VI.2 ELEMENTS FOR A PUBLIC SUMMARY

VI.2.1 Overview of disease epidemiology

Advanced colorectal carcinoma

Cancer of the colon and rectum is the third most common type worldwide. Colon cancer is more frequent than rectal cancer. In Europe around 250.000 new colon cancers and 140,000 rectum cancers are diagnosed each year. Rates increase with industrialisation and urbanisation. About 70% of patients are over 65 years of age. Colorectal cancer is rare under the age of 45 years. Main treatment options include surgery and chemotherapy. The disease is usually incurable in advanced stages; however, modern treatment regimens have prolonged survival significantly.

Advanced hepatocellular carcinoma (liver cancer)

Liver cancer is uncommon in Europe and more common in Asian countries. In 2000, the incidence of liver cancer in Europe was estimated to be about 50,000 new cases a year. About 71% of patients with liver cancer are over 65 years of age. Liver cancer frequently arises in the setting of cirrhosis, appearing 20-50 years following initial insult to the liver. However, 25% of patients have no history or risk factors for the development of cirrhosis. The disease is incurable in advanced stages. Treatment options are very limited.

Advanced gastric carcinoma (stomach cancer)

Stomach cancer is one of the most common cancers in Europe ranking sixth after lung, breast, colorectal, prostate, and bladder cancers with an estimated 174,000 new cases per year in 2002. There is a marked geographic variation in the incidence of gastric cancer with higher rates in eastern and southern Europe than in northern and western Europe. The male/female ratio is about 1.5:1. The disease is usually incurable in advanced stages. Main treatment options include several chemotherapeutic regimens.

Advanced and/or metastatic breast carcinoma

Breast cancer is the most common cancer among women in Europe and the world. Around 430,000 new cases occur each year in Europe, representing 29% of all malignancies in European women, and 13,5% of all cancers diagnosed. Mean age at diagnosis is between 50 and 60 years. The incidence increases dramatically with age, from around 10 cases per 100,000 women between 20 and 30 years old, to more than 300 cases per 100,000 over the age of 60. The disease is usually incurable in advanced stages; however, a lot of effective treatment regimens are available which can prolong the survival of patients significantly.

Advanced oesophageal carcinoma

Oesophageal cancer is the eighth most frequently diagnosed cancer worldwide. Around 32,600 cases occurred in 2006 in Europe. Its incidence varies greatly among different geographical areas. It is particularly frequent in Asian countries. Risk factors include especially tobacco use and alcohol consumption. Treatment is dependent upon the stage of presentation and the options include chemotherapy, radiation therapy, surgery, or palliative care. The disease is usually incurable in advanced stages.

Advanced cervical carcinoma

Worldwide, cervical cancer is the fourth most common cause of cancer in women. Approximately 70% of cervical cancers occur in developing countries. Human papillomavirus infection appears to be involved in the development of more than 90% of cases. Therapy includes surgery, radiotherapy, and chemotherapy.

Non-small cell bronchial carcinoma (Non-small cell lung cancer)

Lung cancer is the most common cancer in the world. In Europe, it is the most common cancer among men, accounting for about one in five cancers (305,000 cases a year). In women it is the fourth most common (72,000 cases a year). Non-small cell lung cancer accounts for about 90-85% of all lung cancers. Smoking cigarettes, pipes, or cigars is the most common cause of lung cancer. The tumour is mostly diagnosed in advanced stages when it cannot be cured. Treatment options aim to prolong survival and include chemotherapy as well as radiation.

Advanced pancreatic carcinoma

Cancer of the pancreas is the tenth most frequent cancer in Europe, accounting for some 2.6% of cancer in both sexes. In the year 2006, an estimated 59,900 new cases were diagnosed in Europe. The disease is slightly more frequent in men than women. Smoking is the only risk factor that has been identified. Most patients are diagnosed in far advanced tumour stages when it cannot be cured. Treatment options aim to prolong survival and include a few chemotherapy regimens.

Advanced tumours of the head and neck

There are about 0.5 million new cases a year worldwide. This tumour is strongly associated with certain environmental and lifestyle risk factors, including tobacco smoking, alcohol consumption, UV light, particular chemicals used in certain workplaces, and certain strains of viruses, such as human papillomavirus. The disease is incurable in advanced stages. Treatment options include chemotherapy and radiation.

Superficial carcinoma of the urinary bladder

In Europe, cancer of the bladder is the fourth most frequent cancer among men, accounting for about 7% of the total cancers. There are an estimated 136,300 new cases each year. Some 70% of patients with bladder cancer are over 65 years of age. Fortunately, this type of cancer is often diagnosed at an early stage, i.e. when the tumour is still superficial and can be resected by surgery. Recurrence of the disease can be effectively prevented by instillation of chemotherapeutic agents.

VI.2.2 Summary of treatment benefits

Advanced colorectal carcinoma

Current gold standard of treatment is a combination of 5-fluorouracil plus oxaliplatin or irinotecan. Survival of patients can be significantly prolonged with such treatment. A couple of other chemotherapeutic treatment regimens exist, including mitomycin-based schedules, which are useful after failure of first-line treatment. The addition of mitomycin to 5-fluorouracil significantly increased the tumour regression rate (from 38% to 54%) and failure free survival rate (from 5.4 to 7.9 months) in a comparative study in 200 patients with advanced colorectal cancer.

Advanced hepatocellular carcinoma (liver cancer)

Surgical resection and liver transplantation are the only chances of cure but have limited applicability. Only a few chemotherapeutic agents have demonstrated some activity against this tumour type, including mitomycin. One treatment approach is based on local administration (into the hepatic artery providing blood supply to the tumour) of chemotherapeutic agents with or without subsequent embolisation of the artery to stop blood supply of the tumour (called chemoembolisation). For this kind of treatment, mitomycin has been investigated in a large number of clinical trials with reported tumour shrinkage rates in about 70% of patients.

Advanced gastric carcinoma (stomach cancer)

Surgery is the mainstay of treatment of this disease. However, curative surgery in these patients is often either impossible (metastatic disease) or exceedingly difficult (locally advanced tumours). In such cases, chemotherapy is the major treatment option that aims to prolong survival of patients. Mitomycin is preferably combined with 5-fluorouracil and cisplatin. In a large clinical trial in 580 patients, such a combination resulted in tumour regression in 42% of patients and a median survival of 8.7 months, data that are comparable to results with other frequently used treatment regimens.

Advanced and/or metastatic breast carcinoma

Chemotherapy plays an important role in the management of patients with advanced/metastatic breast cancer. A large number of highly active treatment regimens (including mitomycin-based schedules) are available; however, a standard regimen has not yet been defined. Given as a single agent, mitomycin has induced tumour regression in 26-38% in previously untreated patients and of 15-25% in those exposed to multiple prior chemotherapy regimens. Combination chemotherapy with mitomycin has proven more effective than single-agent therapy. The combination of mitomycin/mitoxantrone/methotrexate was similar effective as another frequently used chemotherapy regimen in a comparative study in 217 patients, yielding a tumour response rate of about 50% with both treatments and a response duration of 10-11 months.

Advanced oesophageal carcinoma

As a single agent, mitomycin has generated tumour regression in 14-42% of patients. Concurrent administration of chemotherapy and radiation with or without surgery has yielded better local disease control and more prolonged survival than has radiation therapy or surgery alone.

Combinations of 5-fluorouracil and either cisplatin or mitomycin have proven most effective in this setting. The addition of 5-fluorouracil and mitomycin to radiation increased median survival from 9.2 months to 14.8 months in a large comparative trial in 135 patients.

Advanced cervical carcinoma

Standard therapy of patients with cervical carcinoma includes surgery and radiotherapy with or without chemotherapy. Most frequently used chemotherapeutics include cisplatin, 5-fluorouracil, and mitomycin. The combination of radiation plus mitomycin was shown to be more effective than radiation alone in a large clinical trial including 160 patients. The 4-year disease-free survival increased from 44% with radiation alone to 71% with mitomycin plus radiation. In patients with more advanced disease, mitomycin in combination with other chemotherapeutics (especially cisplatin) has resulted in tumour regression in about 45% of patients in several clinical trials.

Non-small cell bronchial carcinoma (Non-small cell lung cancer)

Within five clinical trials, a total of 202 patients had received mitomycin as single-agent chemotherapy. The reported tumour regression rates ranged from 19% to 50%. Today, primary standard treatment for this cancer type is a combination of cisplatin plus another chemotherapeutic medicinal product. In a large clinical trial, the combination of cisplatin and mitomycin was used in 216 patients and compared to a combination of cisplatin and docetaxel in another 217 patients. Tumour regression rate was 32% with both treatment regimens and one year survival rates were quite similar (35-39%). Both regimens can be considered as equally effective.

Advanced pancreatic carcinoma

Standard treatment of this cancer type is gemcitabine or a combination of 5-fluorouracil with other chemotherapeutics. The combination of gemcitabine and mitomycin was studied in a clinical trial in 55 patients. It resulted in tumour regression in 29% of patients. Further 18 patients had a stabilisation of their disease, resulting in an overall tumour growth control in 62% of patients. In another clinical trial in 208 patients with advanced pancreatic carcinoma, the addition of mitomycin to 5-fluorouracil increased the response rate from 8.4% to 17.6% and median survival from 5.1 to 6.5 months. Patients in the combined treatment arm had a better quality of life score.

Advanced tumours of the head and neck

Standard treatment of inoperable tumours is a combination of radiation and chemotherapy. Most frequently used chemotherapeutic agents include 5-fluorouracil, cisplatin and mitomycin. The combination of 5-fluorouracil, mitomycin and radiation was compared to radiation alone in 384 patients. At 5 years, the locoregional control (49.9% versus 37.4%) and overall survival rates (28.6% versus 23.7%) were significantly better with combined radiochemotherapy than with radiotherapy alone.

Superficial carcinoma of the urinary bladder

Intravesical instillation of chemotherapeutics like mitomycin or an immunotherapeutic product (BCG) into the bladder represents the standard of care for treatment as well as prevention of recurrence in patients with superficial bladder cancer. The efficacy and safety of mitomycin has been shown in several comparative clinical trials. Compared to tumour resection alone, mitomycin instillation significantly reduced the recurrence rate. Within a study in 437 patients with primary or recurrent bladder tumours, mitomycin was shown to be equally effective as BCG. After 5 years, 57% in the mitomycin group and 36-54% in the BCG groups were free of tumour recurrence.

VI.2.3 Unknowns relating to treatment benefits

The tumour types for which mitomycin is authorised usually occur only in adult patients and not in children. Furthermore, these tumours often occur in patients at an older age. However, clinical studies are often restricted to patients below 65 years of age. This is also true for the mitomycin studies. Therefore, the efficacy and safety of mitomycin in patients older than 65 years has not yet been fully elucidated.

VI.2.4 Summary of safety concerns

Important identified risks

Risk	What is known	Preventability
Myelodysplastic syndrome, acute leukaemia, acute myeloid leukaemia – Conditions that are characterised by disturbed growth of certain blood cells	Occurrence of acute leukaemia and myelodysplastic syndrome has been reported in a few patients treated concomitantly with other agents that inhibit or prevent the growth or development of malignant cells.	How to prevent this side effect is not known.
Suppression of the bone marrow with reduction of the white blood cells and platelets	Mitomycin affects especially fast growing cells such as tumour cells but may also destroy fast growing normal body cells such as bone marrow cells which produce blood cells. Has been reported in 1/10 or more than 1/10 patients.	Do not use this drug if you have a reduced number of blood cells, white blood cells or platelets, or if you have a tendency for bleeding. Blood parameters must be monitored regularly. Be careful when taking this drug over long time.
Severe hypersensitivity reaction – allergic reactions	Only very rare cases of severe allergic reactions to the active substance mitomycin or any other excipients occur. 1 in 10,000 people may experience this event.	Do not use this drug if you know about any allergy to mitomycin or any of the ingredients of the medicine.
Cardiotoxicity	The harmful effect on the heart of Adriamycin (doxorubicin, a medicine belonging to the group of cytostatics) can be intensified by mitomycin. Heart failure (cardiac insufficiency) after previous therapy with anti-cancer medicines (anthracycline) is listed as a rare side effect.	Let you doctor know if you take or have taken doxorubicin before.
Pulmonary toxicity	Mitomycin may cause an inflam-mation of the tissue and space around the air sacs of the lungs. Typical symptoms are dry cough and/or shortness of breath. Has been reported in 1/100 up to less than 10 patients.	Do not use this drug if you have a lung disorder. Stop using the drug immediately if you develop lung symptoms such as dry cough. Prophylactic use of corticosteroids may prevent the occurrence of this risk.
Toxicity in patients with pre-existing lung dysfunction	Patients with pre-existing lung dysfunction are at increased risk to develop lung toxicity	Do not use this drug if you have a lung disorder.
Cellulitis, skin necrosis (following extravasation)	Accidental injection/infusion of mitomycin into the tissue surrounding a vein may cause cellulitis and skin necrosis.	Does not occur when mitomycin injection/infusion is correctly administered into a vein.

Risk	What is known	Preventability
Hepatic toxicity	In rare cases, patients experience an elevation of liver enzymes, icterus (indicated by a yellowish pigmentation of the skin), or a condition in which some of the small veins in the liver are obstructed. It is known that a hepatic dysfunction may occur in rare cases.	Let your doctor know if you are suffering from impaired liver function. Before you receive mitomycin a check of the liver function is recommended to exclude any diseases that could worsen during mitomycin therapy.
Toxicity in patients with liver impairment	Patients with impaired liver function are known to be at increased risk to develop undesirable effects after administration of mitomycin.	Mitomycin should be used in patients with impaired liver function only in exceptional cases after careful risk-benefit assessment.
Toxicity in patients with renal impairment	Patients with impaired kidney function are known to be at increased risk to develop undesirable effects after administration of mitomycin.	Mitomycin should be used in patients with impaired kidney function only in exceptional cases after careful risk-benefit assessment.
Microangiopathic-haemolytic anaemia (destruction of red blood cells caused by factors in small blood vessels)	This syndrome is caused by specific immunological mechanisms involving antibodies against red blood cells. The kidneys are often involved what is then called haemolytic uraemic syndrome (HUS). HUS may result in acute kidney failure. Has been reported in 1/10,000 up to less than 1/1,000 patients	Stop using the drug immediately if you develop signs of rupturing of red blood cells (haemolysis) or impairment of renal function.
Renal failure	Renal failure occurs very rarely in patients treated with mitomycin, especially in patients who developed an HUS (see above).	Renal function should be monitored and treatment with mitomycin stopped as soon as signs of reduced renal function become evident.
Impaired fertility	Adverse effects on spermatogenesis can be induced by mitomycin.	Consider sperm conservation before start of treatment.
Inflammation of the urinary bladder (Cystitis) after bladder instillation of mitomycin	Cystitis has been reported in 10/100 up to 1/10 patients. It may be accompanied with blood in the urine. In less than 1/10,000 patients, bladder inflammation with damage of the bladder tissue (necrotising cystitis) or allergic (eosinophilic) bladder inflammation has been observed.	Do not use mitomycin in case of inflammation of the urinary bladder

Risk	What is known	Preventability
Calcium deposits in the bladder wall (bladder wall calcification); partial conversion of bladder wall tissue into connective tissue (bladder wall fibrosis), and bladder perforation/necrosis	May affect less than 1 in 10,000 patients	Treatment should be terminated when symptoms occur.

Important potential risks

Risk	What is known (Including reason why it is considered a potential risk)
Secondary malignancies	Very rare cases of several types of blood cancer have been reported only in patients treated with mitomycin together with other anticancer drugs, but not with mitomycin alone.

Missing information

Risk	What is known
Use in pregnancy and breastfeeding women	Experience of mitomycin use in pregnant and breastfeeding women is very limited. However, mitomycin can cause inherited genetic damage and can adversely affect the development of an embryo. Mitomycin passes into breast milk.
Use in patients ≥ 65 years of age	Data from clinical studies in this age group are insufficient for evaluation of benefit and risks.
Use in children	Information on the use of mitomycin in children and adolescents is not sufficient. Therefore, mitomycin should not be used in this age group.

VI.2.5 Summary of risk minimisation measures by safety concerns

Not applicable

VI.2.6 Planned post authorisation development plan

Not applicable

VI.2.7 Summary of changes to the Risk Management Plan over time

Version	Date	Safety Concerns	Comment
3	01/09/2015	Safety concern *MDS, acute leukaemia, acute myeloid leukaemia* was included as an important identified risk. Safety concern *Cardiotoxicity* was included as an important identified risk.	As requested by Medicines Evaluation Board (NL)