VI.2 Elements for a Public Summary

VI.2.1 Overview of disease epidemiology

Pemetrexed Reig Jofre is a medicine used in the treatment of lung cancer, malignant pleural mesothelioma and non-small cell lung cancer.

Malignant pleural mesothelioma:

Malignant pleural mesothelioma is an agressive form of cancer that affects the lining of the lung. Its origin has been generally associated with exposure to asbestos. The incidente of this type of tumour has increased steadily since the 1950s and varies from one country to another. Symptoms of this type of cancer include shortness of breath, chest pain and cough. Most patients with mesothelioma are diagnosed between 50 and 70 years of age. Males are at much higher risk for malignant mesothelioma than females.

Non-small cell lung cancer

Lung cancer is one of the most common malignancies and continues to rise in incidence ans is the leading cause of cancer deaths in men and women. One million new cases and over 900,000 deaths related to lung cancer are reported each year worldwide. It is the leading cause of cancer death in men and the third leading cause in women. Almost 80% of lung cancers are classified as non-small cell lung cancer with 65 to 75 % of cases considered non-operable. Inopearble patients generally receive chemotherapy alone as first treatment. Patients with this type of tumours have a very poor outlook, with a 5-year survival rate of approximately 6%. Incidence rates of non-small cell lung cancer are often higher among males than females.

VI.2.2 Summary of treatment benefits

Pemetrexed Reig Jofre is a generic medicine used in the treatment of cancer. Pemetrexed Reig Jofre 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 Reig Jofre is also given in combination with cisplatin for the initial treatment of patients with advanced stage of lung cancer.

It can also be prescribed to you if you have lung cancer at an advanced stage if your disease has responded to treatment or it remains largely unchanged after initial chemotherapy. Pemetrexed Reig Jofre is also a treatment for patients with advanced stage of lung cancer whose disease has progressed after other initial chemotherapy has been used.

The clinical efficacy of pemetrexed for these types of lung cancer has been evaluated in several clinical trials whose results are are published and available in the scientific literature.

VI.2.3 Unknowns relating to treatment benefits

There is no information about pemetrexed use in children and women who are pregnant or breast feeding in malingnat pleaural mesothelioma and non-small cell lung cancer. For this reason, this product is not recommended for use in children as safety and efficacy have not been established in this group of patients. Pemetrexed should be avoided in pregnant women, and its use is contraindicated in breastfeeding women.

VI.2.4 Summary of safety concerns

Important identified risks

Risk	**What is known**	**Preventability**
Noncompliance with vitamin supplementation manifested mainly as blood disorders and gastrointestinal disordres (nausea, vomiting diarrhea)	Treatment with pemetrexed is associated with blood disorders such as neutropenia (low levels of neuthophils, the white blood cells that fight bacterial infection), neutropenia with fever and infection with severe neutrhopenia and gastrointestinal disorders such as feeling or being sick and diarrhea (treatment related toxicity). In clinical trials, patients who received pre-treatment with folic and vitamin B12 experienced less toxicity and less severe toxicity.	All patientas treated with permetrexed must be instructed to take folic acid and vitamin B12 as a preventive measure to reduce treatment-related toxicity.
Condition in which a person's bone marrow produces fewer normal blood cells. (Bone marrow suppression)	The most commonly reported undesirable effects related to pemetrexed, wether used as monotheraphy or in combination, are bone marrow suppression manifested as anaemia (low blood count), neutropenia (low white blood cell), and thrombocyytopenia (low platelet count).	Before each infusion, patients, will have samples of their blood taken to evaluate if they have sufficient blood cells to receive Pemetrexed Reig Jofre. • Tell your doctor at once if you experience tiredness, feeling faint, or becoming easily breathless, or if you look pale (since you might have low blood count than a normal which is very common). • Tell your doctor at once if you experience bleeding from the gums, nose or mouth or any bleeding that would not stop, reddish or pinkish urine, or unexpected bruising (since you might

Risk	What is known	Preventability
		have less platelets than normal which is very common).
Disease of the stomach and intestine (Gastrointestinal disorders)	Due to the infection or irritation of the stomach and intestine by pemetrexed given in combination with cisplatin, severe dehydration has been observed.	Patients should receive adequate treatment and appropriate hydration prior to and/or after receiving treatment. • Tell your doctor at once if you develop signs of inflammation or irritation in the stomach, such as stomach upset, including nausea, vomiting, diarrhea, constipation (very common), and heart burn (common). • If you are also receiving cisplatin, tell your doctor, as he should make sure that you are properly hydrated and receive appropriate treatment before and after receiving cisplatin to prevent vomiting.
Disease of the kidney (Renal disorders)	Serious kidney events, including acute kidney failure, have been reported with pemetrexed alone or in combination with other chemotherapeutic agents. Many of the patients in whom these events occurred had underlying risk factors for the development of kidney events including dehydration or pre-existing hypertension or diabetes.	Patients should received adequate hydration prior to and/or after receiving pemetrexed treatment. • Tell your doctor at once if you develop signs of kidney disorder, pain in legs, back and sides, abnormal blood tests (very common), or kidney failure (common), Acute renal Failure(Uncommon). • Your kidney function will be closely monitored will each clinic visit. • 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).
A clinical condition of severe blood infection (Sepsis)	Severe blood infection (sepsis), sometimes fatal, has been commonly reported during clinical trials with pemetraxed.	One of the risk factors of sepsis is low levels of the white blood cells that fight bacterial infection (severe neutropenia). Therefore prevention of sepsis is to great extent linked to the occurrence and prevention of severe neutropenia.

Risk	What is known	Preventability
		You must contact your doctor immediately if you notice any of the following symptoms: fever or infection (common). If you have a temperature of 38ºC or greater, sweating or other signs of infection (since you might have fewer white blood cells than normal, which is very common). Infection (sepsis) may be severe and could lead to death.
A rare, severe skin and mucous membrane reaction to drug. (skin reaction including Stevens-Johnson Syndrome and toxic epidermal necrolysis)	Skin reactions have been reported in patients not pre-treated with corticosteroid. Rare cases of severe skin reaction conditions have been reported which in some cases were fatal.	Further exposure to the suspected including drug, should be strictly avoided. • A rare skin reaction may be severe and could lead to death. Contact your doctor if you get a severe rash, itching, or blistering (Stevens-Johnson Syndrome or toxic epidermal necrolysis).
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 patients treated with pemetraxed.	No risk factors predictive of lung disease have been identified in patients treated with pemetrexed. • Tell your doctor If you experience sudden breathlessness, intense chest pain or cough with bloody sputum (uncommon)(may indicate a blood clot in the blood vessels of the lungs)
Inflamation in the lungs after radiation therapy. (Radiation pneumonitis).	Radiation pneumonitis (scarring of the air sacs of the lung associated with radiation therapy) may occur in patients who are also treated with radiation either before, during or after their Pemetrexed therapy.	Particular attention should be paid to these patients and caution exercised with use of other radio-sensitising agents. 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.
Inflammatory skin reaction that sometimes occurs when people receive chemotherapy following radiation therapy. (radiation recall)	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.	Radiation recall with pemetrexed is a very rare reaction that cannot be predicted. • You must contact your doctor as soon as possible when you start experiencing any of the side effects of skin rash, severe sunburn, or prickling sensation or fever.

Important potential risks

Risk	What is known (including Reason Why it is Considered a Potential Risk)
None	--

Missing information

Risk	What is known
None	--

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

These medicinal products have no additional risk minimisation measures. Routine pharmacovigilance should be sufficient for post-marketing safety monitoring of the risks.

VI.2.6 Planned post authorisation development plan

Not applicable.

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

SUMMARY OF CHANGES TO THE RMP		
VERSION NUMBER	**VERSION NUMBER**	**CHANGES**
01	February 2015	As per RMS preliminary assessment report, the following changes to the RMP have been addressed: 1. The safety concern "Cardiovascular disorder" was changed from important identified to important potential risk. 2. The following safety concerns were added as important potential risk: • SOC: Vascular disorders (PT: Peripheral ischaemia) • SOC: Ear and labyrinth disorders (Hearing loss, Hypoacusis) 3. The routine risk minimisation measures in the RMP were updated as necessary to reflect the changes made to the list of safety concerns. 4. The reference safety documents have been updated.
02	September 2016	Changes to align the RMP to the one of the innovator as requested by RMP assessor as per assessment performed during authorisation assessment: **1.- Important Identified Risks**: SOCs: Metabolism and nutrition disorders (PT: Dehydration); Skin and subcutaneous tissue disorders (PT: skin reaction); Injury, poisoning and procedural complications (PT: Toxicity to

		various agents); Interaction with other medicinal products according to the secretion mechanism of Permetrexed, Class interactions; Blood and lymphatic System disorders (PT Haemolytic anaemia); Immune System disorders (PT: Anaphylactic shock) have been removed. SOC: Gastrointestinal disorders (PT. Gastrointestinal toxicity manifested as anorexia, nausea, vomiting, diarrhoea, constipation, pharyngitis, mucositis, and stomatitis) and SOC: Gastrointestinal disorders (PT: Colitis, including intestinal and rectal bleeding, sometimes fatal, intestinal perforation, intestinal necrosis and typhlitis) are joined to one risk named "gastrointestinal disorders". SOC: Blood and the lymphatic System disorders (PT: Myelosuppression including anaemia, neutropenia, leukopenia, pancytopenia and thrombocytopenia) has been renamed to Bone marrow suppression. SOC: Renal and urinary disorders (PT: Renal failure) has been renamed as Renal disorders. SOC: Respiratory, thoracic and mediastinal disorders (PT: Interstitial lung disease) has been renamed as Interstitial pneumonitis. The risk "Noncompliance with folic acid and vitamin B12 regimens manifested mainly as haematological and gastrointestinal toxicities";" radiation recall" have both been added. **2.- Important potential risks/ Missing information** All the safety concerns that were characterised under this section have been removed. **3. - Sections V and VI (V.1, V.3, VI.2.4)** have been changed in order to align them with the changes described in numbers 1 and 2. **Section VI.2, *elemments for a public summary*** has been reworded to simplify language used.