## VI.2 Elements for a Public Summary

### VI.2.1 Overview of Disease Epidemiology

***Malignant Pleural Mesothelioma:***
Malignant pleural mesothelioma (a cancer of the lining of the lungs that is usually caused by exposure to asbestos) is a slowly progressive tumor involving the lining of the lungs; approximately 80% of cases are linked to prior asbestos exposure. In the US, approximately 2,500 new cases of mesothelioma are diagnosed each year. Asbestos use was banned in the US in 1971, and so the incidence of mesothelioma in the US is expected to continue to steadily decline. In contrast, asbestos use continued in Australia until 2003 and in Europe until 2005. As a result, the incidence of mesothelioma in European countries continues to rise and is projected to peak in 2020, and may account for as many as 250,000 European deaths in the next 35 years. In 2020, over 18,000 Australian cases will be diagnosed.

***Non-Small Cell Lung Cancer:***
Lung cancer is one of the most common malignancies and continues to rise in incidence. One million new cases and over 900,000 lung cancer-related deaths are reported each year worldwide. It is the leading cause of cancer death in men and the third leading cause in women. In Europe, approximately 381,500 patients are diagnosed with non-small cell lung cancer (NSCLC) every year. 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 but increase by 7% in females (thus becoming the second leading cause of cancer mortality). 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.

### VI.2.2 Summary of Treatment Benefits

For the treatment of malignant pleural mesothelioma (a cancer of the lining of the lungs that is usually caused by exposure to asbestos), Pemetrexed in combination with cisplatin has been compared with cisplatin alone in one main study in 456 patients who had not received chemotherapy for their disease before. For the treatment of locally advanced or metastatic non-small cell lung cancer, Pemetrexed was compared with gemcitabine (another anticancer medicine), in combination with cisplatin, in a study involving 1,725 patients who had not received chemotherapy before. Pemetrexed was also compared with docetaxel (another anticancer medicine) in one study involving 571 patients who had received chemotherapy in the past. For maintenance treatment, Pemetrexed was compared with placebo (a dummy treatment) in two main studies involving 1,202 patients whose cancer had not got worse during platinum-based chemotherapy.

The main measures of effectiveness were how long the patients survived and how long they lived without their cancer getting worse.

Pemetrexed increased the survival time of patients with malignant pleural mesothelioma. Patients receiving Pemetrexed and cisplatin survived for an average of 12.1 months, compared with 9.3 months in those receiving cisplatin alone.

In non-small cell lung cancer, Pemetrexed was as effective as the comparators, with survival times around 10.3 months in patients who had not received chemotherapy in the past and around 8.1 months in those who had received chemotherapy in the past. In one maintenance treatment study, patients receiving

Pemetrexed lived for a further 4.3 months from the start of maintenance treatment without their cancer getting worse, compared with 2.6 months in those receiving placebo. In the second maintenance study, the figures were 4.1 months in the Pemetrexed and 2.8 months in the placebo group. Improved survival times with Pemetrexed were only seen in patients with non-small cell lung cancer of the non-squamous type.

### VI.2.3 Unknowns relating to treatment benefits

Different people respond differently to medication depending on which ethnic group, genetic they come, from their age or genetic background.

Experience with Pemetrexed in the paediatric population is very limited as the efficacy and safety profile has not been studied in these patients.

Due to the lack of availability of data Pemetrexed should not be used in the pregnancy and lactation. So women of child bearing potential should use contraception.

It is not known whether pemetrexed is excreted in human milk and adverse reactions on the suckling child cannot be excluded. Breast-feeding must be discontinued during pemetrexed therapy.

### VI.2.4 Summary of safety concerns

| **Safety Concern** | **What is known** | **Preventability** |
|---|---|---|
| **Important Identified Risks** | | |
| Non-compliance with vitamin supplementation, manifested mainly as blood disorders and gastrointestinal (stomach and gut) disorders | Treatment with pemetrexed is associated with blood disorders such as neutropenia (low levels of neutrophils, the white blood cells that fight bacterial infection), neutropenia with fever (febrile neutropenia), and infection with severe neutropenia, and gastrointestinal disorders such as feeling or being sick and diarrhoea (treatment-related toxicity). In clinical trials, patients who received pre-treatment with folic acid and vitamin $B_{12}$ experienced less toxicity and less severe toxicity. | All patients treated with Pemetrexed Fresenius Kabi must take folic acid and vitamin $B_{12}$, in order to reduce the occurrence of blood and gut side effects related to treatment with pemetrexed. |

| Safety Concern | What is known | Preventability |
|---|---|---|
| Stomach and gut disorders (gastrointestinal disorders) | When pemetrexed is given in combination with cisplatin, infection or irritation of the stomach and intestine can occur; severe dehydration has been observed in these patients. Feeling or being sick, diarrhoea, and constipation, are very common side effects (seen in more than 1 in 10 patients); stomach upset and heartburn are common side effects (seen in more than 1 in 100 patients). | Patients should receive adequate treatment and appropriate hydration before and/or after receiving treatment with Pemetrexed Fresenius Kabi.<br><br>Patients should inform their doctor immediately if they develop signs of inflammation or irritation in the stomach.<br><br>All patients treated with Pemetrexed Fresenius Kabi must take folic acid and vitamin $B_{12}$, in order to reduce the occurrence of blood and gut side effects related to treatment with pemetrexed. |
| Kidney problems (Renal disorders) | Serious kidney problems, including acute kidney failure, have been reported with pemetrexed alone or in combination with other chemotherapy medicines. Many of the patients in whom these side effects occurred had underlying risk factors for the development of kidney problems including dehydration or pre-existing hypertension (high blood pressure) or diabetes. | Patients should receive adequate hydration before and/or after receiving treatment with Pemetrexed Fresenius Kabi.<br><br>Patients should inform their doctor immediately if they develop signs of kidney problems, such as changes in urination, swelling, pain in legs, back and sides, abnormal blood tests.<br><br>Patients' kidney function should be closely monitored with each clinic visit. |
| Lung disease causing progressive scarring of the air sacs of the lung (interstitial pneumonitis) | In clinical trials, cases of lung disease with respiratory insufficiency, sometimes fatal, have been reported uncommonly in patients treated with pemetrexed. | No risk factors that can predict lung disease have been identified in patients treated with pemetrexed.<br><br>Patients should inform their doctor immediately if they develop signs of breathlessness, intense chest pain or cough with bloody sputum which may indicate a blood clot in the vessels of the lungs |

| Safety Concern | What is known | Preventability |
|---|---|---|
| Radiation-related scarring of the air sacs of the lung (radiation pneumonitis) | Cases of radiation pneumonitis (scarring of the air sacs of the lung associated with radiation therapy) have been reported in patients treated with radiation either before, during or after being treated with pemetrexed. | Pemetrexed Fresenius Kabi is not currently authorised for use with radiation therapy. Doctors should pay particular attention to these patients and exercise caution when using other radio-sensitising agents.<br><br>Patients should tell their doctor if they have had or are going to have radiation therapy, as there may be an early or late radiation reaction with Pemetrexed Fresenius Kabi. |
| Inflammatory skin reaction that sometimes occurs when people receive chemotherapy after radiation therapy (radiation recall) | Rare cases of a severe skin reaction have been reported in patients who received chemotherapy (including treatment with pemetrexed) after they had undergone radiation therapy weeks or years previously. | Radiation recall with pemetrexed is a rare reaction that cannot be predicted.<br><br>Patients must inform their doctor as soon as possible if they start experiencing any side effects such as skin rash, severe sunburn, prickling sensation or fever. |
| Severe blood infection (sepsis) | Severe blood infection (sepsis), sometimes fatal, has been commonly reported during clinical trials with pemetrexed (in more than 1 in 100 patients).<br><br>Neutropenia (low levels of neutrophils, a type of white blood cells) is very common following treatment with pemetrexed (seen in more than 1 in 10 patients). | Sepsis is an important risk with pemetrexed. One of the risk factors for sepsis is very low levels of neutrophils (severe neutropenia), the white blood cells that fight bacterial infection. Therefore, prevention of sepsis is to a great extent linked to the occurrence and prevention of severe neutropenia.<br><br>Patient must inform their doctor immediately if they have a temperature of 38ºC or greater, are sweating or present other signs of infection since they might have neutropenia. Sepsis may be severe and could lead to death. All patients treated with Pemetrexed Fresenius Kabi must take folic acid and vitamin $B_{12}$, in order to reduce the occurrence of blood and gut side effects related to treatment with pemetrexed. |

| Safety Concern | What is known | Preventability |
|---|---|---|
| Rare, severe skin and mucous membrane reactions (including Stevens-Johnson syndrome and toxic epidermal necrolysis) | Skin reactions have been reported with pemetrexed in patients not pre-treated with a corticosteroid (anti-inflammatory) medicine.<br><br>Rare cases of severe skin reactions including Stevens-Johnson syndrome and toxic epidermal necrolysis have been reported with pemetrexed (seen in less than 1 in 1,000 patients), which in some cases were fatal. | Doctors should be aware that Stevens-Johnson syndrome and toxic epidermal necrolysis may occur during treatment with Pemetrexed Fresenius Kabi. Doctors should monitor patients for any signs of these conditions. Patients should inform their doctor immediately if they experience a severe rash, itching, or blistering.<br><br>Pre-treatment with dexamethasone (or equivalent) can reduce the incidence and severity of skin reactions.<br><br>If patients experienced a skin reaction in the past, further exposure to the suspected inducing medicine should be strictly avoided. |
| Reduction in the number of white blood cells (Neutropenia) which may associated with fever (Neutropenic fever), red blood cells (Anaemia), low platelet count (Thrombocytopenia) (Bone marrow suppression) | Reduction in the number of white blood cells may or may not associate with fever (symptoms included frequent infections such as fever, severe chills, sore throat or mouth ulcers) and red blood cells (symptoms included tiredness, headaches, being short of breath when exercising, dizziness and looking pale) have been reported with the use of Pemetrexed therapy. | Yes by monitoring of early symptoms. You should inform your doctor immediately if you feel tiredness, headache, chill, fever or any infection.<br><br>Routine monitoring of blood cell counts is recommended.<br><br>Your doctor may reduce the dose of Pemetrexed if your blood cell count is low.<br><br>Do not take Pemetrexed if you suffer from severe suppression of bone marrow functionality, symptoms may be: extreme tiredness, easy bruising or bleeding, occurrence of infections. |

| **Important Potential Risks** | |
|---|---|
| **Risk** | **What is known (Including reason why it is considered a potential risk)** |
| None | None |

| **Missing Information** | |
|---|---|
| **Risk** | **What is known** |
| None | None |

### VI.2.5 Summary of risk minimisation measures by safety concern

The Summary of Product Characteristics and the Package Leaflet for Pemetrexed Fresenius Kabi contain information about routine risk minimisation measures.

### VI.2.6 Planned post authorisation development plan

None Planned.

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

Not applicable.