VI.2 Elements for a public summary

VI.2.1 Overview of disease epidemiology

Pemetrexed is used to treat two types of lung cancer:

- Malignant pleural mesothelioma, a cancer of the lining of the lungs that is almost always caused by exposure to asbestos; asbestos workers have a 1 in 10 chance to get this cancer during their lives (4). Mesothelioma develops in average 30 years after exposure to asbestos (4). Mesothelioma is an incurable cancer, and patients usually survive 9-12 months after diagnosis (4). Treatment (surgery, radiation therapy, chemotherapy, or other) aims to reduce patient's pain and other symptoms (4);
- Advanced 'non small cell' lung cancer of the type known as 'non-squamous', a lung cancer caused by cigarette smoking in about 85% of cases (3). Treatments vary depending on how aggressive the tumour is, which is indicated by the stage (II, III, IV, from less to more aggressive) (3). Patients without metastases (pieces of tumour spreading to other parts of the body), or with metastases only in the lymph nodes (stages II or III), may be cured with surgery, radiation therapy, chemotherapy, or a combination of therapies (3). For patients with metastases in other parts of the body (stage IV), the treatments aim to relieve the symptoms, and to improve quality of life (3). Five years after diagnosis, 39-55% of patients in stage II, and 5-25% of patients in stage III are still alive. Patients with stage IV cancer survive about six months without treatment; less than 25% are still alive one year after diagnosis, and less than 1% are still alive after five years (3).

VI.2.2 Summary of treatment benefits

Pemetrexed can be given in combination with cisplatin, another anti-cancer medicine, as treatment for malignant pleural mesothelioma to patients who have not received prior chemotherapy (1).
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. Patients receiving pemetrexed and cisplatin survived for an average of 12.1 months, about three months more than those receiving cisplatin alone (2).

In patients with an advanced stage of lung cancer, pemetrexed can either be given in combination with cisplatin as initial treatment, or, if another chemotherapy was already given as initial treatment, alone as second treatment (1).

- 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 (2). Pemetrexed was also compared with docetaxel (another anticancer medicine) in one study involving 571 patients who had received chemotherapy in the past. Pemetrexed was as effective as the comparators (*i.e.* gemcitabine or docetaxel), 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 (2).
- Pemetrexed was also compared with placebo (a dummy treatment) in two main studies involving 1,202 patients whose cancer had not got worse during the previous chemotherapy (2). In one of these studies, patients receiving pemetrexed lived for a further 4.3 months without their cancer getting worse, compared with 2.6 months in those receiving placebo; in

the second study, the figures were 4.1 months in the pemetrexed and 2.8 months in the placebo group (2).

VI.2.3 Unknowns relating to treatment benefits

There is not enough information on the use of pemetrexed in children and adolescents, in patients with liver problems, and in pregnant and breast-feeding women.

VI.2.4 Summary of safety concerns

Important identified risks

Risk	What is known	Preventability
A blood disorder in which the bone marrow produces less blood cells than normal (Bone marrow suppression).	More than one in 10 patients treated with pemetrexed may have less than the normal amount of blood cells (such as white blood cells, red blood cells or platelets).	Doctors should monitor patients for this event. Patients with too few white blood cells or platelets should not use pemetrexed until their levels increase again to a minimum value.
Serious skin disorders (Bullous skin reaction including Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis)	Less than one in 1,000 patients treated with pemetrexed had serious skin disorders (such as Stevens-Johnson Syndrome and Toxic epidermal necrolysis).	Treating a patient with a costicosteroid (*e.g.* dexamethasone) before pemetrexed treatment can reduce the frequency and severity of skin reactions.
Bowel problems (Gastrointestinal disorders)	Gastrointestinal disorders can occur in more than one in 10 patients taking pemetrexed. These disorders include loss of appetite, nausea, vomiting, diarrhoea, constipation, inflammation of the pharynges, inflammation of the lining of mouth, oesophagus (gullet) and large bowel (sometimes with bleeding). Pemetrexed taken with cisplatin can cause gastrointestinal side effects, which can lead to loss of body fluids (dehydration). Pemetrexed taken with medicines called NSAIDs (*e.g.* ibuprofen, piroxicam, rofecoxib) can increase the chance of getting gastrointestinal side effects.	Not always preventable. The doctor should ensure that patients received enough fluids and take anti-vomiting medicines before and/or after taking pemetrexed. Ibuprofen should not be taken for two days before, on the day of, and two days following pemetrexed administration; piroxicam or rofecoxib should not be taken for at least five days prior to, on the day of, and at least two days following pemetrexed administration.
Scarring of the air sacs of the lung (Interstitial pneumonitis)	During clinical trials, less than one in 100 patients treated with pemetrexed got interstitial pneumonitis and could not breathe properly any more (respiratory insufficiency).	Not preventable.

Risk	What is known	Preventability
Side effects affecting the blood, and stomach, which related to not taking folic acid and vitmine B_{12} during the treatment with pemetrexed (Noncompliance with folic acid and vitamin B_{12} regimens manifested mainly as haematological and gastrointestinal toxicities)	More than one in 10 patients treated with pemetrexed had side effects affecting the stomach and blood. Reduction in severe side effect of blood and stomach including low white blood cells, low haemoglobin level (anaemia), low platelet count and diarrhoea, were reported when pre-treatment with folic acid and vitamin B_{12} was administered.	To reduce these side effects, patients treated with pemetrexed must: 1) take oral folic acid or a multivitamin containing folic acid (350 to 1000 micrograms) on a daily basis. At least five doses of folic acid must be taken during the seven days preceding the first dose of pemetrexed, and dosing must continue during the full course of therapy and for 21 days after the last dose of pemetrexed; 2) receive an intramuscular injection of vitamin B_{12} (1000 micrograms) in the week preceding the first dose of pemetrexed and once every three cycles thereafter. Subsequent vitamin B_{12} injections may be given on the same day as pemetrexed.
Scarring of the air sacs of the lung associated with radiation therapy (Radiation pneumonitis)	Less than one in 100 patients who received radiation therapy just before, during, or after treatment with pemetrexed, developed radiation pneumonitis.	The chance of radiation pneumonitis can be reduced if the doctor pays particular attention to patients receiving pemetrexed and radiation treatment almost at the same time.
Skin rash like severe sunburn associated with radiation therapy (Radiation recall)	Less than one in 1,000 patients who had received radiation therapy weeks or years before treatment with pemetrexed, developed radiation recall.	Radiation recall is not preventable.
Kidney problems (Renal disorders)	During clinical trials, some patients treated with pemetrexed alone or in combination with other chemotherapeutic medicines had kidney problems. Less than one in 100 patients experienced a sudden inability of the kidneys to work properly (acute renal failure). Many of these patients were already at risk of kidney problems before treatment, *e.g.* they had dehydration, high blood pressure (hypertension) or diabetes.	To reduce dehydration, the doctor should ensure that patients receive enough fluids and take anti-vomiting medicines before and/or after taking pemetrexed. Other kidney problems are not preventable.
Severe infection (Sepsis)	During clinical trials, up to one in 10 patients treated with pemetrexed had sepsis. Some of them even died.	Not preventable. However, the chance to get infection can be reduced if patients take folic acid and vitamin B_{12} before pemetrexed treatment.

Important potential risks

Risk	What is known (Including reason why it is considered a potential risk)
None	Not applicable

Missing information

Risk	What is known
None	Not applicable

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

No additional risk minimisation measures have been proposed.

VI.2.6 Planned post authorisation development plan

No post-authorization development is planned.

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

Not applicable, since this is the first Risk Management Plan for the Applicant's Pemetrexed 25 mg/ml concentrate for solution for infusion.