VI.2 Elements for a public summary

VI.2.1 Overview of disease epidemiology

Pemetrexed is a medicine used in the treatment of cancer. It is given in combination with cisplatin, another anti-cancer medicine, as treatment for malignant pleural mesothelioma, a form of cancer that affects the lining of the lung, or for another type of lung cancer; 'non small cell' lung cancer. It is also given in combination with cisplatin for the initial treatment of patients with advanced stage of lung cancer.

Lung cancer (malignant pleural mesothelioma and non-small cell lung cancer)

Lung cancer is the most commonly diagnosed cancer worldwide. In 2012, an estimated 1.8 million new cases of lung cancer were diagnosed globally, accounting for approximately 13% of the global cancer burden. Among all cancers, lung cancer now has the highest death rate in most countries, with industrialised regions such as North America and Europe having the highest rates. Generally, global lung cancer trends have followed the trends in smoking, with a lag time of several decades (reference 1). The American Cancer Society predicted 224,210 new cases of lung cancer in the United States in 2014, with 159,260 deaths (Reference 2). Lung cancer occurs predominately in persons aged 50-70 years. The risk of developing lung cancer remains higher among men in all age groups after age 40 years (Reference 3).

VI.2.2 Summary of treatment benefits

The effectiveness of pemetrexed in the indications discussed above has been studied in many clinical trials.

Malignant pleural mesothelioma (MPM) (Lung cancer)
In one study, 226 patients with the lung cancer MPM were treated with pemetrexed, followed by another chemotherapy treatment; cisplatin. 222 patients were treated with cisplatin alone. During the study, the patients were given vitamin supplementations to reduce toxicity/side effects. A statistically significant survival benefit was observed in patients treated with pemetrexed plus cisplatin compared with those receiving cisplatin alone. Severe side effects such as low white blood cell count, nausea and vomiting, were more common in patients receiving pemetrexed plus cisplatin than in those receiving cisplatin alone. However, vitamin supplementations resulted in a consistent reduction in the severity and incidence of side effects (except for dehydration) in the pemetrexed plus cisplatin group.

Non-small cell lung cancer (NSCLC)
Three studies examined the effectiveness of pemetrexed in combination with other chemotherapy treatments in the initial treatment of patients with advanced NSCLC. In the first two studies, pemetrexed plus cisplatin was administered every 3 weeks. 38.9% and 44.8% of patients responded, respectively. The average survival times were 10.9 and 8.9 months, respectively.

In the third study, patients were treated with pemetrexed plus carboplatin or pemetrexed plus oxaliplatin. Patients in this study received vitamin supplementation. The overall response rate in the pemetrexed plus carboplatin group was 31.6% and in the pemetrexed plus oxaliplatin group was 26.8%. The corresponding median survival times were 9.9 months and 9.3 months, respectively. These studies show that pemetrexed in combination with cisplatin or carboplatin was as effective as other platinum treatments.

If administered as indicated in the Summary of Product Characteristics and taking into account the contra-indications, the warnings and precautions, pemetrexed can be considered effective in the approved indications and generally well tolerated.

VI.2.3 Unknowns relating to treatment benefits

Based on the currently available data, no gaps in knowledge about efficacy in the target population were identified, that would warrant post-authorisation efficacy studies. Furthermore, there is no evidence to suggest that treatment results would be different in any subgroup of the target population, for any of the indications, taking into account factors such as age, sex, race or organ impairment. However as stated in the proposed SmPC, the safety of use in children, use in patients with hepatic impairment and use in patients with renal impairment has not yet been established.

VI.2.4 Summary of safety concerns

Important identified risks

Risk	What is known	Preventability
Failure or refusal to take vitamin supplements- folic acid and vitamin B12 (Noncompliance with folic and vitamin B12 regimens manifested mainly as haematological and gastrointestinal toxicities)	It is very important to take folic acid and vitamin B12 during your treatment with pemetrexed to lower your chances of harmful side effects, including stomach problems (nausea, vomiting, diarrhoea, constipation, inflammation) and blood problems (low blood cell counts) These side effects may be life-threatening.	Vitamin supplementation will be prescribed to patients before their treatment with pemetrexed begins. Folic acid (vitamin) or a multivitamin containing folic acid (350 to 1000 micrograms) must be taken once a day while you are taking pemetrexed. You must take at least 5 doses during the seven days before the first dose of pemetrexed. You must continue taking the folic acid for 21 days after the last dose of pemetrexed. You will also receive an injection of vitamin B_{12} (1000 micrograms) in the week before administration of pemetrexed and then approximately every 9 weeks (corresponding to 3 courses of pemetrexed treatment). Vitamin B_{12} and folic acid are given to you to reduce the possible toxic effects of the anticancer treatment. Always take your medicines exactly as explained to you by your doctor, nurse or pharmacist. Without vitamin supplementation side effects such as low blood count and diarrhoea can be worse
Suppressed development of red blood cells, white blood cells and platelets (Bone marrow suppression)	It is very common that this medication will cause low white blood cells, low haemoglobin level (anaemia) and low platelet count.	Patients should contact their doctor immediately if they feel tired or faint, become easily breathless or look pale (since you might have less haemoglobin than normal). Or if they experience bleeding from the gums, nose or mouth or any bleeding that will not stop, reddish or pinkish urine, unexpected bruising (since you might have less platelets than normal).

Kidney problems (Renal disorders)	Abnormal blood tests relating to kidney function are very common and kidney failure is common during treatment with pemetrexed.	If patients currently have or have previously had problems with their kidneys, they should talk to their doctor or hospital pharmacist as they may not be able to receive pemetrexed. Before each infusion patients will have samples of their blood taken to evaluate if they have sufficient kidney function.
Stomach and intestine problems (Gastrointestinal disorders)	It is very common that treatment with this medication will cause diarrhoea, vomiting, nausea, dehydration, upset stomach and constipation. Inflammation of the lining of the oesophagus (gullet) has been reported uncommonly. Colitis (inflammation of the lining of the large bowel, which may be accompanied by intestinal or rectal bleeding) was uncommonly reported.	If patients get any of these side effects, they should talk to their doctor or pharmacist. If the patients are also receiving cisplatin, the doctor will make sure that they are properly hydrated and receive appropriate treatment before and after receiving cisplatin to prevent vomiting. Doctor should be notified if the patient is taking any medicine for pain or inflammation (swelling), such as medicines called “nonsteroidal anti-inflammatory drugs” (NSAIDs), including medicines purchased without a doctor’s prescription (such as ibuprofen).
Scarring of the air sacs of the lung (Interstitial pneumonitis)	Scarring of the air sacs of the lung may uncommonly occur in patients.	Patients must contact their doctor immediately if tehy are becoming easily breathless.
Scarring of the air sacs of the lung associated with radiation therapy (Radiation pneumonitis)	Scarring of the air sacs of the lung associated with radiation therapy may occur in patients who are also treated with radiation before, during or after their pemetrexed therapy.	Patients who have had or are going to have radiation therapy should tell their doctor, as there may be an early or late radiation reaction with pemetrexed.
A skin rash like severe sunburn, which can occur on skin that has previously been exposed to radiotherapy (Radiation recall)	A skin rash like severe sunburn can occur on skin that has previously been exposed to radiotherapy, from days to years after the radiation.	Patients who have had or are going to have radiation therapy should tell their doctor, as there may be an early or late radiation reaction with pemetrexed.
Serious infection (Sepsis)	This medicine is known to weaken the immune system, this leads to a greater risk of infection. Infection (sepsis) may be severe and could lead to death.	Patients should contact their doctor immediately if they have a temperature of 38ºC or greater, sweating or other signs of infection (since they might have fewer white blood cells than normal which is very common).

Serious skin reactions (Bullous skin reaction including Stevens Johnson Syndrome (SJS) and toxic epidermal necrolysis (TEN)	Rarely, during treatment with this medicine, serious skin reactions may develop which can be severe and could lead to death.	The doctor should be contacted in case of a severe rash, or itching, or blistering (Stevens-Johnson Syndrome or Toxic epidermal necrolysis). Corticosteriods are given to patients to reduce the frequency and severity of skin reactions that may be experienced during the anticancer treatment.

VI.2.5 Summary of additional 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.

This medicine has no additional risk minimisation measures.

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

There are no studies in the post authorisation development plan.

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

Major changes to the Risk Management Plan over time

Not applicable