Gemkabi 38 mg/ml concentrate for solution for infusion

6.10.2014, Version 1.2

PUBLIC SUMMARY OF THE RISK MANAGEMENT PLAN

VI.2 Elements for a public summary

VI.2.1 Overview of disease epidemiology

Gemcitabine can be used as monotherapy and in combination therapy. It is intended for the treatment of:

- Locally advanced or metastatic bladder cancer in combination with cisplatin.
- Patients with locally advanced or metastatic adenocarcinoma of the pancreas.
- 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.
- 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.
- 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.

Ovarian Cancer:

Ovarian cancer is the ninth most common cancer, with an estimated 22,240 new cases in 2013, but is the fifth most deadly, with an estimated 14,030 deaths in 2013. The incidence of ovarian cancer is 33 cases per 100,000 women aged 50 years or older. The average patient age at diagnosis is 57 years. The estimated lifetime risk is 1 case in 70 women, which is a 1.4% lifetime incidence. The annual incidence and mortality rates have dropped 1.6% and 0.3% per year on average for the years 1997–2006.[15]

Non-Small Cell Lung Cancer:

Lung cancer is a major cause of morbidity and mortality. Cancer that forms in tissues of the lung, usually in the cells lining air passages. Estimated new cases from lung cancer (non-small cell and small cell combined) in the United States in 2013 are 228,190 and deaths are 159,480.[1] In Europe Lung cancer, with an estimated 265,000 deaths (21.0% of total) was by far the most common cause of death from cancer. Lung cancer retains its status as the leading cause of cancer death in Europe in 2012. In Europe, approximately 381,500 patients are diagnosed with non-small cell lung cancer (NSCLC) every year.[10]

A study on cancer mortality in the countries of the European Union predicted that, compared to 2007, in 2012 mortality from lung cancer will decrease by 10% in males (while remaining the leading cause of death by cancer) but increase by 7% in females (thus becoming the second leading cause of cancer mortality).[16] In 2012, an estimated 33,900 new cases of SCLC will occur in the United States. Nearly all cases of SCLC are attributable to cigarette smoking. Although the overall incidence of SCLC has been decreasing, in women it is increasing, with the male-to-female incidence ratio now 1:1. [17]

Bladder Cancer:

Cancer that forms in tissues of the bladder (the organ that stores urine). Bladder cancer ranks ninth in worldwide cancer incidence. The number of new cases of bladder cancer was 20.7 per 100,000 men and women per year. Estimated new cases from bladder cancer in the United States in 2013 are 72,570 and deaths are 15,210.[1] The proportions of carcinoma *in situ* of the urinary bladder are 51% for All Races, 52% for Whites, and 37% for African Americans. In Europe 2012 bladder (118,000, 6.5%) was among the most common primary sites to develop cancer in men.[10] Bladder cancer is the tenth leading cause of cancer death in the United States. The number of deaths was 4.4 per 100,000 men and women per year.[1]

The earlier bladder cancer is caught, the better chance a person has of surviving five years after being diagnosed. For bladder cancer, 34.9% are diagnosed at the local stage. The 5-year survival for localized bladder cancer is 70.2%. The survival rate for carcinoma *in situ* of the urinary bladder is 96% for all Races. [18]

Adenocarcinoma of the Pancreas:

A disease in which malignant (cancer) cells are found in the tissues of the pancreas. Estimated new cases from pancreatic cancer in the United States in 2013 are 45,220 and deaths are 38,460.[1] The number of new cases of pancreas cancer was 12.2 per 100,000 men and women per year.[1] The number of deaths was 10.9 per 100,000 men and women per year. In Europe also Pancreas cancer is the fourth leading cause of cancer death (78,000, 6.2%).[10]

In a reported recent analysis of mortality trends from PC in 54 countries including 19 European Union countries found that in 2007, the highest mortality rates were among men in the Czech Republic, Hungary, Slovakia, and the Nordic countries (rates over 9/100,000); whereas rates were lowest in Latin America and Hong Kong (rates less than 5/100,000). [10]

Breast Cancer:

Among women, breast cancer is the most commonly diagnosed cancer after nonmelanoma skin cancer, and it is the second leading cause of cancer deaths after lung cancer. In 2013, an estimated 234,580 new cases will be diagnosed, and 40,030 deaths from breast cancer will occur.[1] The death rate is also higher among African American women than white women despite the lower incidence. From 2000 to 2003, the breast cancer death rate was highest in African Americans (34.3 cases per 100,000 women), followed by whites (25.3), Hispanics (16.2), American Indians/Alaska Natives (13.4), and Asian-Americans/Pacific Islanders (12.6).[3]

In reported cross-sectional studies of adult populations, 5% to 10% of women have a mother or sister with breast cancer, and about twice as many have either a first-degree relative (FDR) or a second-degree relative with breast cancer. [4,5,6]

Other Risk Factors for Breast Cancer[7]

Other risk factors for breast cancer include age, reproductive and menstrual history, hormone therapy, radiation exposure, mammographic breast density, alcohol intake, physical activity, anthropometric variables, and a history of benign breast disease.

VI.2.2 SUMMARY OF TREATMENT BENEFITS

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Gemcitabine belongs to the class of pyrimidine analogue and shows significant cytotoxic effects against a variety of cultured murine and human tumour cells. It is an inhibitor of DNA synthesis and primarily kills cells that are undergoing DNA (deoxyribonucleic acid) synthesis (S-phase) and, under certain circumstances, blocks the progression of cells at the junction of the G1/S phase boundary.

Gemcitabine (dFdC) is metabolised intracellularly by nucleoside kinase to the active diphosphate (dFdCDP) and triphosphate (dFdCTP) nucleosides. dFdCDP inhibits ribonucleotide reductase, which is uniquely responsible for catalysing the reactions that produce deoxynucleoside triphosphates (dCTP) for DNA synthesis and dFdCTP competes with dCTP for incorporation into DNA (self-potentiation). After incorporation into DNA, gemcitabine appears to induce the programmed cell death process known as apoptosis.

VI.2.3 UNKNOWNS RELATING TO TREATMENT BENEFITS

Not applicable.

VI.2.4 SUMMARY OF SAFETY CONCERNS

Safety Concern	What is known	Preventability
Important Identified Risks		
Reduction in the number of white blood cells, Reduction in blood platelets, Reduction in red blood cell, Bone marrow suppression (Myelosuppression)	Therapy with Gemcitabine can suppress bone marrow function as manifested by leucopaenia, thrombocytopaenia and anaemia.	Yes can be preventable by close monitoring of the low blood count symptoms like frequent infections such as fever, severe chills, sore throat or mouth ulcers, tiredness, being short of breath and looking pale etc. Patients receiving gemcitabine should be monitored prior to each dose for platelet, leucocyte and granulocyte counts.
Leakage of Fluids from small blood vessels into the tissue (Capillary leak syndrome)	Capillary leak syndrome has been reported in patients receiving gemcitabine as single agent or in combination with other chemotherapeutic agents.	Yes can be preventable by regular monitoring of the symptoms. Discontinue therapy with gemcitabine and contact your doctor immediately if you notice any generalised oedema, weight gain, body swelling (hypoalbuminaemia), severe low blood pressure, kidney problems and difficulty in breathing.
Low haemoglobin and kidney problems (Haemolytic uremic syndrome)	Therapy with gemcitabine can leads to microangiopathic haemolytic anaemia, such as rapidly falling haemoglobin with concomitant thrombocytopaenia, elevation of serum bilirubin, serum creatinine, blood urea nitrogen, or LDH etc.	Yes can be preventable by monitoring of early detection symptoms. Tell your doctor immediately if you have any prior history of anaemia, liver problems or kidney related problems. Your physician may perform some kidney or liver function tests before starting therapy with gemcitabine.

Safety Concern	What is known	Preventability
Severe skin reactions (toxic epidermal necrolysis and Stevens-Johnson Syndrome)	Therapy with gemcitabine can cause large blisters with peeling of layers of skin, fever and chills (toxic epidermal necrolysis) and severe blisters and bleeding in the lips, eyes, mouth, nose and genitals (Stevens-Johnson Syndrome)	Yes can be prevent by monitoring of early detection symptoms. Discontinue treatment with the gemcitabine and visit your doctor immediately if you noticed any skin related problems like blisters with peeling of layers of skin, fever and chills, bleeding in the lips, eyes, mouth, nose and genitals etc. Inform your doctor if you have any prior history of skin related problems with any substance/medicines.
Interaction with radiotherapy (Radiosensitisation)	Concurrent use of gemcitabine and radiotherapy can leads to significant toxicity in the form of sore, red mouth (severe mucositis), especially inflammation of the food pipe (oesophagitis) and swelling of the lungs (pneumonitis) 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.	Your doctor may need to reduce the dose of either gemcitabine or radiotherapy or may stop the concomitant use of gemcitabine with the radiotherapy. Inform your doctor immediately if you noticed coughing, difficulty breathing, wheezing and pain in food pipe or difficulty in swelling.
Pulmonary toxicity [pulmonary oedema, interstitial pneumonitis or adult respiratory distress syndrome (ARDS)]	Pulmonary toxicity like fluid in lungs, swelling of the lungs, shortness of breath (dyspnea), increased rate of breathing (tachypnea), and low oxygen saturation (hypoxemia) can be reported with the use of gemcitabine therapy.	Yes can be preventable by detection of early monitoring symptoms. Inform your doctor immediately if you noticed shortness of breath, increased rate of breathing, tiredness etc.

Safety Concern	What is known	Preventability
Allergic reaction (Hypersensitivity)	Hypersensitivity or allergic reactions can be reported with the therapy of gemcitabine.	Yes can be preventable by detection of early monitoring symptoms. Inform your doctor immediately if you noticed any allergic symptoms like shortness of breath, wheezing or difficulty breathing; swelling of the face, lips, tongue or other parts of the body; rash, itching or hives on the skin. Inform your doctor if you have any prior history of allergy or allergic to any other substances/medicines before starting the therapy with gemcitabine.
Headache with changes in vision, confusion, seizures or fits, increase in blood pressure (Posterior Reversible Encephalopathy Syndrome)	Some case have been reported with the use of gemcitabine alone or in combinations with other drugs used to treat cancer causes posterior reversible encephalopathy syndrome symptoms included Headache with changes in vision, confusion, seizures or fits, increase in blood pressure etc.	Yes can be preventable by detection of early monitoring symptoms. Tell your doctor immediately if you are feeling or have any prior history of headache, confusion, blood pressure increase, seizures and visual loss. Discontinue treatment with gemcitabine if you are feeling these symptoms and contact your doctor immediately.
Important Potential Risks		
Reproductive and development toxicity	There are no adequate data from the use of gemcitabine in pregnant women. Studies in animals have shown reproductive toxicity. It is not known whether gemcitabine is excreted in human milk. Animal data	If you are pregnant, or thinking about becoming pregnant, tell your doctor. The use of gemcitabine should be avoided during pregnancy. Your doctor will discuss with you the

Safety Concern	What is known	Preventability
	showed decrease in the sperm production (hypospermatogenesis).	potential risk of taking gemcitabine during pregnancy. If you are breast-feeding, tell your doctor. You must discontinue breast-feeding during gemcitabine treatment. Men are advised not to father a child during and up to 6 months following treatment with gemcitabine. 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.
Induce mutations (Mutagenicity)	Reported animal data suggest that gemcitabine can be mutagenic.	Consult your doctor before starting of gemcitabine therapy.
Important Missing Information		
Experience with gemcitabine with paediatric population	Gemcitabine is not recommended for use in children under 18 years of age due to insufficient data on safety and efficacy.	Do not use gemcitabine therapy if your age is below 18 years. Gemcitabine is not recommended if your age is below 18 years. Consult your doctor before starting of gemcitabine therapy.
Information on clear dosage recommendation in patients with hepatic and renal impairment	Gemcitabine should be used with caution in patients with liver or kidney impairment as there is insufficient information from clinical studies to allow for clear dose recommendations for these patient populations.	Do not use gemcitabine therapy if you have any or have prior history of liver or kidney problems. Consult your doctor before starting of gemcitabine therapy.

Safety Concern	What is known	Preventability
	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 liver impairment.	Laboratory evaluation of kidney and liver function (including virological tests) should be performed periodically.

VI.2.5 SUMMARY OF RISK MINIMISATION MEASURES BY SAFETY CONCERN

The Summary of Product Characteristics and the Package Leaflet for Gemcitabine 38 mg/ml concentrate for solution for infusion contain information about routine risk minimisation measures.

VI.2.6 PLANNED POST-AUTHORISATION DEVELOPMENT PLAN

Not applicable.

VI.2.7 SUMMARY OF CHANGES TO THE RISK MANAGEMENT PLAN OVER TIME

Not applicable.