VI.2 Elements for a Public Summary

VI.2.1 Overview of disease epidemiology

Malignant pleural mesothelioma

Mesothelioma is a type of cancer that occurs in mesothelial cells. These cells form a covering, called the mesothelium, over the surfaces of many organs in the body. Mesothelioma usually develops in the tissues (called the pleura) covering the lungs. This is known as pleural mesothelioma. Cancer is described as being malignant if it is capable of spreading to surrounding tissues or other parts of the body. Symptoms of malignant pleural mesothelioma include shortness of breath, chest pain and fluid on the lungs. People may also experience tiredness, weight loss, sweating and difficulty swallowing.

Non-small cell lung cancer

Cancer affecting the lungs is grouped into two main types depending on how it looks under the microscope: small-cell lung cancer and non-small-cell lung cancer (NSCLC). NSCLC is the most common type of lung cancer. It usually grows and spreads more slowly than small cell lung cancer. There are three types of NSCLC. Adenocarcinomas are often found in an outer area of the lung. Large cell carcinomas can occur in any part of the lung. For the third type, squamous cell carcinoma, treatment with pemetrexed is not indicated. Early lung cancer may not cause any symptoms. Symptoms include chest pain, cough that does not go away, coughing up blood, fatigue, loss of appetite, losing weight without trying, shortness of breath and wheezing. Other symptoms often in the late stages are bone pain or tenderness, hoarseness or changing voice, joint pain, swallowing difficulty, swelling of the face, weakness and shoulder pain.

VI.2.2 Summary of treatment benefits

Pemetrexed is an anti-cancer drug. It works by interfering with an enzyme that cancer cells need to survive and multiply.

Pemetrexed is given in combination with cisplatin, another anti-cancer drug, as treatment for malignant pleural mesothelioma in patients who have not received prior chemotherapy.

Pemetrexed is recommended as a treatment for malignant pleural mesothelioma in patients with advanced disease, whose cancer is not suitable for surgery.

Pemetrexed is also given in combination with cisplatin for the initial treatment of patients with advanced stage of lung cancer. Pemetrexed can be used if the disease has responded to treatment or it remains largely unchanged after initial chemotherapy. Pemetrexed is also a treatment for patients with advanced lung cancer whose disease has progressed after other initial chemotherapy has been used.

The efficacy of pemetrexed plus cisplatin was compared against cisplatin alone in 779 patients with malignant pleural mesothelioma. Patients treated with pemetrexed and cisplatin survived longer, and

improvement of symptoms associated with mesothelioma (pain and breathlessness) and improvement of lung function was better.

Pemetrexed versus docetaxel was studied in 571 patients with locally advanced or metastatic NSCLC who had received previous chemotherapy treatment. The study showed that treatment effect on overall survival was better with pemetrexed than with docetaxel.

Pemetrexed plus cisplatin or gemcitabine plus cisplatin was studied in 862 and 863 patients, respectively, with locally advanced or metastatic NSCLC. Both treatments showed similar clinical efficacy. However, there were clinically relevant differences in survival according to the type of NSCLC. Patients treated with pemetrexed plus cisplatin required fewer blood transfusions and less treatment for anemia.

Maintenance treatment with pemetrexed compared against placebo was studied in patients with locally advanced or metastatic NSCLC who had received previous chemotherapy. Both groups received best supportive care (BSC) and were treated until disease progression. The study showed a significant improvement of progression-free survival of patients with pemetrexed (441 patients) compared to placebo (222 patients).

Continuation maintenance treatment with pemetrexed plus BSC (359 patients) was compared to placebo plus BSC (180 patients). The patients had locally advanced or metastatic NSCLC. A significant improvement of progression-free survival and statistically higher overall survival of patients with pemetrexed continuation maintenance treatment could be shown compared to placebo.

VI.2.3 Unknowns relating to treatment benefits

Paediatric population

There is no relevant use of pemetrexed in the paediatric population in malignant pleural mesothelioma and non-small cell lung cancer.

Patients with renal impairment

There are insufficient data on the use of pemetrexed in patients with low creatinine clearance and therefore, the use of pemetrexed is not recommended for these patients.

Patients with hepatic impairment

No relationships between liver function and pemetrexed pharmacokinetics were identified. However patients with hepatic impairment, hepatic metastases absent as well as hepatic metastases present, have not been specifically studied.

Patients with third space fluid such as pleural effusion or ascites

The effect on pemetrexed is not fully defined. A clinical trial did not reveal a difference in pemetrexed dose normalised plasma concentrations or clearance compared to patients without third space fluid

collections. Thus, drainage of third space fluid collection prior to pemetrexed treatment should be considered, but may not be necessary.

VI.2.4 Summary of safety concerns

Important identified risks

Risk	What is known	Preventability
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 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.
Serious kidney problems (serious renal events)	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. 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. Patients' kidney function should be closely monitored with each clinic visit.
Serious stomach and gut disorders (serious 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. Symptoms can be e.g. feeling or being sick, diarrhoea, constipation, stomach upset and	Patients should receive adequate treatment and appropriate hydration before and/or after receiving treatment with pemetrexed. Patients should inform their doctor immediately if they develop signs of inflammation or irritation in the stomach.

	heartburn	
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 in patients treated with pemetrexed.	No risk factors that can predict lung disease have been identified in patients treated with pemetrexed. 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.
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.	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.
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. 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 reported during clinical trials with pemetrexed	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. 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.

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. Rare cases of severe skin reactions including Stevens-Johnson syndrome and toxic epidermal necrolysis have been reported with pemetrexed, which in some cases were fatal.	Patients should inform their doctor immediately if they experience a severe rash, itching, or blistering. Pre-treatment with dexamethasone (or equivalent corticosteroid) can reduce the incidence and severity of skin reactions. If patient has experienced a serious skin reaction in the past, further exposure to pemetrexed should be strictly avoided.

Important potential risks

Risk	**What is known (Including reason why it is considered a potential risk)**
Heart and blood vessel problems (cardiovascular events)	Some patients have experienced serious and life-threatening cardio-vascular effects, such as heart attack, stroke, or a "mini-stroke" while receiving pemetrexed, usually in combination with other cancer medicines. . Most of the patients in whom these events have been observed had pre-existing cardiovascular risk factors.
Circulatory problem in which narrowed arteries reduce blood flow to limbs (peripheral vascular disease)	Patients undergoing cancer treatment may be at increased risk of peripheral vascular disease. Symptoms can be e.g. pain, low temperature and discolouration of the limbs. In severe cases lack of oxygen due to restricted blood flow may result in necrosis.
Hearing loss (hypoacusis)	For the majority of cases of hearing loss seen during treatment with pemetrexed, there were other possible causes, including use of cisplatin/carboplatin, greater age of the patients, and significant medical history. Considering these factors, the hearing loss events are unlikely to be causally related to pemetrexed, and it is unclear what role pemetrexed may have played in the events.

VI.2.5 Summary of risk minimisation measures by safety concern

All medicines have a Summary of Product Characteristics (SmPC) which provides physicians, pharmacists and other health care professionals with details on how to use the medicine, the risks and recommendations for minimising them. An abbreviated version of this in lay language is provided in the form of the package leaflet (PL). The measures in these documents are known as routine risk minimisation measures. The Summary of Product Characteristics and the Package leaflet for this medicinal product can be found in the national authority's web page.

This medicine has no additional risk minimisation measures.

VI.2.6 Planned post authorisation development plan (if applicable)

Not applicable.

VI.2.7 Summary of changes to the risk management plan over time

Not applicable.