmacist if you are taking, or have recently taken, any other medicines, including vaccinations and medicines obtained without a prescription.

Pregnancy and breast-feeding and fertility

If you are pregnant or breast feeding, think you may be pregnant or planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.
The use of <Product name>should be avoided during pregnancy. Your doctor will discuss with you the potential risk of taking <Product name>during pregnancy.

If you are breast-feeding, tell your doctor.
You must discontinue breast-feeding during <Product name>treatment.

Driving and using machines
<Product name> may make you feel sleepy, particularly if you have consumed any alcohol. Do not drive a car or use machinery until you are sure that <Product name> treatment has not made you feel sleepy.

Important information about some of the ingredients of <Product name>
<Product name> contains 35 mg (< 1.52 mmol) of sodium in each 2000 mg vial. To be taken into consideration by patients on a controlled sodium diet.

3. How to use <product name>

The usual dose of <Product name> is 1000-1250 mg for every square metre of your body's surface area. Your height and weight are measured to work out the surface area of your body. Your doctor will use this body surface area to work out the right dose for you. This dosage may be adjusted, or treatment may be delayed depending on your blood cell counts and on your general condition.

How frequently you receive your <Product name> infusion depends on the type of cancer that you are being treated for.
A hospital pharmacist or doctor will have dissolved the <Product name> powder before it is given to you.

You will always receive <Product name> by infusion into one of your veins. The infusion will last approximately 30 minutes.

If you have further questions on the use of this product ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, <Product name>can cause side effects, although not everybody gets them.

Frequencies of the observed side effects are defined as:
- very common: affects more than 1 user in 10
- common: affects 1 to 10 users in 100
- uncommon: affects 1 to 10 users in 1,000
- rare: affects 1 to 10 users in 10,000
- very rare: affects less than 1 user in 10,000
- not known: frequency can't be estimated from the available data

You must contact your doctor immediately if you notice any of the following:
- Fever or infection (common): if you have a temperature of 38ºC or greater, sweating or other signs of infection (since you might have less white blood cells than normal which is very common).
- Irregular heart rate (arrhythmia) (frequency not known).
- Pain, redness, swelling or sores in your mouth (common).
- Allergic reactions: if you develop skin rash (very common) / itching (common), or fever (very common).
- Tiredness, feeling faint, becoming easily breathless or if you look pale (since you might have less haemoglobin than normal which is very common).
- Bleeding from the gums, nose or mouth or any bleeding that would not stop, reddish or pinkish urine, unexpected bruising (since you might have less platelets than normal which is very common).
- Difficulty breathing (it is very common to have mild breathing difficulty soon after the <Product name> infusion which soon passes, however uncommonly or rarely there can be more severe lung problems)

Side effects with <Product name> may include:

Very common
- Low haemoglobin level (anaemia)
- Low white blood cells
- Low platelet count
- Difficulty breathing
- Vomiting
- Nausea
- Skin rash- allergic skin rash, frequently itchy
- Hair loss
- Liver problems: found through abnormal blood test results
- Blood in urine
- Abnormal urine tests: protein in urine
- Flu like symptoms including fever
- Oedema (swelling of ankles, fingers, feet, face)

Common side effects
- Fever accompanied by low white blood cell count (febrile neutropaenia)
- Anorexia (poor appetite)

- Headache
- Insomnia
- Sleepiness
- Cough
- Runny nose
- Constipation
- Diarrhoea
- Pain, redness, swelling or sores in the mouth
- Itching
- Sweating
- Muscle pain
- Back pain
- Fever
- Weakness
- Chills

Uncommon side effects:
- Interstitial pneumonitis (scarring of the air sacs of the lung)
- Spasm of the airways (wheeze)
- Abnormal chest X ray/scan (scarring of the lungs)

Rare side effects*:*
- Heart attack (myocardial infarction)
- Low blood pressure
- Skin scaling, ulceration or blister formation
- Injection site reactions

Very rare side effects*:*
- Increased platelet count
- Anaphylactic reaction (severe hypersensitivity/ allergic reaction)
- Sloughing of skin and severe skin blistering

Side effects with frequency not known
- Irregular heart beat (arrhythmia)
- Adult Respiratory Distress Syndrome (severe lung inflammation causing respiratory failure)
- Radiation recall-(a skin rash like severe sunburn) which can occur on skin that has previously been exposed to radiotherapy.
- Fluid in the lungs
- Radiation toxicity- scarring of the air sacs of the lung associated with radiation therapy
- Ischemic colitis (inflammation of the lining of the large bowel, caused by reduced blood supply)
- Heart failure
- Kidney failure
- Gangrene of fingers or toes
- Serious liver damage, including liver failure
- Stroke

You might have any of these symptoms and/or conditions. You must tell your doctor as soon as possible when you start experiencing any of these side effects.

If you are concerned about any side effects, talk to your doctor.

If any of the side effects gets serious, or if you notice any side effects not mentioned in this leaflet, please tell your doctor.

If you get any side effects, talk to your doctor. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system. By reporting side affects you can help provide more information on the safety of this medicine

5. How to store <product name>

Keep the medicinal product out of the reach and sight of children.

Do not use <Product Name> after the expiry date (EXP) which is stated on the carton. The expiry date refers to the last day of that month.

Unopened vial: This medicinal product does not require any special storage conditions.

Reconstituted solution:
The product should be used immediately. When prepared as directed, chemical and physical in-use stability of reconstituted solutions of gemcitabine were demonstrated for 24 hours at 20-25°C Further dilution by a healthcare provider may be done. Solutions of reconstituted gemcitabine should not be refrigerated, as crystallisation may occur.

This medicine is for single use only; any unused solution should be discarded under the local requirements.

6. Contents of the pack and other information

What <Product Name> contains
The active substance is gemcitabine hydrochloride. Each vial contains 2g of gemcitabine (as gemcitabine hydrochloride).

The other ingredients are mannitol, sodium acetate trihydrate, hydrochloric acid and sodium hydroxide used as pH adjusters and nitrogen as an inert gas.

What <Product Name> looks like and contents of the pack
A white to off-white powder. On reconsitution with sterile sodium chloride the solution is a clear colourless to light straw-coloured solution.

Each pack of <Product name> contains:

1 vial

Marketing Authorisation Holder and Manufacturer

Marketing Authorisation Holder:
Hikma Farmacêutica (Portugal), S.A.
Estrada do Rio da Mó, 8
Fervença
2705-906 Terrugem SNT
Portugal

Manufacturer:
Thymoorgan Pharmazie GmbH
Schiffgraben 23
38690 Vienenburg
Germany

This leaflet was last approved in MM/YYYY

This medicinal product is authorised in the Member States of the EEA under the following names:

DE: Ribozar 2g Pulver zur Herstellung einer Infusionslösung
IT: Gemcitabina Hikma 2 g polvere per soluzione per infusione

---

The following information is intended for medical or healthcare professionals only:

Instructions for use, handling and disposal.

1. Use aseptic techniques during the reconstitution and any further dilution of gemcitabine for intravenous infusion administration.

2. Calculate the dose and the number of Gemcitabine vials needed.

3. To reconstitute, add 50 mL of 0.9% Sodium Chloride Injection to the 200-mg vial. Shake to dissolve. The obtained solution contains 38mg/ml of active ingredient. Complete withdrawal of the vial contents will provide 2g of gemcitabine, respectively. The appropriate amount of drug may be administered as prepared or further diluted with 0.9% Sodium Chloride Injection to concentrations as low as 0.1 mg/ml.

Reconstituted Gemcitabine Solution is a clear, colourless to light straw-coloured solution. After reconstitution with 0.9% Sodium Chloride Injection, the pH of the resulting solution lies in the range of 2.7 to 3.3. The solution should be inspected visually for particulate matter and discoloration, prior to administration, whenever solution or container permits. If particulate matter or discoloration is found, do not administer.

4. Parenteral medicinal products should be inspected visually for particulate matter and discolouration prior to administration. If particulate matter is observed, do not administer.

5. Solutions of reconstituted Gemcitabine should not be refrigerated, as crystallization may occur. Chemical and physical in-use stability has been demonstrated for 24 hours at 20-25°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 20-25°C, unless reconstitution has taken place in controlled and validated aseptic conditions.

6. Gemcitabine solutions are for single use only. Any unused product or waste material should be disposed of in accordance with local requirements.

Preparation and administration precautions

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 a safety box and protective coats and gloves should be used. If no safety box is available, the equipment should be supplemented with a mask and protective glasses.
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.

Disposal

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

MODULE 4

Labelling

PARTICULARS TO APPEAR ON THE CARTON BOX AND THE BLISTER

CARTON

1. NAME OF THE MEDICINAL PRODUCT

GEMCITABINA HIKMA 2g powder for solution for infusion
Gemcitabine

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each vial contains gemcitabine hydrochloride equivalent to 2g gemcitabine

3. LIST OF EXCIPIENTS

Mannitol, Sodium acetate trihydrate, Hydrochloric acid (pH adjuster), Sodium hydroxide (pH adjuster). See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

1 vial, powder for solution for infusion.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For intravenous use after reconstitution.
Read the package leaflet before use.
For single use only

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the reach and sight of children.

. OTHER SPECIAL WARNING(S), IF NECESSARY

Do not refrigerate the reconstituted solution

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Read the leaflet for the shelf life of the reconstituted product

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Discard unused contents appropriately

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

<[To be completed nationally]>

12. MARKETING AUTHORISATION NUMBER(S)

<[To be completed nationally]>

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Gemcitabine 2g

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

Vial label

1. NAME OF THE MEDICINAL PRODUCT

GEMCITABINA HIKMA 2 g powder for solution for infusion
Gemcitabine

For intravenous use only

2. METHOD OF ADMINISTRATION

For intravenous use after reconstitution

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

1 vial contains 2000mg of Gemcitabine
Powder for solution for infusion

2g

6. OTHER

Module 5

Scientific discussion during the initial procedure

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States involved in the procedure have granted a marketing authorisation for **GEMCITABINA HIKMA** 2 g powder for solution for infusion from **HIKMA Farmacêutica.**

The therapeutic indications approved are as follows:

- The product is indicated for the treatment of locally advanced or metastatic bladder cancer in combination with cisplatin.
- Gemcitabine is indicated for the 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.

This application was submitted using the Decentralised Procedure (DCP), with Italy (IT) as Reference Member State (RMS) and Germany, as Concemed Member States (CMS). This application submitted in accordance with Directive 2001/83/EC, as amended, Article 10(3)application.

The product **GEMCITABINE HIKMA** 2 g powder for solution for infusion was proposed as line extention of **GEMCITABINE HIKMA** 200/1000 mg powder for solution for infusion **already authorizated on 08/01/2009**

.

The reference product was Gemzar 200 mg/ml, 1 g/ml, power for solution for infusion, Marketing Authorisation Holder: Eli Lilly Italia S.p.A.

The first authorisation for the reference product was granted on the 27rd of March 1995 in NL.

A comprehensive description of the indications and posology is given in the SmPC."

GEMCITABINE pd.sol.if 2000mg/vial contain the active ingredients Gemcitabine that is an analog nucleoside of cytidine (a pyrimidine nucleoside antimetabolite).

It is a pro-drug that requires intracellular phosphorylation by nucleoside kinases to active diphosphate (dFdCDP) and triphosphate (dFdCTP) nucleosides.

Both gemcitabine diphosphate (dFdCDP) and gemcitabine triphosphate (dFdCTP) inhibit processes required for DNA synthesis.
The antitumor activity is characterised by a mechanism of action which includes cytotoxic self-potentiation, masked DNA chain termination and potent inhibition of DNA repair.

Gemcitabine is clinically used as monotherapy or in combination for the treatment of non-small cell lung cancer, pancreatic cancer, breast cancer, bladder cancer, and in some Member States, for ovarian cancers.

II About the product

Proposed name of the medicinal product in the RMS	**GEMCITABINA HIKMA**
Name of the drug substance (INN name):	**Gemcitabine hydrochloride**
Pharmaco-therapeutic group (ATC Code):	L01BC05
Pharmaceutical form(s) and strength(s):	2000 mg powder for solution for infusion
Reference Number(s) for the Decentralised Procedure	IT/H/167/03/DC
Reference Member State:	ITALY
Concerned Member States:	DE
Marketing Authorisation Numbers	AIC No: 039727058
Applicant (name and address)	Hikma Farmacêutica, S.A. Estrada do Rio da Mó, nº8, 8A e 8B, Fervença, 2705-906 Terrugem SNT Portugal

III SCIENTIFIC OVERWIE AND DISCUSSION

QUALITY ASPECTS

I.1 QUALITY ASPECTS

I.2 Introduction

I.3 2.2 Drug Substance

INN : Gemcitabine (as hydrochloride

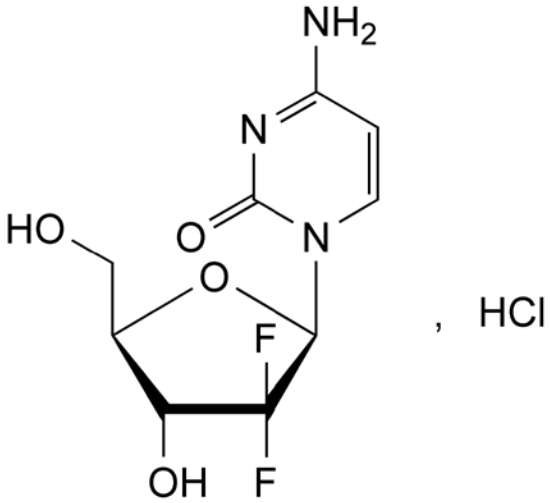
Chemical Name - 2'-Deoxy-2',2'-difluorocytidine monohydrochloride (β-isomer

Molecular Formula: $C_9H_{11}F_2N_3O_4$. HCl

CAS number : 122111-03-9

MOLECULAR WEIGHT 299.66

STRUCTURAL FORMULA



, HCl

All aspects of the manufacture and control of the active substance including the proposed packaging specifications and stability data are covered by a European Directorate for the Quality of Medicines (EDQM) Certificate of Suitability

Medicinal Product

GEMCITABINE HIKMA powder for solution for infusion 2000mg/vial is proposed as line extention of
GEMCITABINE HIKMA powder for solution for infusion 200/1000mg/vial of the marketed product of reference **Gemzar®** (**Lilly)** in Europe.

The presentation of 2000mg/vial of the product is identical with the presentation of 200mg/vial and 1000mg/vial, since all raw materials, test procedures and manufacturing steps (except from the mass of powder filled into each vial) are the same.
The product **GEMCITABINE HIKMA powder for solution for infusion 2000mg/vial** is a sterile lyophilizide powder for IV infusion for the preparation of an aqueous solution (after reconstitution with dilution medium of NaCl 0.9%) for intravenous administration only, of Gemcitabine (as Hydrochloride) filled in clear glass Type I vials of 100ml nominal capacity (100H DIN).

Other ingredients are: mannitol, sodium acetate anhydrous, hydrochloric acid 36%, sodium hydroxide, water for injection, nitrogen. All the excipients comply with their respective European Pharmacopeia monographs

Pharmaceutical Development

GEMCITABINE HIKMA powder for solution for infusion 2000mg/vial has been developed in order to facilitate the administration of the product and the easier dose adjustment following the patient's needs. The development of the 2000g presentation followed the other presentations and has been based on development studies and know data acquired during the first developments of 200 and 1000mg

Manufacturing Process

Satisfactory pilot batches of the product have been manufactured and submitted to all necessary IPCs, finished product controls and stability tests, in order to create an acceptable process validation protocol and report.

Control of Finished Product
The finished product specifications are satisfactory. Test methods have been described and adequately validated, as appropriate. Batch data have been provided and comply with the release specifications. Certificates of Analysis have been provided for any working standards used.

Container Closure System

GEMCITABINE HIKMA powder for solution for infusion 2000mg/vial is filled in, type I clear glass vials (Ph. Eur. Cur. Ed., 3.2.1) of 100ml . Each vial is sealed with *injection stoppers 20mm of bromobutyl, grey,* (Ph.Eur. cur. ed. § 3.2.9.) and *aluminium flip-off caps* with colored polypropylene disks.
Specifications, routine tests and test procedures of the primary packaging materials are provided.

Stability

Finished product stability studies are performed in accordance with current guidelines on batches of finished product packed in the packaging proposed for marketing. Based on the results, a shelf-life of 36 months has been proposed without the temperature storage statement.

II. NON-CLINICAL ASPECTS

GEMCITABINE HIKMA powder for solution for infusion 2000mg/vial is a generic medicinal product of Gemzar.

The pharmacodynamic, pharmacokinetic and toxicological properties of gemcitabine are well known. As gemcitabine is a widely used, well-known active substance, no further studies are required and the applicant has not provided any.

The environmental risk assessment of Gemcitabine (as HCl) pd.sol.inf. has followed the Guideline on the Environmental Risk Assessment of Medicinal Products for Human Use (Doc.Ref.EMEA/CHMP/SWP/4447/00).

III. CLINICAL ASPECTS

III.1 Introduction

As the product is a solution for injection,"containing the same active substance in the same concentration as the currently authorised product" according to Note for Guidance on Bioavailability and Bioequivalence (CPMP/EWP/QWP/1401/98) ,a bioequivalence study has not been carried out.

Pharmacokinetics

The dose range studied was between 500 and 2592 mg/m2 and the infusion time varied between 0.4 and 1.2 hours. The maximum plasma concentration was reached within 5 minutes after the infusion was stopped and reached a level between 3.2 and 45.5 microg/ml (12.1-172.9 micromol/ml). Distribution volume (central volume): 12.4 L/m2 for women and 17.5 L/m2 for men. The interindividual variability was 91.9%. Distribution volume (peripheral volume): 47.4 L/m2, and there was no difference between men and women. Binding to plasma proteins was negligible.

Systemic clearance varied from 29.2 L/hour/m2 to 92.2 L/hour/m2 depending on sex and age. The interindividual variability was 52.2%. Clearance for women was approximately 25% lower than that for men. The clearance appears to fall with age in both men and women. The proportion of unchanged gemcitabine excreted in the urine is less than 10%.

Renal clearance: 2-7 L/hour/m2. The half-life varied between 42 and 94 minutes depending on age and sex. For the recommended dosage regimen, gemcitabine is eliminated almost completely within 5 to 11 hours after the start of infusion. Gemcitabine does not accumulate when administered once weekly.

Pharmacodynamics

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 catalyses the reactions that produce deoxynucleoside triphosphates (dCTP) for the 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. In the same way, a small amount of gemcitabine may also be incorporated into RNA. Thus, the reduced intracellular concentration of dCTP means that the DNA uptake of dFdCTP increases. DNA polymerase epsilon lacks the ability to eliminate gemcitabine and repair the DNA strand that is formed. When gemcitabine is incorporated into DNA, the DNA strand is increased by one nucleotide. In principle, this increase means that there is complete inhibition of further DNA synthesis, which leads to cellular death (apoptosis).

III.2 Clinical efficacy

GEMCITABINE HIKMA powder for solution for infusion 2000mg/vial is a generic medicinal product of Gemzar .The efficacy of Gemcitabin is well-known. No new efficacy data have been submitted and none are required for applications of this type.

III.3 Clinical safety

GEMCITABINE HIKMA powder for solution for infusion 2000mg/vial is a generic medicinal product of Gemzar .The safety of Gemcitabin is well-known. No new safety data have been submitted and none are required for applications of this type

PHARMACOVIGILANCE SYSTEM AND RISK MANAGEMENT PLAN

The Applicant holds a Pharmacovigilance System Master File. All the documentation foreseen by the “Questions and Answers to support the implementation of the Pharmacovigilance legislation - UPDATE, NOVEMBER 2012” has been provided.

The MAH has submitted a risk management plan, in accordance with the requirements of Directive 2001/83/EC as amended, describing the p activities to identify, characterise, prevent or minimise risks relating to **GEMCITABINA HIKMA** 2 g powder for solution for infusion .

IV. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

GEMCITABINE HIKMA powder for solution for infusion 2000mg/vial is a generic medicinal product of Gemzar and the quality characteristics are well-defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

Efficacy and safety of gemcitabine are well-known, thus no new non clinical and clinical data were submitted. A biowever for the bioequivalence study has been accepted taking into account that the formulation proposed ia a solution for injection,"containing the same active substance in the same concentration as the currently authorised product".

PRODUCT LITERATURE

The SmPCs, PILs and labelling, approved for **GEMCITABINE HIKMA powder for solution for infusion 2000mg/vial** are consistent with those for the reference products, where appropriate, along with current guidelines.

The quality of the products is acceptable, and no new non-clinical or clinical safety concerns have been identified. Extensive clinical experience with **GEMCITABINA HIKMA** 2 g powder for solution for infusion is considered to have demonstrated the therapeutic value of the products. The benefit/risk balance is, therefore, considered to be positive.