VI.2 Elements for a Public Summary

VI.2.1 Overview of disease epidemiology

Malignant mesothelioma is a malignant tumour arising from the protective lining that covers thoracic cavity and is strongly linked to asbestos exposure. It has been reported that the incidence is much higher in men than women with male-to-female ratio of 3.7:1, respectively. The incubation period for mesothelioma after initial exposure to asbestos is typically longer than 30 years. All forms of mesothelioma predominantly affect elderly individuals aged over 70 years. The tumour gradually encases the lungs and invades the chest wall, producing excess fluid in thoracic cavity in about 75% of patients. The prognosis is dismal, with poor response to radical surgery, chemotherapy, radiation therapy, or combination therapy and the median survival time after diagnosis is 9–12 months. Incidence rates are still on the increase in Europe, but deceleration has started in some countries.

Lung cancer is the most common cancer in terms of both incidence and mortality worldwide (1.35 million new cases per year and 1.18 million deaths), with the highest rates in Europe and North America. Population segment most likely to develop lung cancer is over-fifties with a history of smoking. Lung cancer is the second most commonly occurring form of cancer in most Western countries, and it is the leading cancer-related cause of death. In contrast to the mortality rate in men, which began declining, women's lung cancer mortality rates have been rising. It is the third cause of death from cancer in women in European Union, with high death rates observed in Northern and Central Europe. For localized cancers, surgery is usually the treatment of choice. Because the disease has usually spread by the time it is discovered, radiation therapy and chemotherapy are often used, sometimes in combination with surgery.

VI.2.2 Summary of treatment benefits

Teva has not performed any clinical studies; however, the treatment benefits for the originator's product are presented below.

For the treatment of malignant pleural mesothelioma, 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 the treatment of 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.

Based on the available data, pemetrexed represents an effective medicine in the treatment of chemotherapy naïve patients with malignant pleural mesothelioma (tumour that cannot be completely removed by surgery) in combination with cisplatin and for the treatment of locally advanced or metastatic non-small cell lung cancer other than predominantly squamous cell type.

VI.2.3 Unknowns relating to treatment benefits

Not applicable.

VI.2.4 Summary of safety concerns

Important identified risks

Risk	What is known	Preventability
Noncompliance with folic acid and vitamin B12 regimens manifested mainly as haematological and gastrointestinal (GI) toxicities *(Ignoring the medical advice on taking vitamins manifested mainly as blood disorders or stomach and gut disorders)*	Vitamin B_{12} and folic acid are given to you to reduce the possible toxic effects of the anticancer treatment.	Vitamin supplementation: your doctor will prescribe you oral folic acid (vitamin) or a multivitamin containing folic acid (350 to 1000 micrograms) that you must take 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).
Renal disorders *(Kidney problems)*	More than 1 in 10 people may experience abnormal blood tests related to disorder in kidney function. Up to 1 in 10 people may experience kidney failure.	If you currently have or have previously had problems with your kidneys, talk to your doctor or hospital pharmacist as you may not be able to receive pemetrexed. Before each infusion you will have samples of your blood taken to evaluate if you have

Risk	What is known	Preventability
		sufficient kidney function to receive pemetrexed.
Gastrointestinal disorders *(Disorders of stomach and gut)*	Up to 1 in 10 people may experience dehydration and upset stomach. More than 1 in 10 people may experience diarrhoea, vomiting, nausea, loss of appetite, constipation or pain, redness, swelling or sores in the mouth. Up to 1 in 100 people may experience colitis (inflammation of the lining of the large bowel, which may be accompanied by intestinal or rectal bleeding). Inflammation of the lining of the oesophagus (gullet) has been experienced by more than 1 in 100 people undergoing pemetrexed/radiation therapy.	You must contact your doctor immediately if you have pain, redness, swelling or sores in your mouth (very common). If you are also receiving cisplatin, your doctor will make sure that you are properly hydrated and receive appropriate treatment before and after receiving cisplatin to prevent vomiting. Please tell your doctor if you are 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).
Interstitial pneumonitis *(Lung tissue disease causing scarring of the air sacs of the lung)*	Up to 1 in 100 people may experience interstitial pneumonitis (scarring of the air sacs of the lung).	You must contact your doctor immediately if you if you are becoming easily breathless.
Radiation Pneumonitis *(Lung disease caused by radiation therapy)*	Up to 1 in 100 people, who are also treated with radiation either before, during or after their pemetrexed therapy, may experience radiation pneumonitis (scarring of the air sacs of the lung associated with radiation therapy).	If you have had or are going to have radiation therapy, please tell your doctor, as there may be an early or late radiation reaction with pemetrexed.
Radiation recall *(Inflammatory skin reaction that sometimes occurs when people receive chemotherapy after radiation therapy)*	Up to 1 in 1000 people may experience radiation recall (a skin rash like severe sunburn) which can occur on skin that has previously been exposed to radiotherapy, from days to years after the radiation.	If you have had or are going to have radiation therapy, please tell your doctor, as there may be an early or late radiation reaction with pemetrexed.
Sepsis *(Severe blood infection)*	Up to 1 in 10 people may experience infection including sepsis.	Contact your doctor immediately if you notice any of the following:

Risk	What is known	Preventability
	Infection (sepsis) may be severe and could lead to death.	Fever or infection (common): if you have a temperature of 38ºC or greater, sweating or other signs of infection (since you might have less white blood cells than normal which is very common).
Bullous skin reactions including Stevens Johnson Syndrome (SJS) and toxic epidermal necrolysis (TEN) *(Rare, severe skin and mucous membrane disorders)*	Up to 1 in 1000 people may experience bullous conditions (blistering skin diseases), including Stevens-Johnson syndrome and Toxic epidermal necrolysis (serious skin diseases). Rarely, skin reactions may be severe and could lead to death. Allergic reaction such as: skin rash (very common)/burning or prickling sensation (common), or fever (common) and also severe rash, or itching, or blistering (Stevens-Johnson Syndrome or Toxic epidermal necrolysis) must be reported to the doctor immediately.	Contact your doctor immediately if you get 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.
Bone marrow suppression *(Decrease in production of blood cells)*	Up to 1 in 10 people may experience a decreased level of white blood cells, haemoglobin level (anaemia) or low platelet count. When the number of white blood cells is low, infection (sepsis) may be severe and could lead to death.	Contact your doctor immediately if you notice any of the following: • If you experience tiredness, feeling faint, becoming easily breathless or if you look pale (since you might have less haemoglobin than normal). • If you experience bleeding from the gums, nose or mouth or any bleeding that would not stop, reddish or pinkish urine, unexpected bruising (since you might have less platelets than normal). • Fever or infection (common): if you have a temperature of 38ºC or

Risk	What is known	Preventability
		greater, sweating or other signs of infection (since you might have less white blood cells than normal). Vitamin B12 and folic acid are given to reduce the possible toxic effects of the anticancer treatment.

Important potential risks

Not applicable

Missing information

Not applicable

VI.2.5 Summary of risk minimisation measures by safety concern

No additional risk minimisation measures are proposed.

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.

VI.2.6 Planned post authorisation development plan

Not applicable.

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

Major changes to the Risk Management Plan (RMP) over time

Version	Date	Safety Concerns	Comment
1.0	05 Sep 2014	**Important identified risks** • Noncompliance with vitamin supplementation manifested mainly as haematological and gastrointestinal toxicities • Serious Renal Events • Gastrointestinal Disorders • Interstitial Pneumonitis • Radiation Pneumonitis • Radiation Recall **Important potential risks** • Cardiovascular events • Oesophagitis • Peripheral vascular disorders	First RMP.

Version	Date	Safety Concerns	Comment
		• Serious skin disorders **Missing information** • Hearing loss/Hypoacusis • Toxicities due to administration to patients with third-space fluid collections • Safety and efficacy in paediatric patients is not known	
1.1	19 Jun 2015	**Important identified risks** • Noncompliance with folic acid and vitamin B12 regimens manifested mainly as haematological and gastrointestinal toxicities • Serious renal events • Serious gastrointestinal disorders (including oesophagitis) • Interstitial pneumonitis (including radiation pneumonitis) • Radiation Recall • Sepsis • Bullous skin reactions including Stevens Johnson Syndrome (SJS) and toxic epidermal necrolysis (TEN); Anaphylactic shock **Important potential risks** • Cardiovascular events • Peripheral vascular disease • Hearing loss/hypoacusis **Missing information** None	Risks were updated in accordance with the RMS Day 70 Preliminary Assessment Report (DE/H/5019/01-03/DC; dated 16.03.2015); CMS day 100 comments; and New SPC/PL
1.2	21 Sep 2015	No changes in safety concerns.	Minor revisions done according to the RMS Day 120 Draft Assessment Report (DE/H/5019/01-03/DC and DE/H/4509/01-03/DC; dated 11.09.2015); New SPC/PL were added.
1.3	15 Oct 2015	**Important identified risks** • Noncompliance with folic acid and vitamin B12 regimens manifested mainly as haematological and gastrointestinal (GI) toxicities • Serious renal events • Gastrointestinal disorders • Interstitial pneumonitis • Radiation Recall • Sepsis • Bullous skin reactions including Stevens Johnson Syndrome (SJS) and toxic epidermal necrolysis (TEN)	Revisions done according to the CMS Day 145 Assessment Report (DE/H/5019/001-003/DC; dated 08.10.2015) and newly published EPARs; New SPC/PL were added.

Version	Date	Safety Concerns	Comment
		Important potential risks • Cardiovascular events • Peripheral vascular disease • Hearing loss/hypoacusis **Missing information** None	
1.4	16 Nov 2015	**Important identified risks** • Noncompliance with folic acid and vitamin B12 regimens manifested mainly as haematological and gastrointestinal (GI) toxicities • Renal disorders • Gastrointestinal disorders • Interstitial pneumonitis • Radiation pneumonitis • Radiation Recall • Sepsis • Bullous skin reactions including Stevens Johnson Syndrome (SJS) and toxic epidermal necrolysis (TEN) • Bone marrow suppression **Important potential risks** None **Missing information** None	Minor revisions done according to the RMS Day 180 Draft Assessment Report