VI.2 Elements for a Public Summary

VI.2.1 Overview of disease epidemiology

Pemetrexed is an anti-cancer drug used to treat malignant pleural mesothelioma and non-small cell lung cancer, and can be given either alone or in combination with other anti-cancer drugs.

Malignant pleural mesothelioma is a rare type of cancer that affects the lining of the lung and whose origin has generally been linked to asbestos exposure. It often takes decades (20 to 50 years) for mesothelioma to develop after someone is first exposed to asbestos and the first signs usually are a persistent cough and shortness of breath. Survival of untreated patients is poor, with the average survival ranging from 6 to 8 months.

Lung cancer is one of the most frequent types of cancer among men and women and is one of the few that continues to show an increasing incidence. Over one million new cases and nearly one million lung cancer-related deaths are reported each year worldwide. Lung cancer is subdivided in two groups, the small cell lung cancer (SCLC) and the non-small cell lung cancer (NSCLC). Almost 80% of lung cancers are classified as NSCLC, with 65% to 75% of cases presenting as locally advanced or metastatic disease.

VI.2.2 Summary of treatment benefits

Pemetrexed has been studied in combination with cisplatin versus cisplatin alone in a study involving 456 previously untreated patients with malignant pleural mesothelioma being not suitable for surgery. The results have shown that patients treated with pemetrexed and cisplatin had a clinically meaningful 2.8-month median survival advantage over patients receiving cisplatin alone.

In locally advanced or metastatic NSCLC pemetrexed has been studied in combination with cisplatin versus combination of gemcitabine plus cisplatin (another combination of anticancer drugs used for treatment of NSCLC) in 1725 patients previously untreated with anticancer drugs. The results have shown a comparable efficacy with median survival of 10.28 months in both groups.

The benefit of pemetrexed alone in the maintenance treatment of locally advanced or metastatic NSCLC in patients whose disease has not worsened immediately following platinum-based therapy has been shown in two studies comparing pemetrexed plus best supportive care group versus placebo (dummy treatment) plus best supportive care group. In the first study with 663 patients in pemetrexed group an increased time until the disease progression (median of 4.0 months compared with median of 2.0 months in placebo group) and increased overall survival time (median of 13.4 months compared with median of 10.6 months in placebo group) have been demonstrated. The second study with 539 patients has further demonstrated pemetrexed benefit with the median time

until disease progression of 4.11 months and median overall survival of 13.86 months in pemetrexed group compared with 2.83 months and 11.10 months in placebo group respectively.
A study of pemetrexed comparing with docetaxel (another anticancer drug) involved 571 patients with locally advanced or metastatic NSCLC previously treated with anti-cancer drugs. The results have shown the median survival times of 8.3 months for patients treated with pemetrexed compared with 7.9 months for patients treated with docetaxel.

VI.2.3 Unknowns relating to treatment benefit

Pemetrexed has not been studied in patients under 18 years old and in patients with severe kidney or liver impairment, and there are no data from the use of pemetrexed in pregnant women. Elderly patients were included into the studies and no differences were observed between them and other adult patients.

VI.2.4 Summary of safety concerns

Important identified risks:

Risk	What is known	Preventability
Noncompliance with folic acid and vitamin B_{12} regimes manifested mainly as haematological and gastrointestinal toxicities (unfollowing to take prescribed folic acid and vitamin B_{12} resulting in toxicities to blood, stomach or intestines)	Supplementation with folic acid and vitamin B_{12} before and throughout the treatment with pemetrexed, reduces side effects without reducing its effectiveness.	Yes, by prescribing folic acid and vitamin B_{12} before and throughout the treatment with pemetrexed.
Bone marrow suppression (decreased ability of the bone marrow to produce blood cells)	Pemetrexed can suppress bone marrow function resulting in low levels of red blood cells, white blood cells and platelets.	Yes, by checking blood cells level before each dose of pemetrexed is given and by monitoring these levels during the treatment with pemetrexed.
Renal disorders (damage to kidneys)	Serious renal events, including acute kidney insufficiency, have been reported while on treatment with pemetrexed alone or in combination with other anti-cancer drugs.	Yes, by avoiding co-administration of NSAIDs (such as aspirin or ibuprofen) and monitoring for underlying risk factors (e.g. dehydration or pre-existing hypertension or diabetes).
Gastrointestinal disorders (damage to stomach and intestines)	Uncommon cases of inflammation of the colon (including intestinal and rectal bleeding and other gastrointestinal disorders) have been reported in patients treated with pemetrexed.	Yes, by prescribing folic acid and vitamin B_{12} before and throughout the treatment with pemetrexed; and with adequate antiemetic treatment and appropriate hydration prior to and/or after receiving treatment with pemetrexed.

Risk	What is known	Preventability
Interstitial pneumonitis (rare, severe lung disease)	Uncommon cases of interstitial pneumonitis with inadequate lung function, sometimes fatal, have been reported in patients treated with pemetrexed.	Yes, by rapid cessation of pemetrexed therapy after first signs are observed.
Radiation pneumonitis (inflammation of the lung caused by radiation therapy to the chest)	Uncommon cases of radiation pneumonitis have been reported in patients treated with radiation before, during or after their pemetrexed therapy.	Yes, by closely monitoring patients treated with radiation either prior, during or subsequent to their pemetrexed therapy, and with caution exercised with use of other radiosensitising agents.
Radiation recall (severe skin reaction)	Rare cases of radiation recall have been reported in patients treated with pemetrexed who have received radiotherapy previously.	Yes, by closely monitoring patients with the history of radiotherapy.
Sepsis (blood infection)	Sepsis, sometimes fatal, has been reported during clinical studies with pemetrexed.	Yes, by prescribing folic acid and vitamin B_{12} before and throughout the treatment with pemetrexed.
Bullous skin reaction (disease marked by eruptions of blisters, or bullae, filled with fluid, on the skin or mucous membranes) including SJS and TEN (Stevens-Johnson syndrome and Toxic epidermal necrolysis – life-threatening skin conditions)	Rare cases of bullous conditions have been reported in patients treated with pemetrexed, including Stevens-Johnson syndrome and Toxic epidermal necrolysis which in some cases were fatal.	Yes, by pre-treatment with corticosteroid (dexamethasone or equivalent).

VI.2.5 Summary of risk minimisation measures by safety concern

All medicines have a Summary of Product Characteristics (SPC) 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)

Not applicable.

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

Not applicable.