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Summary of the risk management plan (RMP) for Pemetrexed Sandoz (pemetrexed)

This is a summary of the risk management plan (RMP) for Pemetrexed Sandoz, which details the measures to be taken in order to ensure that Pemetrexed Sandoz is used as safely as possible. For more information on RMP summaries, see here.

This RMP summary should be read in conjunction with the EPAR summary and the product information for Pemetrexed Sandoz, which can be found on Pemetrexed Sandoz's EPAR page.

Overview of disease epidemiology

Pemetrexed Sandoz is a cancer medicine used to treat two types of lung cancer, malignant pleural mesothelioma and advanced non-small-cell lung cancer of the kind known as 'non-squamous'.

Malignant pleural mesothelioma

Malignant pleural mesothelioma is an aggressive cancer of the lining of the lungs. It is associated with exposure to asbestos: observations from the United Kingdom, Sweden, Croatia, Spain, and Italy showed that the areas with high incidence of mesothelioma exactly correspond to the sites of industries with high asbestos use. Most patients with mesothelioma are diagnosed between 50 and 70 years of age. This age profile may be related to the long delay between the exposure to asbestos and onset of the disease. The incidence of mesothelioma varies markedly from one country to another. Males are at a much higher risk for malignant mesothelioma than females. European findings from 118 cancer registries in 25 countries demonstrate a great geographic variation in the annual incidence rates of mesothelioma; among men, rates range from around 8 per 100,000 in the United Kingdom and the Netherlands to rates lower than 1 per 100,000 in Spain and Poland. Among women, incidence is much lower and less variable, with only the United Kingdom and some Italian regions having rates higher than 1 per 100,000. Malignant pleural mesothelioma can also occur in children; however, these cases are not thought to be associated with asbestos exposure.

Non-small cell lung cancer

Lung cancer is the most common cancer worldwide. It is the leading cause of cancer deaths in men and the second leading cause of cancer deaths in women. In 2012, there were about 410,000 newly diagnosed lung cancer cases in Europe. There are 2 types of lung cancer: small cell lung cancer and non-small cell lung cancer (NSCLC). Non-small cell lung cancer represents approximately 85% of all lung cancer cases. At diagnosis, the majority of patients have non-operable, locally advanced or metastatic disease (when the cancer has spread to other parts of the body). These patients have a very poor outlook, with a 5-year survival rate of approximately 6%. The incidence rates of NSCLC are often higher among males than females.

Summary of treatment benefits

Pemetrexed Sandoz contains the active substance pemetrexed. Pemetrexed Sandoz is a 'generic medicine'. This means that it is similar to a 'reference medicine' already authorised in the European Union (EU) called Alimta.

Because Pemetrexed Sandoz is a generic medicine, its benefits and risks are taken as being the same as those of the reference medicine. The company provided data from the published literature on pemetrexed. No additional studies were needed as Pemetrexed Sandoz is a generic medicine that is given by infusion and contains the same active substance as the reference medicine, Alimta.

Unknowns relating to treatment benefits

There is no information about the use of pemetrexed in children and in women who are pregnant or breastfeeding Pemetrexed is not recommended for use in children as safety and efficacy have not been established in this group of patients. Pemetrexed Sandoz should be avoided in pregnant women, and it must not be used in breastfeeding women.

Summary of safety concerns

Important identified risks

Risk	What is known	Preventability
Non-compliance with vitamin supplementation, manifested mainly as blood disorders and gastrointestinal (stomach and gut) disorders	Treatment with pemetrexed is associated with blood disorders such as neutropenia (low levels of neutrophils, the white blood cells that fight bacterial infection), neutropenia with fever (febrile neutropenia), and infection with severe neutropenia, and gastrointestinal disorders such as feeling or being sick and diarrhoea (treatment-related toxicity). In clinical trials, patients who received pre-treatment with folic acid and vitamin B_{12} experienced less toxicity and less severe toxicity.	All patients treated with Pemetrexed Sandoz must take folic acid and vitamin B_{12}, in order to reduce the occurrence of blood and gut side effects related to treatment with pemetrexed.
Stomach and gut disorders (gastrointestinal disorders)	When pemetrexed is given in combination with cisplatin, infection or irritation of the stomach and intestine can occur; severe dehydration has been observed in these patients. Feeling or being sick, diarrhoea, and constipation, are very common side effects (seen in	Patients should receive adequate treatment and appropriate hydration before and/or after receiving treatment with Pemetrexed Sandoz. Patients should inform their doctor immediately if they develop signs of inflammation or irritation in the stomach.

Risk	What is known	Preventability
	more than 1 in 10 patients); stomach upset and heartburn are common side effects (seen in more than 1 in 100 patients).	All patients treated with Pemetrexed Sandoz must take folic acid and vitamin B_{12}, in order to reduce the occurrence of blood and gut side effects related to treatment with pemetrexed.
Kidney problems (serious renal events)	Serious kidney problems, including acute kidney failure, have been reported with pemetrexed alone or in combination with other chemotherapy medicines. Many of the patients in whom these side effects occurred had underlying risk factors for the development of kidney problems including dehydration or pre-existing hypertension (high blood pressure) or diabetes.	Patients should receive adequate hydration before and/or after receiving treatment with Pemetrexed Sandoz. Patients should inform their doctor immediately if they develop signs of kidney problems, such as changes in urination, swelling, pain in legs, back and sides, abnormal blood tests. Patients' kidney function should be closely monitored with each clinic visit.
Lung disease causing progressive scarring of the air sacs of the lung (interstitial pneumonitis)	In clinical trials, cases of lung disease with respiratory insufficiency, sometimes fatal, have been reported uncommonly (in less than 1 patient in 100) in patients treated with pemetrexed.	No risk factors that can predict lung disease have been identified in patients treated with pemetrexed. Patients should inform their doctor immediately if they develop signs of breathlessness, intense chest pain or cough with bloody sputum which may indicate a blood clot in the vessels of the lungs.
Radiation-related scarring of the air sacs of the lung (radiation pneumonitis)	Cases of radiation pneumonitis (scarring of the air sacs of the lung associated with radiation therapy) have been reported in patients treated with radiation either before, during or after being treated with pemetrexed.	Pemetrexed Sandoz is not currently authorised for use with radiation therapy. Doctors should pay particular attention to these patients and exercise caution when using other radio-sensitising agents. Patients should tell their doctor if they have had or are going to have radiation therapy, as there may be an early or late radiation reaction with Pemetrexed Sandoz.

Risk	What is known	Preventability
Inflammatory skin reaction that sometimes occurs when people receive chemotherapy after radiation therapy (radiation recall)	Rare cases of a severe skin reaction have been reported in patients who received chemotherapy (including treatment with pemetrexed) after they had undergone radiation therapy weeks or years previously.	Radiation recall with pemetrexed is a rare reaction that cannot be predicted. Patients must inform their doctor as soon as possible if they start experiencing any side effects such as skin rash, severe sunburn, prickling sensation or fever.
Severe blood infection (sepsis)	Severe blood infection (sepsis), sometimes fatal, has been commonly reported during clinical trials with pemetrexed (in more than 1 in 100 patients). Neutropenia (low levels of neutrophils, a type of white blood cells) is very common following treatment with pemetrexed (seen in more than 1 in 10 patients).	Sepsis is an important risk with pemetrexed. One of the risk factors for sepsis is very low levels of neutrophils (severe neutropenia), the white blood cells that fight bacterial infection. Therefore, prevention of sepsis is to a great extent linked to the occurrence and prevention of severe neutropenia. Patient must inform their doctor immediately if they have a temperature of 38ºC or greater, are sweating or present other signs of infection since they might have neutropenia. Sepsis may be severe and could lead to death. All patients treated with Pemetrexed Sandoz must take folic acid and vitamin B_{12}, in order to reduce the occurrence of blood and gut side effects related to treatment with pemetrexed.
Rare, severe skin and mucous membrane reactions (including Stevens-Johnson syndrome and toxic epidermal necrolysis)	Skin reactions have been reported with pemetrexed in patients not pre-treated with a corticosteroid (anti-inflammatory) medicine. Rare cases of severe skin reactions including Stevens-Johnson syndrome and toxic epidermal necrolysis have been reported with pemetrexed (seen in less than 1 in 1,000 patients), which in some cases were fatal.	Doctors should be aware that Stevens-Johnson syndrome and toxic epidermal necrolysis may occur during treatment with Pemetrexed Sandoz. Doctors should monitor patients for any signs of these conditions. Patients should inform their doctor immediately if they experience a severe rash, itching, or blistering. Pre-treatment with

Risk	What is known	Preventability
		dexamethasone (or equivalent) can reduce the incidence and severity of skin reactions. If patients experienced a skin reaction in the past, further exposure to the suspected inducing medicine should be strictly avoided.

Important potential risks

Risk	What is known
Heart and blood vessels problems (cardiovascular events)	Some patients have experienced a heart attack, a stroke, or a "mini-stroke" while receiving pemetrexed, usually in combination with other cancer medicines. Possible side effects of Pemetrexed Sandoz include chest pain (common, seen in more than 1 in 100 patients) or having a fast heart rate (uncommon, seen in less than 1 in 100 patients).
Disease of the blood vessels located outside the heart and brain that restricts blood flow (peripheral vascular disease)	Patients undergoing cancer treatment may be at increased risk of peripheral vascular disease. Possible side effects include sudden breathlessness, intense chest pain, or cough with bloody sputum which may indicate a blood clot in the blood vessels of the lungs).
Hearing loss (hypoacusis)	For the majority of cases of hearing loss seen during treatment with pemetrexed, there were other possible causes, including use of cisplatin/carboplatin, greater age of the patients, and significant medical history. Considering these factors, the hearing loss events are unlikely to be causally related to pemetrexed, and it is unclear what role pemetrexed may have played in the events.

Missing information

There is no missing information related to the use of Pemetrexed Sandoz.

Summary of risk minimisation measures by safety concern

All medicines have a summary of product characteristics (SmPC) which provides physicians, pharmacists and other healthcare professionals with details on how to use the medicine, and also describes the risks and recommendations for minimising them. Information for patients is available in lay language in the package leaflet. The measures listed in these documents are known as 'routine risk minimisation measures'.

The SmPC and the package leaflet are part of the medicine's product information. The product information for Pemetrexed Sandoz can be found on Pemetrexed Sandoz's EPAR page.

This medicine has no additional risk minimisation measures.

Planned post-authorisation development plan

Not applicable.

Summary of changes to the risk management plan over time

Not applicable.

This summary was last updated in 09-2015.