## 6.2 Elements for a public summary

### *6.2.1 Overview of disease epidemiology*

*The epidemiology of bladder cancer*

Worldwide, bladder cancer is diagnosed in approximately 275,000 people each year, and about 108,000 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. Diet could influence bladder carcinogenesis, as many compounds contained in foods and their metabolites are excreted through the urinary tract. Other widely investigated lifestyle habits are probably not associated with risk of developing bladder cancer (e.g. coffee consumption, artificial sweetener use, hair dyes) or are difficult to assess (e.g. fluid intake). Infections and stones in the urinary tract might cause chronic irritation of the bladder epithelium, and thus increase bladder cancer risk. First-degree relatives of bladder cancer patients have a 50-100% increased relative risk of developing the disease[3].

*Epidemiology of pancreatic cancer*

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. The highest incidence and mortality rates of pancreatic cancer are found in developed countries. In the United States, pancreatic cancer is the 4$^{th}$ leading cause of cancer death, and in Europe it is the 6th. Treatment has not improved substantially over the past few decades and has little effect on prolonging survival

time. International variations in rates and time trends suggest that environmental factors are likely to play a role in the etiology of pancreatic cancer. In the US, the highest rates of pancreatic cancer incidence and mortality are observed among blacks, who have some of the highest rates in the world. A known cause of pancreatic cancer is tobacco smoking. 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. Recent cohort studies, which are less prone to biases than case-control studies, suggest that obesity increases the risk of pancreatic cancer. Other studies support the hypothesis that glucose intolerance and hyperinsulinemia are important in the development of pancreatic cancer. Other potential risk factors include physical inactivity, aspirin use, occupational exposure to certain pesticides, and dietary factors such as carbohydrate or sugar intake[4].

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

Non-small-cell lung cancer (NSCLC) accounts for 80%–85% of all lung cancer cases. Approximately 90% of lung cancers among men and 80% among women are related to smoking. The majority of patients present with advanced disease. The incidence differs considerably across different countries in Europe. The rates vary from 22 to 63 per Lac and from 5 to 33/Lac per year in men and women, respectively. In most European countries, the incidence continues to rise in women but decreases in men. This trend seems to occur later in Southern and Eastern Europe than in the Northern regions. Five-year age- and area-adjusted relative survival of all lung cancer patients in Europe continues to be low at 11%. Central European countries show slightly higher survival compared with other regions. Trends in lung cancer mortality in men have tended to decrease in many European countries during the last two decades, particularly in North and Western Europe. Among women, mortality rates are still increasing in many countries[5].

*Epidemiology of ovarian cancer*

Ovarian cancer is among the five leading sites for cancer incidence and mortality in women from developed countries. Its incidence and mortality rates have, however, been declining over the last few decades following the introduction of oral contraceptives, which - together with parity - are the best recognized protective factor for the disease. Late menopause and irregular menstrual cycles may also reduce the risk, while the role of hormone replacement therapy in menopause and fertility treatments is still unclear. Cosmetic talc use and some aspect of diet (i.e. saturated fats, refined carbohydrates) have been associated with increased risk, in some-though not all-studies), while vegetable consumption appears to be inversely related to risk. These issues remain open to debate. Women with a family history of ovarian and breast cancer in first-degree relatives are also at increased risk, but family history accounts for only 4-5% of cases. Most

ovarian cancers are therefore environmental in origin and consequently, at least in principle, avoidable[6].

*Epidemiology of 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 of the disease. Many of the established risk factors are linked to oestrogens. 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. Both oral contraceptives and hormonal therapy for menopause cause a small increase in breast-cancer risk, which appears to diminish once use stops. Alcohol increases risk, whereas physical activity is probably protective. Mutations in certain genes greatly increase breast-cancer risk, but these account for a minority of cases[7].

### *6.2.2 Summary of treatment benefits*

**Summary of treatment benefits**

*Clinical efficacy in the treatment of Bladder cancer*

A randomised phase III study in 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, time to disease progression and response rate. However, the combination of gemcitabine and cisplatin had a better toxicity profile than MVAC.

*Clinical efficacy in the treatment of Pancreatic cancer*

In a randomised phase III study in 126 patients with advanced or metastatic pancreatic cancer, gemcitabine showed a statistically significant higher clinical benefit response rate than 5-fluorouracil. Also, a statistically significant prolongation of the time to progression and a statistically significant prolongation of median survival was observed in patients treated with gemcitabine compared to patients treated with 5-fluorouracil.

*Clinical efficacy in the treatment of 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 a statistically significant prolongation of median survival 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 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.

*Clinical efficacy in the treatment of 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 favored the GCb arm.

*Clinical efficacy in the treatment of 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. After 377 deaths, the overall survival was 18.6 months versus 15.8 months in patients treated with gemcitabine/paclitaxel compared to patients treated with paclitaxel and the overall response rate was significantly higher in gemcitabine/paclitaxel arm.

### *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 are not indicated in the elderly or in patients with renal or hepatic insufficiency but caution is advised in case of hepatic or renally impaired patients**.** The SmPC is aligned with that of the reference product and dose modification is clearly indicated under circumstances if haematological and non-haematological toxicity.

### *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, low white blood cells, low platelet count, low haemoglobin level (anaemia), proteinuria (protein in urine), haematuria (blood in urine), dyspnoea (difficulty in breathing), allergic skin rashes with or without itching, fever, flu-like syndrome, pain, alopecia (hair loss) and oedema (swelling of ankles, fingers, feet, face).

Gemcitabine SUN must not be used in people who are hypersensitive (allergic) to gemcitabine or any of

the other ingredients. It must also not be used during breast feeding if mother is on gemcitabine therapy.

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

***Important Identified risks***

| Identified Risk | Known Information | Preventability |
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| Non-hematological toxicities | Events like mucositis, elevation of liver transaminases and alkaline phosphatase, increased bilirubin, haematuria, proteinuria, rarely Serious hepatotoxicity, including liver failure and death, haemolytic uraemic syndrome, renal failure are known to be associated with gemcitabine therapy. | Periodic physical examination and checks of renal and hepatic function should be made to detect non- haematological toxicity.<br><br>Dosage reduction with each cycle or within a cycle may be applied based upon the grade of toxicity experienced by the patient.<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 judgement of the treating physician.<br><br>Generally avoid concurrent use with drugs that can significantly affect hepatic or renal function. |
| Haematological toxicities | Events like leucopaenia, thrombocytopaenia (risk of bleeding), anaemia, febrile neutropenia, 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. |
| Cardiovascular | Events like arrhythmias, predominantly | Caution must be exercised with |

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| Adverse events | supraventricular in nature, heart failure, signs of peripheral vasculitis, gangrene, hypotension, rarely myocardial infarct and cerebrovascular accidents are known to occur with gemcitabine therapy. | patients presenting a history of cardiovascular events. |
| Pulmonary Adverse Events | Events like dysponea (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 discontinue gemcitabine therapy.<br><br>Concurrent radiotherapy should be avoided. |
| Conditions requiring sodium restriction | Gemcitabine SUN contains <1mmol of sodium per vial. | This should be taken into account while prescribing it to patients on a controlled sodium diet for conditions like hypertension. |
| Effects on fertility | Pre-clinical studies have shown to hamper spermatogenesis.<br><br>Cytotoxic agents primarily target rapidly dividing cells. | Men should avoid fathering a child during and up to 6 months after treatment.<br><br>Opting for cryoconservation of sperm prior to treatment considering chances of infertility due to gemcitabine therapy is advised. |
| Effects on ability to drive and use machines | Gemcitabine has been reported to cause mild to moderate somnolence. | Patients should be cautioned against driving or operating machinery while under therapy. |
| Risk of infection | Diminished immunae competence due to gemcitabine therapy may favour disseminated, opportunistic infections. | Periodic physical examination and monitoring of cell count prior and after drug administration.<br><br>Suspension or modification of therapy should be considered if severe infection is identified.<br><br>Generally avoid use of gemcitabine with other |

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| | | immunosuppressive (including monoclonal antibodies) or myelosuppressive agents or phototherapy which may increase the risk of infections.<br><br>Appropriate antibiotic coverage (for underlying infective foci, if any) should be considered. |
| Potential interaction with live vaccines | Risk of systemic, possibly fatal, disease, particularly in immunosuppressed patients. | Yellow fever and other live attenuated vaccines are not recommended while under treatment with gemcitabine. |
| Potential Interactions with radiotherapy | 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***

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| Potential interaction with Palifermin (human recombinant keratinocyte growth factor) | In a clinical trial, administration of Palifermin within 24 hours of chemotherapy resulted in increased severity and duration of oral mucositis, presumably due to increased sensitivity of the rapidly dividing epithelial cells in the immediate post-chemotherapy period.<br>Concurrent administration of Palifermin may increase toxicity of gemcitabine. | Palifermin should not be administered within 24 hours before, during the infusion of, or within 24 hours of myelotoxic chemotherapy. |
| 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 | 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. |

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| | underlying clinical conditions like underlying carcinoma, uncontrolled hypertension (causing endothelial damage), eclampsia, septic shock cannot be ruled out. | |

***Important missing information***

No or very limited information is available regarding safety of gemcitabine in patients who are pregnant or in babies exposed to drug via breast milk, below the age of 18 years, or have hepatic or renal impairment.

***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