Pemetrexed STADA 25 mg/ml concentrate for solution for infusion

7.5.2015, Version V1.1

PUBLIC SUMMARY OF THE RISK MANAGEMENT PLAN

VI.2 Elements for a Public Summary

VI.2.1 Overview of disease epidemiology

Lung cancer is one of the most common types of cancer in European men and women. There are two main types of lung cancer: small cell (SCLC) and non-small cell (NSCLC) lung cancer. Most lung cancers are NSCLCs. There are a variety of NSCLC tumours, but their treatment and prognosis is similar.
Lung cancers are usually carcinomas, i.e. cancers of the skin or tissues that line or cover internal organs. As different types of skin and tissue cells develop into different types of carcinomas, there is a number of carcinoma subtypes: adenocarcinoma, basal cell carcinoma, squamous cell carcinoma and transitional cell carcinoma.
Almost half of all lung cancers are adenocarcinomas (start in glandular cells called adenomatous cells that produce fluids to keep tissues moist). Most of those cases are associated with smoking, but it is also the most common type of lung cancer among those who never-smoked. It is more common in women than in men and is more likely to occur in younger people than other types of lung cancer. Adenocarcinomas tend to grow slower than other types of lung cancer and are more likely to be discovered early.
About 9% of lung cancers are large-cell carcinoma (where cancer cells appear larger than the normal cells). These tend to grow and spread quickly, which can make them harder to treat.
Squamous-cell carcinoma (starts in flat, surface covering cells found in areas such as the skin or the lining of the throat or oesophagus) makes up approximately 30% of lung cancers. It is more common in men than in women, and is more closely correlated with tobacco smoking than other lung cancers. Pemetrexed STADA is indicated for the treatment of NSCLCs which are not predominantly classified as squamous-cell carcinomas.

Treatments of NSCLCs are usually a combination of surgery, a variety of chemotherapies and radiotherapy.

Malignant pleural mesothelioma is an aggressive cancer that stems from mesothelial cells (the protective lining covering many internal organs) and materialises in the pleura (lining of lungs and chest wall); asbestos exposure is considered the main cause. Mesothelioma can affect both genders at any age, but it is more frequent in men than in women and the risk increases with age. Symptoms commonly appear decades after exposure to asbestos and include shortness of breath, cough and chest pain.
Mesothelioma is still relatively rare, although more cases have emerged in the past 20 years. Incidence is lowest in Tunisia and Morocco, and highest in Britain, Australia and Belgium. In Western industrialised nations, incidence ranges from 7 to 40 per million people, depending on the amount of asbestos exposure over the past decades. While the prognosis is not good, chemotherapy has been proven more successful than surgery and subsequent radiotherapy, with pemetrexed and cisplatin as the most hopeful combination.

VI.2.2 Summary of treatment benefits

Pemetrexed STADA is a medicine used in the treatment of certain types of cancer.

Pemetrexed STADA 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, to patients who have not received prior chemotherapy.

Pemetrexed STADA is also given in combination with cisplatin for the initial treatment of patients with advanced stage lung cancer of the NSCLC type.

Pemetrexed STADA can be prescribed to you if you have lung cancer at an advanced stage, if your disease has responded to treatment or if it remains largely unchanged after initial chemotherapy.

Pemetrexed STADA is also a treatment for patients with advanced stage of lung cancer whose disease has progressed after other initial chemotherapy has been used.

Clinical efficacy of Pemetrexed STADA has been shown for each indication in the following studies.

Use of Pemetrexed STADA in mesothelioma (a form of cancer that affects the lining of the lung): EMPHACIS clinical study investigated clinical efficacy of pemetrexed plus cisplatin versus cisplatin alone in chemonaive patients (those who did not receive chemotherapy before) with malignant pleural mesothelioma. Patients were randomly assigned to pemetrexed plus cisplatin (226 patients) or to cisplatin alone group (222 patients). Study was conducted in multiple centres and the patients participating in the study did not know whether they received pemetrexed plus cisplatin or cisplatin alone. Patients treated with pemetrexed and cisplatin had approximately 2.8-month survival advantage over patients receiving cisplatin alone, as well as approximately 25% higher treatment response rate.
There are limited data in patients with malignant pleural mesothelioma treated with pemetrexed alone. Pemetrexed at a dose of 500 mg/m^2 was studied as single-treatment in 64 chemonaive patients (those who did not receive chemotherapy before) with malignant pleural mesothelioma. The overall response rate was 14.1 % (i.e. approx. 14 out of 100 patients responded to pemetrexed treatment alone).

Use of Pemetrexed STADA in non-small cell lung cancer (NSCLC) (a form of lung cancer):
As fist-line treatment: A clinical study investigated the efficacy of pemetrexed plus cisplatin (862 patients) versus gemcitabine plus cisplatin (863 patients) as first-line therapy for locally advanced or metastatic NSCLC. Pemetrexed plus cisplatin showed similar clinical efficacy as gemcitabine plus cisplatin in terms of overall survival, but these results were non-significant. Disease progression-free survival and overall response rate were similar between pemetrexed plus cisplatin and gemcitabine plus cisplatin.
As second-line treatment: A clinical study investigated the efficacy of pemetrexed (283 patients) versus docetaxel (288 patients) as second-line therapy in patients with locally advanced or metastatic NSCLC. Prior chemotherapy did not include pemetrexed. Survival with pemetrexed was approximately 8.3 months and with docetaxel - 7.9 months. However, these results were statistically non-significant. Limited data from another clinical trial suggest that efficacy (overall survival, disease progression-free survival) for pemetrexed are similar between patients previously treated with docetaxel (41 patients) and those who did not receive previous docetaxel treatment (540 patients).
As maintenance treatment: JMEN clinical study compared the efficacy and safety of maintenance treatment with pemetrexed plus best supportive care (441 patients) with that of placebo plus supportive care (222 patients) in patients with locally advanced or metastatic NSCLC (whose disease did not progress after 4 cycles of first line therapy containing cisplatin or carboplatin in combination with gemcitabine, paclitaxel, or docetaxel). Patients received maintenance treatment until disease progression. A statistically significant improvement in progression-free survival in the pemetrexed arm over the placebo arm has been seen. The median overall survival was 13.4 months for the pemetrexed arm and 10.6 months for the placebo arm.

VI.2.3 Unknowns relating to treatment benefits

For the approved indications the treatment benefits have sufficiently been demonstrated.

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 blood and gastrointestinal tract toxicities (Noncompliance with folic acid and vitamin B12 regimens manifested mainly as haematological and gastrointestinal toxicities)	Less toxicity and reduction in blood and non-blood toxicities such as neutropenia (low number of neutrophils, a type of white blood cells), febrile neutropenia (neutropenia with a fever), infection with neutropenia and gastrointestinal tract toxicities (e.g. nausea/vomiting) were reported when pre-treatment with folic acid and vitamin B12 was administered. Therefore, all patients treated with Pemetrexed STADA should take folic acid and vitamin B12 as a measure to reduce treatment-related toxicity.	Your doctor will prescribe you oral folic acid or a multivitamin containing folic acid (350 to 1000 micrograms) to be taken on a daily basis. At least five doses of folic acid must be taken during the seven days preceding the first dose of Pemetrexed STADA, and dosing will continue during the full course of therapy and for 21 days after the last dose of Pemetrexed STADA. Always take folic acid as instructed by your doctor or pharmacist. You will receive an intramuscular injection of vitamin B12 in the week preceding the first dose of Pemetrexed STADA and once every three cycles thereafter. Subsequent vitamin B12 injections will usually be given on the same day as Pemetrexed STADA.
Serious kidney adverse events (Serious renal events)	Serious kidney adverse events, including acute kidney failure (when kidneys suddenly become unable to filter waste products from the blood), have been reported with pemetrexed alone or in association with other chemotherapeutic agents. Many of the patients in whom these occurred had underlying risk factors for the development of kidney adverse events including dehydration or pre-existing hypertension (high blood pressure) or diabetes.	If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in the package leaflet. Inform your doctor if you notice any of the following: • Passing less urine than normally • Swelling in your legs, ankles or feet • Drowsiness • Shortness of breath • Fatigue • Confusion • Nausea • Chest pain or pressure

Serious disorders of the gestroinestinal tract (Serious gastrointestinal disorders)	More than 1 in 10 people may be affected by diarrhoea, vomiting, pain, redness, swelling or sores in your mouth, nausea, loss of appetite or constipation. Severe dehydration has been observed when pemetrexed is given in combination with cisplatin.	If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in the package leaflet. If you are being treated with Pemetrexed STADA and cisplatin simultaneously, you will receive adequate antiemetic treatment (against nausea/vomiting) and appropriate hydration prior to and/or after receiving treatment. Take any medicines you are prescribed as instructed by your doctor or pharmacist. You must contact your doctor **immediately** if you experience pain, redness, swelling or sores in your mouth (very common).
Severe disease causing scarring of lung tissue, which may be induced by radiotherapy (Interstitial pneumonitis (including radiation pneumonitis))	In clinical trials, cases of interstitial pneumonitis (severe disease causing scarring of lung tissue) with respiratory insufficiency, sometimes fatal, have been reported uncommonly in patients treated with pemetrexed. Cases of radiation pneumonitis (lung disease induced by radiotherapy) have been reported in patients treated with radiation either prior, during or subsequent to their pemetrexed therapy.	If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in the package leaflet. Inform your doctor if you notice the following: • Shortness of breath at rest or aggravated by exertion • Dry cough
Acute inflammatory reaction at previously irradiated areas that is triggered when chemotherapy agents are administered (Radiation recall)	Rare cases (up to 1 in 1000 patients) of radiation recall (acute inflammatory reaction at previously irradiated areas that is triggered when chemotherapy agents are administered) have been reported in patients who received radiotherapy weeks or years before starting pemetrexed therapy.	If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in the package leaflet. Inform your doctor if you notice the following skin changes: • Redness • Tenderness • Swelling

		• Wet sores • Peeling skin • Discoloration after the skin has healed
Whole-body inflammation caused by an infection (Sepsis)	Sepsis (whole-body inflammation caused by an infection), sometimes fatal, has been commonly reported (in up to 1 in 10 patients) during clinical trials with pemetrexed.	If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in the package leaflet. Contact your doctor **immediately** if you notice the following: • Fever above 38.5°C • Increased heart rate (pulse) • Significantly decreased urine output • Difficulty breathing • Abdominal pain
Bullous conditions (blistering skin diseases) (Bullous skin reaction including Stevens Johnson Syndrome (SJS) and toxic epidermal necrolysis (TEN))	Up to 1 in 1,000 people may be affected by bullous conditions (blistering skin diseases) - including Stevens-Johnson syndrome and toxic epidermal necrolysis.	If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in the package leaflet. **Immediately** contact your doctor if you notice blistering of your skin, mouth or genitals. This may be a sign of a serious condition.

Important potential risks

Risk	**What is known** **(Including reason why it is considered a potential risk)**
Cardiovascular events	Serious cardiovascular events, including myocardial infarction (heart attack) and cerebrovascular events (those affecting the blood vessels supplying the brain) have been uncommonly reported during clinical studies with pemetrexed, usually when given in combination with another anti-cancer agent. Most of the patients in whom these events have been observed had pre-existing cardiovascular risk factors.
Peripheral vascular disease	Patients treated with Pemetrexed STADA may be at an increased risk of developing peripheral vascular disease (disease of the blood vessels located outside the heart and brain).
Hearing loss/hypoacusis	Patients treated with Pemetrexed STADA may be at an increased risk of developing hearing loss/hypoacusis (partial

	loss of hearing).

Missing Information

Risk	What is known
Pregnancy	There is not enough clinical experience available. If you are pregnant, or thinking about becoming pregnant, tell your doctor. The use of Pemetrexed STADA should be avoided during pregnancy. Your doctor will discuss with you the potential risk of taking Pemetrexed STADA during pregnancy. Women must use effective contraception during treatment with Pemetrexed STADA.
Lactation	There is not enough clinical experience available. Tell your doctor if you are breast-feeding. Breast-feeding must be discontinued during treatment with Pemetrexed STADA.

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.

The Summary of Product Characteristics and the Package leaflet for Pemetrexed STADA can be found in the Pemetrexed STADA's EPAR page

VI.2.6 Planned post authorisation development plan

No post-authorisation studies have been imposed or are planned.

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

Not applicable