## 6.2 Elements for a public summary

### *6.2.1 Overview of disease epidemiology*

*Bladder cancer*

Worldwide, bladder cancer is diagnosed in approximately 275,000 people each year, and about 108,000 people die of this disease (Medscape). Mortality from bladder cancer has shown downward trends over the last 2 decades in several western European countries (albeit 10-15 years later than similar trends in the US), but is still increasing in some eastern European countries. Tobacco smoking and occupational exposure to aromatic amines are the two major established environmental risk factors for bladder cancer[3]. The incidence of bladder cancer continues to increase, with an estimated 53,000 new cases diagnosed in the United States, 90% of which are transitional cell carcinomas. In developing countries, especially in the Middle East and parts of Africa, infections with members of the genus Schistosoma are responsible for a high incidence of bladder cancer-75% of which are squamous cell carcinomas. Arsenic has been indicated as a bladder carcinogen in Argentina, Chile, and Taiwan[4].

*Pancreatic cancer*

Pancreatic cancer has an exceptionally high mortality rate, making it one of the four or five most common causes of cancer mortality. The incidence of pancreatic cancer suggests roles for lifestyle factors, such as diet, or environmental factors, such as vitamin D exposure. Smoking is the most common known risk factor, and is the cause of 20-25% of all pancreatic tumors[5]. Most of the countries have incidence rate of 8 -12 cases per 100000 persons per year. Over 200000 people die annually of pancreatic cancer worldwide. Although familial pancreatic cancer is well-documented, the genes responsible for this condition have not been identified and are unlikely to explain more than 5-10% of all pancreatic cancer cases. Chronic pancreatitis and diabetes mellitus are medical conditions that have been consistently related to pancreatic cancer[6].

*Non-small-cell lung cancer (NSCLC)*

Lung cancer is the leading cause of cancer-related mortality not only in the United States but also around the world. In North America, lung cancer has become more predominant among former than current smokers. Yet in some countries, such as China, which has experienced a dramatic increase in the cigarette smoking rate during the past 2 decades, a peak in lung cancer incidence is still expected. Non-small cell lung cancer accounts for 85% of all lung cancer cases in the

United States. A close to 70% of patients with lung cancer present with locally advanced or metastatic disease at the time of diagnosis[7].

*Ovarian cancer*

Ovarian cancer represents the sixth most commonly diagnosed cancer among women in the world, and causes more deaths per year than any other cancer of the female reproductive system. Despite the high incidence and mortality rates, the etiology of this disease is poorly understood. Established risk factors for ovarian cancer include age and having a family history of the disease, while protective factors include increasing parity, oral contraceptive use, and oophorectomy. Lactation, incomplete pregnancies, and surgeries such as hysterectomy and tubal ligation may confer a weak protective effect against ovarian cancer. Infertility may contribute to ovarian cancer risk among nulliparous women. Other possible risk factors for ovarian cancer include postmenopausal hormone-replacement therapy and lifestyle factors such as cigarette smoking and alcohol consumption[8].

*Breast cancer*

Breast cancer is the commonest cause of cancer death in women worldwide. Rates vary about five-fold around the world, but they are increasing in regions that until recently had low rates. Risk is increased by early menarche, late menopause, and obesity in postmenopausal women, and prospective studies have shown that high concentrations of endogenous oestradiol are associated with an increase in risk. Childbearing reduces risk, with greater protection for early first birth and a larger number of births; breastfeeding probably has a protective effect[9]. Almost 1.4 million women were diagnosed with breast cancer worldwide in 2008 and approximately 459,000 deaths were recorded. Five-year relative survival estimates range from 12% in parts of Africa to almost 90% in the United States, Australia and Canada, with the differential linked to a combination of early detection, access to treatment services and cultural barriers[10].

### *6.2.2 Summary of treatment benefits*

**Summary of treatment benefits**

*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[1].

*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 and prolongation was observed in patients treated with gemcitabine compared to patients treated with 5-fluorouracil[1].

*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. A statistically significant prolongation of the time to progression and median survival were observed in patients treated with gemcitabine/cisplatin compared to patients treated with cisplatin[1].

In another randomised phase III study of 135 patients with stage III-B or IV NSCLC, a combination of gemcitabine and cisplatin showed a statistically significant higher response rate than a combination of cisplatin and etoposide. A statistically significant prolongation of the time to progression was observed in patients treated with gemcitabine/cisplatin compared to patients treated with etoposide/cisplatin[1].

*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 was observed in the patients treated with GCb compared to patients treated with Cb. Differences in response rate and median survival favoured the GCb arm[1].

*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 in patients treated with gemcitabine/paclitaxel compared to patients treated with paclitaxel[1].

### *6.2.3 Unknowns relating to treatment benefits*

No or very limited information is available regarding treatment benefits of gemcitabine in patients below the age of 18 years. A dose reduction is not indicated in the elderly or in patients with renal or hepatic insufficiency but caution is advised in patients with hepatic or renal impairment**.**

### *6.2.4 Summary of safety concerns*

The most commonly reported adverse drug reactions associated with Gemcitabine SUN treatment include: nausea with or without vomiting, raised liver enzymes, proteinuria, haematuria, dyspnoea, allergic skin rashes with or without itching, fever, flu-like syndrome, pain, alopecia and oedema.

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 and clinical findings consistent with the haemolytic uraemic syndrome (HUS). Furthermore, Gemcitabine should be used with caution in patients with hepatic insufficiency or with impaired renal function as there is insufficient information to allow clear dose recommendation for this patient population.

A summary is given in table below and a full list of side-effects is available in the SPC:

| **Important Identified Risk** | **Known Information** | **Preventability** |
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| Hypersensitivity | Allergic skin rashes occur in approximately 25% of patients and are commonly associated with itching, rarely severe skin reactions, including desquamation and bullous skin eruptions have been associated with Gemcitabine use. | Gemcitabine SUN must not be used in people who are hypersensitive (allergic) to gemcitabine or any of the other ingredients.<br><br>For severe (Grade 3 or 4) non-haematological toxicity, except nausea/vomiting, therapy with gemcitabine should be withheld or decreased depending on the |

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| | | judgement of the treating physician. |
| Severe skin reactions (TEN/SJS) | Stevens - Johnson Syndrome and Lyell's syndrome (toxic epidermal necrolysis) are very rare adverse events associated with gemcitabine therapy. | 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. |
| Myelosuppression | Events like leucopaenia, thrombocytopaenia (risk of bleeding), anaemia, febrile neutropenia and rarely thrombocytosis are known to occur with gemcitabine therapy owing to its myelosuppresive effect. | Patient should be monitored prior to each dose for platelet, leucocyte and granulocyte counts.<br><br>Suspension or modification of therapy should be considered when drug-induced bone marrow depression is detected.<br><br>During combination with other cytotoxic agent risk of cumulative bone-marrow suppression must be considered. |
| Capillary leak syndrome: | Capillary leak syndrome has been reported in patients receiving gemcitabine as single agent or in combination with other chemotherapeutic agents The condition involves systemic capillary hyperpermeability during which fluid and proteins from the intravascular space leak into the interstitium. The clinical features include generalised oedema, weight gain, hypoalbuminaemia, severe | Caution must be exercised with patients presenting a history of cardiovascular events.<br><br>Gemcitabine should be discontinued and supportive measures implemented if capillary leak syndrome develops during therapy. |

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| | hypotension, acute renal impairment and pulmonary oedema. | |
| Pulmonary toxicity: | Events like dyspnea (mild, usually self-limiting), cough, rhinitis, mild and transient bronchospasm responding to parenteral therapy, sometimes severe (such as pulmonary oedema, interstitial pneumonitis or adult respiratory distress syndrome-ARDS) have been reported in association with gemcitabine therapy. | Early use of supportive care measure to ameliorate the conditions.<br><br>In case of severe adverse events consideration should be made to discontinuing gemcitabine therapy.<br><br>Concurrent radiotherapy should be avoided. |
| Haemolytic uremic syndrome | Hemolytic Uremic Syndrome to include fatalities from renal failure or the requirement for dialysis can occur in patients treated with Gemcitabine for Injection. Consider the diagnosis of HUS in patients who develops anemia with evidence of microangiopathic hemolysis, elevation of bilirubin or LDH, or reticulocytosis; severe thrombocytopenia; or evidence of renal failure (elevation of serum creatinine or BUN) | Periodic physical examination and checks of renal and hepatic function should be made to detect non- haematological toxicity.<br><br>Permanently discontinue Gemcitabine for Injection in patients with HUS or severe renal impairment. Renal failure may not be reversible even with discontinuation of therapy.<br>Generally avoid concurrent use with drugs that can significantly affect hepatic or renal function. |

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| Posterior reversible encephalopathy syndrome | Few reports of Gemcitabine associated PRES have been reported in the literature. Similar cases have previously been described with cisplatine, cytarabine or cyclosporine. However, no single anti-neoplastic drug has been consistently associated with PRES. The exact mechanism of toxic induced PRES is still not fully understood although impairment in cerebrovascular auto regulatory control due to toxic damage to vascular endothelium and blood -brain barrier is a major hypothesis. Moreover, role of other underlying clinical conditions like underlying carcinoma, uncontrolled hypertension (causing endothelial damage), eclampsia, septic shock cannot be ruled out. | Avoiding concomitant use with other immunosuppressant and chemotherapeutic agents which are known to be associated with PRES.<br><br>Gemcitabine to be used with caution in patients having clinical conditions like uncontrolled hypertension, eclampsia and septic shock which can cause endothelial damage. |
| Radiosensitisation: | Events like radiation toxicity and radiation recall are known to occur with concomitant radiotherapy. | Gemcitabine shall be started after the acute effects of radiation have resolved or at least one week after radiation. |
| **Important potential risks** | **Known Information** | **Preventability** |
| Reproductive and development toxicity: | Preclinical fertility studies, gemcitabine caused reversible hypospermatogenesis | Men should avoid fathering a child during and up to 6 months after treatment.<br>Opting for cryoconservation of sperm prior to treatment considering chances of infertility due to gemcitabine |

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| | | therapy is advised. |
| Mutagenicity: | Cytotoxic agents primarily target rapidly dividing cells. Insufficient data is available on mutagenic potential of Gemcitabine | Prescription only status, to be used under medical supervision, by an experienced professional (careful clinical monitoring). |
| **Missing Information** | **Known Information** | **Preventability** |
| Information on clear dosage recommendation in patients with hepatic and renal 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. | No dosing recommendations can be made for this subpopulation based on available data. |
| 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. | No dosing recommendations can be made for this subpopulation based on available data. |

### *6.2.5 Summary of additional risk minimisation measures by safety concern*

Not applicable

### *6.2.6 Planned post authorisation development plan*

Not applicable

### *6.2.7 Summary of changes to the risk management plan over time*

Not applicable since this is the initial version.