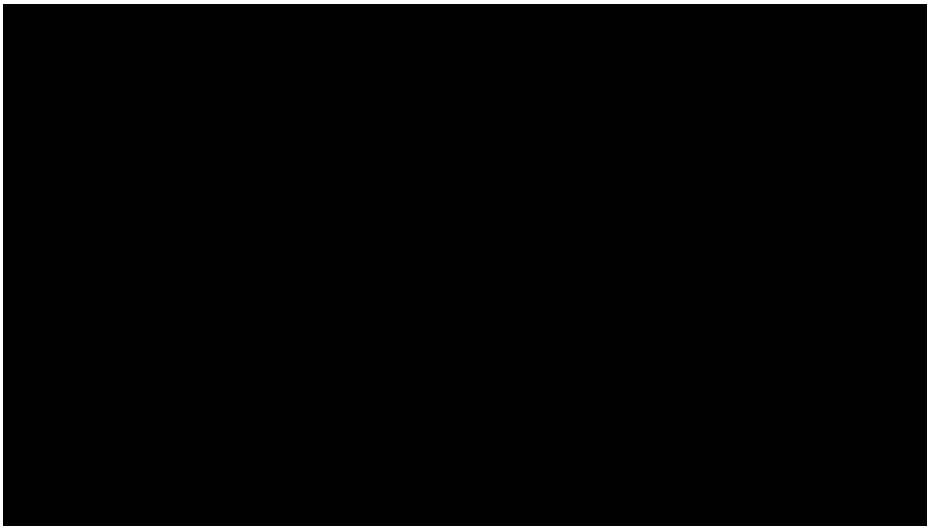

EU Risk Management Plan (Version 6.1)

Global Patient Safety
Signatory information is available on request.
EU Risk Management Plan electronically approved by Lilly on date provided below.

Approval Date: 20-Aug-2019 GMT

EU Risk Management Plan (RMP) for ALIMTA (pemetrexed) and Pemetrexed Lilly (pemetrexed)

RMP Version to be Assessed as Part of the Application: 6.1

Data Lock Point for This RMP: 04 February 2019

Date of Final Sign Off: See front page.

Rationale for Submitting an Updated RMP:

With the transition of the previous EU RMP for pemetrexed to that determined by Good Pharmacovigilance Practices (GVP) Module V (Rev 2), the Marketing Authorisation Holder (MAH) was requested by Pharmacovigilance Risk Assessment Committee during the Periodic Safety Update Report single assessment (PSUSA) procedure number EMEA/H/C/PSUSA/00002330/201802 to delete the safety concerns previously classified as important identified risks.

Additionally, the opportunity was taken to submit a single RMP for pemetrexed rather than separate RMPs for each pemetrexed-containing product (i.e., ALIMTA and Pemetrexed Lilly).

Summary of Significant Changes in This RMP:

- Conversion to the GVP Module V (Rev 2) format.
- Removal of the following important identified risks: noncompliance with folic acid and vitamin B_{12} regimens manifested mainly as haematological and gastrointestinal toxicities, bone marrow suppression, gastrointestinal disorders, renal disorders, sepsis, bullous skin reaction including Stevens-Johnson syndrome and toxic epidermal necrolysis, interstitial pneumonitis, radiation pneumonitis, radiation recall.
- Inclusion of Pemetrexed Lilly within this RMP.

Other RMP Versions Under Evaluation

None.

Details of the Currently Approved RMP for ALIMTA (pemetrexed)

Version number: 6.0

Approved with procedure: EU (centralised procedure)

Date of approval (opinion date): 07/04/2015

Details of the Currently Approved RMP for Pemetrexed Lilly (pemetrexed)

Version number: 1.0

Approved with procedure: EU (centralised procedure)

Date of approval (opinion date): 24/11/2014

QPPV oversight declaration: The content of this RMP has been reviewed and approved by the MAH's Qualified Person for Pharmacovigilance (QPPV). The electronic signature is available on file.

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Part I: Product(s) Overview

Table Part I.1. Product Overview

Active substance(s) (INN or common name)	Pemetrexed
Pharmacotherapeutic group(s) (ATC Code)	L01BA04
Marketing Authorisation Holder	Eli Lilly Nederland B.V.
Medicinal products to which this RMP refers	2
Invented name(s) in the EEA	ALIMTA® Pemetrexed Lilly
Marketing authorisation procedure	EU (centralised procedure)
Brief description of the product	**Chemical class:** Folic acid analogues
	Summary of mode of action: Converted intracellularly by folylpolyglutamate synthetase to a polyglutamate form, pemetrexed inhibits several key folate-dependent enzymes including thymidylate synthase, dihydrofolate reductase, glycinamide ribonucleotide formyltransferase, and aminoimidazole carboxamide ribonucleotide formyltransferase. Inhibition of these enzymes interferes with folate-dependent metabolic processes essential for cell replication**.**
	Important information about its composition: Each 100- or 500-mg vial of pemetrexed contains pemetrexed disodium equivalent to 100 mg pemetrexed and 106 mg mannitol, or 500 mg pemetrexed and 500 mg mannitol, respectively. Hydrochloric acid and/or sodium hydroxide may have been added to adjust pH.
Hyperlink to the Product Information	Updated Product Information for both ALIMTA and Pemetrexed Lilly are provided with the submission of this RMP.
Indication(s) in the EEA	**Current:** <u>Malignant pleural mesothelioma</u> • Pemetrexed is indicated for the treatment of patients with malignant pleural mesothelioma in combination with cisplatin. <u>Non-small cell lung cancer</u> • Pemetrexed is indicated for the treatment of patients with locally advanced or metastatic nonsquamous non-small cell lung cancer after prior chemotherapy. • Pemetrexed is indicated in combination with cisplatin therapy for the initial treatment of patients with locally advanced or metastatic nonsquamous non-small cell lung cancer. • Pemetrexed is indicated for the treatment of patients with locally advanced or metastatic nonsquamous non-small cell lung cancer

	immediately following initial chemotherapy.
	Proposed: Not applicable.
Dosage in the EEA	**Current:** Pemetrexed should be administered under the supervision of a qualified physician experienced in the use of antineoplastic agents. Malignant Pleural Mesothelioma Combination use with cisplatin (adults): The recommended dose of pemetrexed is 500 mg/m^2 administered as an IV infusion over 10 minutes on the first day of each 21-day cycle. The recommended dose of cisplatin is 75 mg/m^2 infused over 2 hours approximately 30 minutes after completion of the pemetrexed infusion on the first day of each 21-day cycle. Patients should receive appropriate hydration prior to and/or after receiving cisplatin. Non-Small Cell Lung Cancer Single-agent use (adults): The recommended dose of pemetrexed is 500 mg/m^2 administered as an IV infusion over 10 minutes on the first day of each 21-day cycle. Combination use with cisplatin (adults): The recommended dose of pemetrexed is 500 mg/m^2 administered as an IV infusion over 10 minutes on the first day of each 21-day cycle. The recommended dose of cisplatin is 75 mg/m^2 infused approximately 30 minutes after completion of the pemetrexed infusion on the first day of each 21-day cycle. Patients should receive appropriate hydration prior to and/or after receiving cisplatin.
	Proposed: Not applicable.
Pharmaceutical form(s) and strengths	**Current:** ALIMTA 100-mg or 500-mg powder for concentrate for solution for infusion. Pemetrexed Lilly 100-mg or 500-mg powder for concentrate for solution for infusion.
	Proposed: Not applicable.

Abbreviations: ATC = Anatomical Therapeutic Chemical; EEA = European Economic Area; EU = European Union; INN = International Nonproprietary Names; RMP = Risk Management Plan.

Product Overview

Is/will the product be subject to additional monitoring in the EU?	No

Abbreviation: EU = European Union.

Part II: Safety Specification

Module SI - Epidemiology of the Indication(s) and Target Population(s)

SI.1 Malignant Pleural Mesothelioma

Malignant mesothelioma (MM) can arise at 4 anatomic sites: the pleura, the peritoneum, the pericardium, and in males, the tunica vaginalis testis (Mezei et al. 2017). Malignant pleural mesothelioma comprises approximately 80% to 95% of cases (Marinaccio et al. 2012; Neumann et al. 2013); therefore, the mesothelioma epidemiology largely reflects the epidemiology of MPM.

SI.1.1 Incidence

The incidence of MPM is steadily rising in most parts of the world, despite the reduction of asbestos exposure due to bans and restrictions across more than 50 countries (Ceresoli et al. 2014, Bibby et al. 2016; Geltner et al. 2016; Andujar et al. 2016).

The continued increase in incidence may be attributed to long latency periods of roughly 40 years between exposure and onset of disease (Andujar et al. 2016; Bibby et al. 2016). The estimated number of incident cases of mesothelioma worldwide is expected to rise from 30,443 in 2018 to 37,279 in 2025 and 55,224 in 2040 (Ferlay et al. 2018).

The 2018 age-standardised annual incidence rates (per 100,000) for mesothelioma globally and across the European regions are summarised below (Ferlay et al. 2018):

- World: Overall, 0.31; Male, 0.48; Female, 0.18
- Central and Eastern Europe: Overall, 0.41; Male, 0.58; Female, 0.28
- Northern Europe: Overall, 1.3; Male, 2.3; Female, 0.45
- Southern Europe: Overall, 0.73; Male, 1.2; Female, 0.34
- Western Europe: Overall, 0.8; Male, 1.4; Female, 0.34

There is considerable geographic variation in incidence rates of mesothelioma across the European Union (EU). Among men, age-standardised rates (per 100,000) range from 6.1 in Luxembourg and 2.9 in the United Kingdom (UK) to rates lower than 1 in Spain (0.77), Greece (0.38), and Portugal (0.35; Ferlay et al. 2018). In comparison, the incidence in women is much lower and less variable with only Luxembourg (3.8) reporting rates greater than 1, and countries such as Spain, Sweden, and Greece reporting rates as low as 0.22, 0.31, and 0.09, respectively (Ferlay et al. 2018).

According to the United States (US) Surveillance, Epidemiology, and End Results (SEER) data (2012 to 2016), the age-adjusted incidence rate (per 100,000) of mesothelioma was estimated at 0.9 (1.6 in men and 0.4 in women; Noone et al. 2018).

SI.1.2 Prevalence

In 2018, there were approximately 31,250 people worldwide living with mesothelioma that had been diagnosed within 5 years. In Europe, the 5-year prevalence for mesothelioma was estimated to be 13,325 (Ferlay et al. 2018).

SI.1.3 Demographics of the Population in the Authorised Indication – Age, Gender, Racial, Ethnic Origin and Risk Factors for the Disease

Age, Gender, and Race

Patients affected by MPM are mostly elderly male Caucasians (Howlader et al. 2014). The median age at MPM diagnosis is approximately 69 years, with most patients being diagnosed between 50 and 79 years old (Yang et al. 2008; van der Bij et al. 2012; Budroni et al. 2014; Beckett et al. 2015). This age profile would likely be related to the long delay needed between exposure to asbestos and onset of the disease (CDC 2009), with a 20- to 40-year delay before disease onset (Taioli et al. 2014; Andujar et al. 2016, Bibby et al. 2016).

Incidence rates are much higher in men than women, and much higher in Caucasians than in other races/ethnicities (Howlader et al. 2014).

Risk Factors

Both occupational and environmental exposures to asbestos are the well-established major etiological risk factors for mesothelioma (Ascoli et al. 2014; Ceresoli et al. 2014). While occupational exposure to asbestos is the most frequently cited risk factor for MPM, accounting for more than 80% of cases, other factors such as genetic predisposition, irradiation, and exposure to certain chemicals and metals can also be risk factors (Baas et al. 2015, Domen et al. 2017). Neighbourhood exposures to people residing close to asbestos mines and factories, as well as domestic cases in households with asbestos workers, have also been described in the literature (Andujar et al. 2016). On the other hand, tobacco smoking is not considered a risk factor for mesothelioma (Scherpeel et al. 2010).

SI.1.4 Main Existing Treatment Options

Surgical resection and radiotherapy represent the standard treatment in patients with resectable MPM, but only a few patients with localised disease and adequate pulmonary and cardiac function are eligible. For patients with unresectable MPM, the combination of pemetrexed and cisplatin (PC) is the standard treatment because it improved overall survival (OS), some relevant quality of life (QoL) parameters, and lung function, compared to cisplatin monotherapy. No other treatments tested in this patient population thus far, including other chemotherapies, targeted agents, and immunotherapy, have succeeded in improving efficacy outcomes of the PC combination.

SI.1.5 Natural History of the Indicated Condition in the Untreated Population, Including Mortality and Morbidity

Most patients with MPM present with breathlessness, chest pain, or both (Bibby et al. 2016). Breathlessness is common (approximately 70%) in the early stages of disease usually due to pleural effusion, and as the disease progresses, because of the tumour. Other symptoms also include bone and neuropathic pain and general malaise (Bibby et al. 2016). Although some patients are diagnosed at an asymptomatic and probably earlier stage to have a better prognosis, mesotheliomas most often become noticeable only after the occurrence of distinct clinical symptoms (Lehnert et al. 2017).

Accurate staging for MPM is challenging and difficult (Bibby et al. 2016). Identification of nodal metastases is hard to determine using computed tomography (CT) scans and chest wall or diaphragm invasion may be missed (Bibby et al. 2016). Historically, no validated staging system for clinical assessment of mesothelioma stage exists and it has only been possible to accurately define stage in patients undergoing surgery (Beckett et al. 2015).

Malignant mesothelioma generally has a poor prognosis and long-term survival is rare (Andujar et al. 2016). There are 4 main histological subtypes of MPM: epitheloid (81%), sarcomatoid (11%), biphasic or mixed (6%), and desmoplastic (2%; Domen et al. 2017). Median survival ranges from 8 to 14 months from diagnosis, with sarcomatoid associated with the worst outcome (4 months) and epitheloid with a favourable outcome (13 months; Bibby et al. 2016). Differences in survival are also associated with age at diagnosis, sex, performance status (PS), and tumour- and environment-related factors (Burgers and Damhuis 2004).

Worldwide, age-standardised mortality rates (per 100,000) for mesothelioma in 2018 were estimated at 0.3 overall (0.4 in males and 0.1 in females), with an estimated 25,600 deaths (Ferlay et al. 2018). The rates were higher across regions of Europe, ranging from 0.99 in males and 0.2 in females in Sweden, to 2.2 in males and 0.27 in females in the Netherlands (Ferlay et al. 2018). In the US between 1999 and 2015, the age-adjusted mortality rates were 2.5 in males and 0.5 in females (Mazurek et al. 2017).

SI.1.6 Important Comorbidities

The most predominant comorbid conditions among patients affected by pleural mesothelioma are chronic obstructive pulmonary disease (COPD; 31.7% of patients) and coronary heart disease (18%; Lindenmann et al. 2013). Besides cardiovascular disease (28.7%), findings from the US showed that cerebrovascular diseases (6.2%), respiratory diseases (31.8%), arthritis (8.5%), diabetes (8.5%), and hypertension (40.3%) were also commonly observed in this population (Ogle et al. 2000). Due to the poor prognosis and limited treatment options for MPM, many patients also experience depression and anxiety more frequently in MPM when compared to other tumours (Bibby et al. 2016).

SI.2 Non-Small Cell Lung Cancer

Lung cancer is broadly categorized as either small cell lung cancer (SCLC) or non-small cell lung cancer (NSCLC; de Rijke et al. 2004; Hardy et al. 2010), with NSCLC comprising adenocarcinoma (37%), squamous cell carcinoma (20%), large cell carcinoma (4%) and all other types (25%; Montesinos et al. 2011). Most lung cancer statistics include both SCLC and NSCLC. Because NSCLC comprises approximately 80% to 85% of lung cancers and nonsquamous subtypes represents more than 75% of NSCLC (Alberg et al. 2007, Perez-Moreno et al. 2012, Montesinos et al. 2011), the lung cancer epidemiology largely reflects the epidemiology of nonsquamous NSCLC.

SI.2.1 Incidence

Lung cancer remains the most common cancer worldwide, affecting approximately 2.1 million people (11.6% of the total cancer cases) in 2018. In Europe, 470,000 new cases of lung cancer

were estimated in 2018 (Ferlay et al. 2018). The highest age-standardised incidence rates among men are observed in Central and Eastern Europe and Eastern Asia, with notably low incidence rates in Middle and Western Africa. In women, the incidence rates are generally lower and the geographical pattern is a little different, mainly reflecting different historical exposure to tobacco smoking. The highest age-standardised rates among women are in Northern America and Northern Europe (Ferlay et al. 2015).

The 2018 age-standardised annual incidence rates (per 100,000) globally and across European regions are summarised below (Ferlay et al. 2018):

- World: Male, 31.5; Female, 14.6
- Central and Eastern Europe: Male, 49.3; Female, 11.9
- Northern Europe: Male, 34.0; Female, 26.9
- Southern Europe: Male, 43.1; Female, 15.7
- Western Europe: Male, 43.3; Female, 25.7

SI.2.2 Prevalence

In 2018, there were approximately 2.1 million people worldwide living with lung cancer that had been diagnosed within 5 years. In Europe, the 5-year prevalence for lung cancer was estimated to be 497,000 (Ferlay et al. 2018).

With the estimated proportion of nonsquamous NSCLC (approximately 64% of lung cancer), it is estimated that nonsquamous NSCLC would account for approximately 1.4 million of the prevalent lung cancer patients worldwide and 317,000 patients in Europe in 2018.

SI.2.3 Demographics of the Population in the Authorised Indication – Age, Gender, Racial, Ethnic Origin and Risk Factors for the Disease

Age, Gender, and Race

Lung cancer incidence varies by age, gender, and race. The average age of lung cancer patients at diagnosis in the US and in EU-28 counties was similar, with a mean age approximately 70 years, ranging from 69 years in Denmark to 72 years in the UK (Walters et al. 2013; Howlader et al. 2014). The National Lung Cancer Audit in England found that 6.7% of NSCLC cases were diagnosed in patients less than 54 years of age, compared to 64% of NSCLC cases diagnosed in patients between the ages of 65 and 84 years (Khakwani et al. 2013).

Lung cancer incidence among men invariably exceeds that among women with male:female gender ratios ranging from 1.1:1 in the US, 1.27:1 in Denmark, 1.35:1 in England, and 4.7:1 in the Netherlands (Janssen-Heijnen et al. 1998; Ferlay et al. 2013b; Kaergaard Starr et al. 2013; Khakwani et al. 2013).

Risk factors

Smoking is by far the leading risk factor for NSCLC (Alberg et al. 2007), regardless of histological subtypes (Saito et al. 2017). On average, smokers are at a 5- to-10-fold increased

risk of developing lung cancer compared with non-smokers (WHO 2014). The risk for lung cancer correlates with the number of cigarettes smoked per day, lifetime duration of smoking, age at onset of smoking, degree of inhalation, tar and nicotine content of the cigarettes, and use of unfiltered cigarettes (Ettinger 2012). In populations with prolonged cigarette use, such as Europe and North America, the proportions of lung cancer cases attributable to smoking are high, with 90% to 95% of male cases and 74% to 85% of female cases attributed to smoking (Parkin et al. 2005). More than 50 epidemiological studies have also reported a nearly 26% increased risk of lung cancer for second-hand smoke (Hackshaw et al.1997; Boffetta 2006).

Other risk factors for NSCLC include outdoor air pollution (Boffetta 2006), and home and occupational exposures to agents, such as arsenic, asbestos, chromates, chloromethyl ethers, nickel, polycyclic aromatic hydrocarbons, and radon progeny (Alberg et al. 2007). It has been estimated that approximately 1 out of 10 lung cancer cases in Europe is attributed to urban air pollution (Boffetta 2006). Some of the environmental and occupational carcinogens have been reported to have a synergistic effect with smoking (Alberg et al. 2007).

Excess risk of lung cancer has been also described in relation to a family history (Schwartz 2004; Alberg et al. 2007) and cancer treatment. Individuals with a history of radiation therapy on the chest for Hodgkin's lymphoma and breast cancer has been associated with an increased risk of lung cancer in a dose-dependent manner (Moser et al. 2006; Maddams et al. 2011).

SI.2.4 Main Existing Treatment Options

Systemic therapy should be offered to all Stage IV patients with good PS (0 to 2). Platinum-based chemotherapy is the gold standard, but a nonplatinum doublet may be considered if platinum therapy is contraindicated (Reck et al. 2014). Single-agent therapy, such as taxanes, gemcitabine, or vinorelbine, is an option in patients with a PS of 2, as well as in elderly unfit or comorbid patients (Reck et al. 2014).

First-Line Therapy

Chemotherapy

Most patients with inoperable NSCLC are candidates for palliative chemotherapy consisting of standard induction therapy with 4 cycles of chemotherapy recommended, notably when maintenance treatment is considered, for a maximum of 6 cycles of a platinum-based chemotherapy doublet, per the American Society of Clinical Oncology (Azzoli et al. 2011) and the European Society for Medical Oncology (ESMO; Reck et al. 2014) guidelines. Choice of either cisplatin or carboplatin is acceptable; drugs that may be combined with platinum include third-generation cytotoxic drugs such as taxanes (paclitaxel, docetaxel), etoposide, pemetrexed, gemcitabine, and vinorelbine (NCCN 2013; Reck et al. 2014). There may, however, be an OS advantage by using cisplatin compared to carboplatin. Pemetrexed is preferred to gemcitabine in patients with nonsquamous NSCLC, based upon an OS benefit (Scagliotti et al. 2008; NCCN 2013; Reck et al. 2014).

Targeted Therapies

Monoclonal Antibodies

Bevacizumab significantly prolongs OS and progression-free survival (PFS) when added to first-line paclitaxel and carboplatin in patients with advanced NSCLC (Sandler et al. 2006; NCCN 2013).

Tyrosine Kinase Inhibitors

Epidermal growth factor receptor (EGFR)-tyrosine kinase inhibitor (TKI) therapy statistically significantly delays disease progression in EGFR mutation-positive (EGFRmut[+]) patients but has no demonstrable impact on OS. These findings support EGFR mutation assessment before initiation of treatment. EGFR-TKIs should be considered as front-line therapy in EGFRmut(+) advanced NSCLC patients (Lee et al. 2013). Patients with tumours bearing an activating (sensitising) EGFR mutation may benefit from gefitinib, erlotinib, or afatinib (Gridelli et al. 2014).

Anaplastic Lymphoma Kinase Inhibitor

The inhibition of anaplastic lymphoma kinase (ALK) in lung tumours with the ALK rearrangement resulted in tumour shrinkage or stable disease (SD) in most patients (Kwak et al. 2010). Patients with NSCLC harbouring an ALK rearrangement should be considered for crizotinib, a dual ALK and MET TKI, during the course of their disease (Reck et al. 2014).

Second-Line Therapy

Single-agent docetaxel, erlotinib, gefitinib, and pemetrexed are acceptable as second-line treatment for patients with advanced NSCLC with adequate PS of 0 to 2 when disease has progressed during or after first-line platinum-based therapy. Single agents improve disease-related symptoms and survival. Docetaxel is superior to vinorelbine or ifosfamide; pemetrexed is considered equivalent to docetaxel with less toxicity in patients with nonsquamous histology (Hanna et al. 2004); and erlotinib is superior to best supportive care, improving OS in second- or third-line NSCLC patients of all histologies not eligible for further chemotherapy, including patients with a PS of 3 (Shepherd et al. 2005). Gefitinib was proven noninferior to docetaxel in a large randomised trial with a better toxicity profile and QoL (Kim et al. 2008).

Any patient with an activating (sensitising) EGFR mutation should receive an EGFR TKI as second-line treatment, if not received previously. In the presence of an ALK rearrangement, second-line treatment with crizotinib should be considered if not received as part of first-line treatment (Reck et al 2014).

Maintenance Therapy

Significant survival benefit was achieved in the study by Sandler and colleagues (2006) in the paclitaxel and carboplatin plus bevacizumab arm using bevacizumab both during induction and as maintenance therapy until progressive disease (Sandler et al. 2006; NCCN 2013). Switch maintenance with erlotinib versus placebo demonstrated PFS and OS benefit in all histologies, with a greater benefit in efficacy in patients with SD after induction treatment leading to a label restriction for such patients (Cappuzzo et al. 2010; Peters et al. 2012; NCCN 2013). Two randomised Phase 3 trials showed a statistically significant PFS and OS advantage for

pemetrexed in patients with Stage IIIB or IV nonsquamous NSCLC that had not progressed after 4 cycles of standard platinum-based chemotherapy (Ciuleanu et al. 2009; Paz-Ares et al. 2013).

SI.2.5 Natural History of the Indicated Condition in the Untreated Population, Including Mortality and Morbidity

Despite improvements in the management of NSCLC, the long-term survival for NSCLC remains poor. The prognosis of NSCLC substantially varies by tumour stage: the 5-year survival rate is over 68% for Stage I NSCLC and decreases to 13% to 26% for Stage IIIB/C and less than 1% to 10% for Stage IVA/B NSCLC (Goldstraw et al. 2016). Histology also plays a role in survival of NSCLC; in a Spanish study, the median survival time for patients with squamous cell carcinoma was 272 days, 222 days in adenocarcinoma, and 156 days in cases of large cell/undifferentiated carcinomas (Montesinos et al. 2011). The clinical outcome of untreated NSCLC has been summarised in a systematic review. Without anticancer treatment, a pooled median OS was 11.9 months for the Stage I/II NSCLC patients from 6 cohort studies (N = 4,125); and 5.0 months for the Stage III/IV NSCLC patients from the control arm of 15 randomised clinical trials (N = 1031; Wao et al. 2013).

Symptoms associated with lung cancer include haemoptysis, loss of weight, loss of appetite, dyspnoea, thoracic pain, fatigue, and cough. They may not be present until the disease progresses, and, even if symptoms do occur, they are often mistaken for respiratory symptoms due to infection and a history of smoking, causing further delay in diagnosis (Hamilton et al. 2005b). Low-dose CT is an effective method for the early detection for lung cancer that has recently shown to decrease a mortality, yet it is still waiting for a broad implementation (Oudkerk et al. 2017).

Non-small cell lung cancer is generally diagnosed at an advanced stage. The reported proportion with metastatic disease (Stage IV) ranged from 32% to 55% in different European and US Cancer Registries (Morgensztern et al. 2010; Khakwani et al. 2013; Walters et al. 2013). In addition, 30% to 55% of patients develop recurrence despite curative resection, of which the majority (greater than 75%) involve distant metastasis (Uramoto and Tanaka 2014).

Tumour burden including extensive metastases (30%) was a major cause of death for patients with lung cancer in an autopsy study. Other common immediate causes of death were infection, including sepsis and pneumonia (20%); complications of metastases (18%); pulmonary haemorrhage (12%); pulmonary thromboembolism (10%); and pulmonary diffuse alveolar damage (7%; Nichols et al. 2012). Infection is a common complication associated with an increased morbidity and mortality among cancer patients. Patients with lung cancer are particularly susceptible to pulmonary infection due to bronchial obstruction, aspiration, damage to both normal and tumour tissues, disruption of host defence mechanism resulting from tumour invasion, and radiation and/or chemotherapy (Akinosoglou et al. 2013). In a cohort of hospitalised lung cancer patients (N = 442), 62% experienced 435 episodes of fever and/or documented infection. More than half of infections (56%) occurred in the tracheobronchial tree, such as bronchitis and pneumonia. Approximately 10% of infection episodes did not resolve after antibiotic therapy (Berghmans et al. 2003).

Because of the high incidence and fatality, lung cancer is the most common cause of death from cancer worldwide, responsible for nearly 1 in 5 cancer deaths (1.76 million deaths, 18.4% of the total; Bray et al. 2018). The age-standardised rates (per 100,000) of lung cancer mortality for the year 2018 are 18.6 globally, and range between 21.3 and 24.6 in different regions of Europe (Ferlay et al. 2018).

SI.2.6 Important Comorbidities

Smoking-related comorbidities such as chronic pulmonary disease and cardiovascular disease are commonly diagnosed among NSCLC patients; these comorbidities increase with increasing age and are approximately twice as high as the general population (Janssen-Heijnen et al. 1998; Wang et al. 2012).

The prevalence of COPD in the mostly NSCLC populations ranged from 22% in a cancer registry-based study in the Netherlands (Janssen-Heijnen et al. 1998) to 50% among patients receiving surgical treatments in Spain (López-Encuentra 2002). The higher prevalence of COPD for the Spanish patients may be a result of more meticulous preoperative evaluations for those who were potential surgical candidates (López-Encuentra 2002). In the Dutch registry study, the prevalence of cardiovascular diseases in patients with lung cancer was 23%. Cardiovascular diseases included myocardial infarction, cardiac decompensation, angina pectoris, intermittent claudication, abdominal aneurysm, and cerebrovascular diseases. As expected, the prevalence increased with age and was higher among males. After cardiovascular diseases and COPD, the next most frequent comorbidities were hypertension (12%) and diabetes mellitus (7%; Janssen-Heijnen et al. 1998). The prevalence of cardiac disease and peripheral vascular disease was 14% and 10% in the Spanish study (López-Encuentra 2002).

Interstitial lung disease (ILD) shares risk factors with NSCLC. Approximately 2% to 4% of NSCLC patients were estimated as having coexisting ILD in previous studies of Japanese patients (Chiyo et al. 2003; Miyazaki et al. 2009). Interstitial lung disease was more common among male patients and was not associated with age or tumour stage (Chiyo et al. 2003; Miyazaki et al. 2009). Compared with patients without ILD, patients with ILD had significantly higher pulmonary complications (Chiyo et al. 2003).

Besides, the prevalence of self-reported depression in the UK has been reported in 33% of lung cancer patients and 21% of NSCLC patients during 3 studies over 3 years (Hopwood and Stephens 2000).

Module SII – Nonclinical Part of the Safety Specification

SII.1 Toxicity

Key toxicity findings from nonclinical studies include:

- Gastrointestinal (GI) toxicity: watery, mucoid or soft faeces as well as enteropathy throughout the GI tract in dogs treated with pemetrexed. Gastrointestinal toxicity is an established clinically relevant adverse effect of pemetrexed.
- Haematotoxicity: decreases in neutrophil, platelet, reticulocyte, and lymphocyte counts, as well as bone marrow hypocellularity in dogs treated with pemetrexed. Haematotoxicity was the dose-limiting toxicity in dogs and was reversible with interruption of treatment. Haematotoxicity is an established clinically relevant adverse effect of pemetrexed.
- Testicular toxicity: testicular degeneration consisting of tubules with necrotic spermatocytes. Based on nonclinical findings, administration of pemetrexed poses a potential risk to male reproductive organs. Testicular toxicity is expected for many anticancer drugs.
- Reproductive and developmental toxicity: Decreased foetal weight, incomplete ossification of some skeletal structures and cleft palate were observed in pregnant mice treated with pemetrexed. Based on nonclinical findings and reported literature findings with folate antagonists, administration of pemetrexed to patients poses a potential risk to embryo-foetal development.
- Skin lesions: redness, desquamation, scabbing, exudate, and blistering were observed in repeat-dose studies in dogs. Skin lesions are established clinically adverse findings with treatment of pemetrexed. The skin reaction seen in nonclinical studies and in patients is similar to that seen with other antifolate drugs.
- Mechanism for drug interaction: Pemetrexed is primarily eliminated unchanged renally as a result of glomerular filtration and tubular secretion. In vitro studies indicate that pemetrexed is actively secreted by organic anion transporter. Pemetrexed should not be administered when creatinine clearance (CrCl) is <45 mL/min. Concomitant administration of nephrotoxic drugs and/or substances that are tubularly-secreted could result in the delayed clearance of pemetrexed. Because both pemetrexed and nonsteroidal anti-inflammatory drugs (NSAIDs) are eliminated renally, NSAIDs could cause a slowing of pemetrexed elimination. Caution should be used when administering NSAIDs to patients with mild to moderate renal insufficiency (CrCl of 45 to 79 mL/min).

SII.2 Safety Pharmacology

Key safety pharmacology findings from nonclinical studies include:

- Mild effects on renal and cardiovascular function and alterations in pain sensitivity were observed in dogs at doses in excess of the proposed clinical dose (500 mg/m^2). None of these effects are expected to substantively influence the clinical use of pemetrexed.

Module SIII - Clinical Trial Exposure

Exposure data presented in this section apply to both ALIMTA and Pemetrexed Lilly.

Table SIII.1. Duration of Exposure

Total Patient Population		
Duration of Exposure[a]	**Persons**	**Total Cycles**
Up to 3 weeks	662	662
3 to 6 weeks	1179	2378
9 to 12 weeks	2300	8520
15 to 18 weeks	2221	12,951
21 to 24 weeks	469	3595
27 to 30 weeks	230	2186
>30 weeks	374	6239

[a] All studies included in this table administered pemetrexed on Day 1 of a 21-day cycle.

Table SIII.2. Duration of Exposure (Malignant Pleural Mesothelioma)

Malignant Pleural Mesothelioma		
Duration of Exposure[a]	**Persons**	**Person-Time**
Randomised Trials (JMCH, JMEW)		
Up to 3 weeks	33	33
3 to 6 weeks	61	122
9 to 12 weeks	54	195
15 to 18 weeks	144	841
21 to 24 weeks	45	352
27 to 30 weeks	5	49
>30 weeks	5	80
All Trials (JMAU, JMCH, JMDR, JMEW, JMFE, JMFL)		
Up to 3 weeks	304	304
3 to 6 weeks	434	868
9 to 12 weeks	958	3358
15 to 18 weeks	1353	7873
21 to 24 weeks	321	2471
27 to 30 weeks	162	1531
>30 weeks	162	2442

[a] All studies included in this table administered pemetrexed on Day 1 of a 21-day cycle.

Table SIII.3. Duration of Exposure (First-Line Non-Small Cell Lung Cancer)

First-Line NSCLC		
Duration of Exposure[a]	**Persons**	**Person-Time**
Randomised Trials (JMEK, JMEM, JMDB, JMIL)		
Up to 3 weeks	108	108
3 to 6 weeks	174	348
9 to 12 weeks	248	931
15 to 18 weeks	583	3421
21 to 24 weeks	19	147
27 to 30 weeks	0	0
>30 weeks	0	0
All Trials (JMAL, JMBZ, JMCD, JMAY, S124, S114, JMEK, JMEM, JMEZ, JMDB, JMIL)		
Up to 3 weeks	243	243
3 to 6 weeks	368	756
9 to 12 weeks	1086	4200
15 to 18 weeks	651	3814
21 to 24 weeks	40	310
27 to 30 weeks	4	38
>30 weeks	11	144

Abbreviation: NSCLC = non-small cell lung cancer.

[a] All studies included in this table administered pemetrexed on Day 1 of a 21-day cycle.

Table SIII.4. Duration of Exposure (Second-Line Non-Small Cell Lung Cancer)

Second-Line NSCLC		
Duration of Exposure[a]	**Patients**	**Total Cycles**
Randomised Trials (JMBQ, JMEI, JMID)		
Up to 3 weeks	37	37
3 to 6 weeks	129	258
9 to 12 weeks	74	274
15 to 18 weeks	62	361
21 to 24 weeks	36	275
27 to 30 weeks	10	95
>30 weeks	26	388
All Trials (JMBQ, JMBR, JMEI, JMIC, JMID)		
Up to 3 weeks	55	55
3 to 6 weeks	169	338
9 to 12 weeks	97	358
15 to 18 weeks	83	484
21 to 24 weeks	39	290
27 to 30 weeks	11	105
>30 weeks	34	495

Abbreviation: NSCLC = non-small cell lung cancer.

[a] All studies included in this table administered pemetrexed on Day 1 of a 21-day cycle.

Table SIII.5. Duration of Exposure (Maintenance Non-Small Cell Lung Cancer)

Maintenance NSCLC		
Duration of Exposure[a]	**Patients**	**Total Cycles**
Randomised Trials (JMEN, S124, S114)		
Up to 3 weeks	54	54
3 to 6 weeks	202	404
9 to 12 weeks	153	581
15 to 18 weeks	124	723
21 to 24 weeks	67	510
27 to 30 weeks	53	512
>30 weeks	166	3147

Abbreviation: NSCLC = non-small cell lung cancer.

[a] All studies included in this table administered pemetrexed on Day 1 of a 21-day cycle.

Table SIII.6. Duration of Exposure (Malignant Pleural Mesothelioma and Non-Small Cell Lung Cancer in Patients with Third-Space Fluid)

MPM and NSCLC (Patients with Third-Space Fluid)		
Duration of Exposure[a]	**Patients**	**Total Cycles**
Randomised Trials (JMHX)		
Up to 3 weeks	6	6
3 to 6 weeks	6	12
9 to 12 weeks	6	23
15 to 18 weeks	10	57
21 to 24 weeks	2	14
27 to 30 weeks	0	0
>30 weeks	1	11

Abbreviations: MPM = malignant pleural mesothelioma; NSCLC = non-small cell lung cancer.

[a] Study JMHX administered pemetrexed on Day 1 of a 21-day cycle.

Table SIII.7. Age Group and Gender

Indication/Age Group	Patients		Total Cycles	
	Male	Female	Male	Female
Malignant Pleural Mesothelioma				
Randomised Trials (JMCH, JMEW)				
18-65	192	55	951	275
>65	86	14	386	60
All Trials (JMAU, JMCH, JMDR, JMEW, JMFE, JMFL)				
18-65	1605	467	8226	2607
>65	1350	266	6619	1360
First-Line NSCLC				
Randomised Trials (JMEK, JMEM, JMDB, JMIL)				
18-65	445	229	1980	1056
>65	342	114	1364	488
All Trials (JMAL, JMBZ, JMCD, JMAY, S124, S114, JMEK, JMEM, JMEZ, JMDB, JMIL)				
18-65	966	560	3818	2262
>65	638	314	2615	1291
Second-Line NSCLC				
Randomised Trials (JMBQ, JMEI, JMID)				
18-65	183	94	789	477
>65	76	21	315	107
All Trials (JMBQ, JMBR, JMEI, JMIC, JMID)				
18-65	231	124	968	613
>65	104	29	412	140
Maintenance NSCLC				
Randomised Trials (JMEN, S124, S114)				
18-65	351	200	2488	1591
>65	187	81	1163	689

Abbreviation: NSCLC = non-small cell lung cancer.

Table SIII.8. Exposure by Dose and Duration

Indication/Dose of Exposure	Patients	Total Cycles
Malignant Pleural Mesothelioma		
Randomised Trials (JMCH, JMEW)		
400 mg/m^2	27	132
500 mg/m^2	320	1540
All Trials (JMAU, JMCH, JMDR, JMEW, JMFE, JMFL)		
400 mg/m^2	82	423
500 mg/m^2	3571	18,222
600 mg/m^2	7	34
First-Line NSCLC		
Randomised Trials (JMEK, JMEM, JMDB, JMIL)		
400 mg/m^2	13	47
500 mg/m^2	1116	4844
600 mg/m^2	2	4
All Trials (JMAL, JMBZ, JMCD, JMAY, S124, S114, JMEK, JMEM, JMEZ, JMDB, JMIL)		
400 mg/m^2	18	76
500 mg/m^2	2341	9117
600 mg/m^2	52	206
Second-Line NSCLC		
Randomised Trials (JMBQ, JMEI, JMID)		
400 mg/m^2	0	0
500 mg/m^2	371	1676
All Trials (JMBQ, JMBR, JMEI, JMIC, JMID)		
400 mg/m^2	1	1
500 mg/m^2	484	2120
Maintenance NSCLC		
Randomised Trials (JMEN, S124, S114)		
500 mg/m^2	819	5931

Abbreviation: NSCLC = non-small cell lung cancer.

Table SIII.9. Ethnic and Racial Origin

Indication/Origin	Patients	Total Cycles
Malignant Pleural Mesothelioma		
Randomised Trials (JMCH, JMEW)		
Caucasian	313	1527
African Descent	2	7
Asian	10	48
Hispanic	19	79
Other	3	11
All Trials (JMAU, JMCH, JMDR, JMEW, JMFE, JMFL)		
Caucasian	3629	18,555
African Descent	8	26
Asian	16	70
Hispanic	23	102
Other	12	59
First-Line NSCLC		
Randomised Trials (JMEK, JMEM, JMDB, JMIL)		
Caucasian	820	3456
African Descent	18	78
Asian	267	1245
Hispanic	25	105
Other	2	12
All Trials (JMAL, JMBZ, JMCD, JMAY, S124, S114, JMEK, JMEM, JMEZ, JMDB, JMIL)		
Caucasian	1967	7458
African Descent	39	181
Asian	330	1456
Hispanic	29	119
Other	15	59
Multiple	2	7
Second-Line NSCLC		
Randomised Trials (JMBQ, JMEI, JMID)		
Caucasian	191	836
African Descent	6	39
Asian	169	781
Hispanic	4	19
Other	4	13
All Trials (JMBQ, JMBR, JMEI, JMIC, JMID)		
Caucasian	272	1085
African Descent	6	39
Asian	202	977
Hispanic	4	19
Other	4	13
Maintenance NSCLC		
Randomised Trials (JMEN, S124, S114)		
Caucasian	638	4707
African Descent	12	102
Asian	156	1068
Hispanic	13	54
Other	0	0

Abbreviation: NSCLC = non-small cell lung cancer.

Module SIV - Populations Not Studied in Clinical Trials

SIV.1 Exclusion Criteria in Pivotal Clinical Studies Within the Development Programme

In the pemetrexed clinical development programme, the primary population studied were patients with advanced nonsquamous NSCLC. All studies had common key exclusion criteria, most of which were intended to ensure safety and minimise risk in a research setting. Specific and relevant exclusion criteria that are important to pemetrexed are addressed below.

Criterion: Patients with renal impairment were excluded.

Reason for exclusion: Pemetrexed is primarily eliminated unchanged renally as a result of glomerular filtration and tubular secretion. In vitro studies indicate that pemetrexed is actively secreted by organic anion transporter 3. Pemetrexed should not be administered when CrCl is < 45 mL/min.

Is it considered to be included as missing information? No

Criterion: Patients who are unable to interrupt aspirin or other nonsteroidal anti-inflammatory drugs (other than an aspirin dose ≤ 1.3 grams per day) for a 5-day period (8-day period for long-acting agents, such as piroxicam) were excluded.

Reason for exclusion: Pemetrexed is primarily eliminated unchanged renally as a result of glomerular filtration and tubular secretion. In vitro studies indicate that pemetrexed is actively secreted by organic anion transporter 3. Concomitant administration of nephrotoxic drugs and/or substances that are tubularly-secreted could result in the delayed clearance of pemetrexed. Because both pemetrexed and NSAIDs are eliminated renally, NSAIDs could cause a slowing of pemetrexed elimination.

Is it considered to be included as missing information? No

SIV.2 Limitations to Detect Adverse Reactions in Clinical Trial Development Programmes

The clinical development programme is unlikely to detect certain types of adverse reactions such as rare adverse reactions, adverse reactions with a long latency, or those caused by prolonged and/or cumulative exposure.

SIV.3 Limitations in Respect to Populations Typically Under-Represented in Clinical Trial Development Programmes

Table SIV.1. Exposure of Special Populations Included or Not in Clinical Trial Development Programmes

Type of special population	Exposure
Pregnant women Breastfeeding women	Four cases of pregnancy have been reported (source of reports: 2 spontaneous reports, 1 report from an investigator-initiated trial, and 1 report from a clinical trial): 1. A [redacted] year-old female patient participating in a study of pemetrexed in combination with cisplatin for neoadjuvant treatment of MPM received the last dose of study drug on [redacted] 2006. The date of first dose and length of exposure were not reported. The patient's last menstrual cycle was reported as [redacted] 2007. No medical history or laboratory data were provided, and the outcome of this case is unknown. 2. A [redacted]-year-old male patient with MPM received the first dose of PC on [redacted] 2005. His wife became pregnant on [redacted] 2005, 13 days after initiation of treatment. A normal male baby weighing 3.4 kg was born full term on [redacted] 2006. 3. A [redacted]-year-old female patient received the first dose of PC for treatment of NSCLC on [redacted] 2009. At baseline (on [redacted] 2009), the patient had a BHCG level of 19 IU/I (value within 5 to 50 IU/I, corresponding to the first week of pregnancy). The patient's last menstrual cycle was reported as having occurred several years ago. On [redacted] 2009, the patient's BHCG was 9 IU/I, and the patient was assessed as having experienced a spontaneous abortion. The event of spontaneous abortion was assessed by the investigator as related to study drugs. 4. A [redacted]-year-old female [redacted] accidently inhaled some pemetrexed powder from a broken vial while 4.5 months pregnant. The outcome of this event is unknown.
Patients with other relevant comorbidities	Not included in the clinical development programme.

Patients with hepatic impairment	Pemetrexed is not extensively metabolised by the liver. However, patients with hepatic impairment such as bilirubin >1.5 times the ULN or transaminase >3 times the ULN (hepatic metastases absent) or >5 times the ULN (hepatic metastases present) have not been specifically studied. A small number of case reports in patients with pre-existing hepatic impairment have been reported during postmarketing experience. Review of AE reports with identifiable history of hepatic impairment, entered in the Lilly safety database, is conducted periodically. Review of cases in this population of patients has not identified any new safety issues.
Patients with renal impairment	In clinical studies, patients with CrCl of at least 45 mL/min required no dose adjustments other than those recommended for all patients. Insufficient numbers of patients with CrCl below 45 mL/min have been treated to make dosage recommendations for this group of patients. Therefore, patients whose CrCl is <45 mL/min (using the standard Cockcroft and Gault [1976] formula or glomerular filtration rate measured by Tc99m-DPTA serum clearance method) should not receive pemetrexed. A small number of case reports in patients with pre-existing renal impairment have been reported during postmarketing experience. Review of AE reports with identifiable history of renal impairment, entered in the Lilly safety database, is conducted periodically. Review of cases in this population of patients has not identified any new safety issues.
Patients with cardiovascular impairment	Not included in the clinical development programme.
Immunocompromised patients	Not included in the clinical development programme.
Patients with a disease severity different from inclusion criteria in clinical trials	Not included in the clinical development programme.
Population with relevant different ethnic origin	No effect of age on the PK of pemetrexed was observed over a range of 26 to 80 years. The PK of pemetrexed was not different in male and female patients. The PK of pemetrexed was similar in Caucasians and patients of African descent. No differences in pemetrexed PK were observed between Western and Japanese patients (Nakagawa et al. 2006; Latz et al. 2009).
Subpopulations carrying relevant genetic polymorphisms	Not included in the clinical development programme.

Children	Two studies to assess the efficacy and safety of pemetrexed in paediatric patients have been completed: a Phase 1 PK study (ADVL0311 [H3E-US-JMFC (JMFC)]) and a Phase 2 study in children with recurrent malignancies (H3E-MC-JMHW [JMHW]). In Study JMFC, pemetrexed was given as a single agent every 3 weeks to paediatric patients. The maximum tolerated dose was 1910 mg/m2; the main dose-limiting toxicity, as with adults, was neutropoenia; and the PK was similar to those reported for adults. Study JMHW was a nonrandomised, open-label, Phase 2 study in children with recurrent malignancies. Seventy-two patients (median age, 11.5 years) were enrolled into the study. Pemetrexed 1910 mg/m^2 (or 60 mg/kg if the patient was <12 months old) was administered as a 10-minute IV infusion once every 21 days. Five patients had a best overall response of SD, and no patients had a partial response or complete response. The most common toxicities seen regardless of causality, including all-grade toxicities and Grade 3/4 toxicities, were haematologic. The most common all-grade nonhematologic toxicities were liver function abnormalities (predominantly alanine transaminase elevation), fatigue, and nausea. The frequency of haematologic and transaminase elevation was higher than that seen in adult studies, which may at least in part be due to the higher dose of pemetrexed used in this study. There were no deaths in Study JMHW considered as possibly related to study treatment. Pemetrexed is not recommended for use in children.
Elderly	In clinical trials, there has been no indication that patients 65 years of age or older are at increased risk of experiencing clinically relevant AEs compared with patients younger than age 65. No dose reductions other than those recommended for all patients are necessary.

Subpopulations by Histologic Subtype of NSCLC	Information currently available from 4 studies (Studies H3E-MC-JMEI, H3E-MC-JMDB, H3E- MC-JMEN, and H3E-JE-NS01) of nearly 1800 NSCLC patients treated with pemetrexed indicates that the nonsquamous patient population consistently benefits from pemetrexed treatment. In addition, none of these studies has shown evidence to suggest that the safety profile of pemetrexed varies by histologic subtype. The similarity observed across these 4 studies suggest that these results are reproducible and clinically important to patients and physicians in assessing the benefits and risks of pemetrexed treatment. The results of these studies provide supportive evidence for the efficacy of pemetrexed in patients with nonsquamous NSCLC.

Abbreviations: AE = adverse event; BHCG = beta human chorionic gonadotropin; CrCl = creatinine clearance; IV = intravenous; MPM = malignant pleural mesothelioma; NSCLC = non-small cell lung cancer; PC = pemetrexed and cisplatin; PK = pharmacokinetics; SD = stable disease; ULN = upper limit of normal.

Module SV - Post-Authorisation Experience

Post-authorisation data presented in this section apply to both ALIMTA and Pemetrexed Lilly.

SV.1.1 Method Used to Calculate Exposure

Worldwide sales of pemetrexed have been collected for the cumulative time period through 31 January 2019. The patient exposure methodology uses sales data with the following assumptions to calculate an estimate of patient exposure:

- An estimate of pemetrexed patient exposure is calculated based on a typical single adult dosage of 500 mg/m^2, an average body surface area of 1.73 m^2.
- Total dose per patient is then calculated by multiplying the average dose per cycle by an estimate for average number of cycles per patient (n = 6).
- Total sale of pemetrexed is then divided by total dose per patient to calculate an estimate of total patients exposed.

SV.1.2 Exposure

As of 31 January 2019, approximately 1,550,000 patients have been exposed to pemetrexed worldwide since 04 February 2004.

Table SV.1. Exposure Table by Region

Country/Region	Region				
	Europe	Japan	United States	Other Countries	Global Totals[a]
Overall	559,000	[redacted]	[redacted]	309,000	1,550,000

[a] Totals may not sum due to independent rounding.

Module SVI - Additional EU Requirements for the Safety Specification

SVI.1 - Potential for Misuse for Illegal Purposes

Pemetrexed is administered only by healthcare professionals and is a cytotoxic drug. Therefore, the potential for misuse for illegal purposes is negligible.

Module SVII - Identified and Potential Risks

SVII.1 Identification of Safety Concerns in the Initial RMP Submission

SVII.1.1 Risks Not Considered Important for Inclusion in the List of Safety Concerns in the RMP

Not applicable as this is not an initial RMP.

SVII.1.2 Risks Considered Important for Inclusion in the List of Safety Concerns in the RMP

Not applicable as this is not an initial RMP.

SVII.2 New Safety Concerns and Reclassification with a Submission of an Updated RMP

With the transition of the previous EU RMP for pemetrexed to that determined by GVP Module V (Rev 2), the MAH was requested by Pharmacovigilance Risk Assessment Committee during the PSUSA procedure number EMEA/H/C/PSUSA/00002330/201802 to delete the following safety concerns previously classified as important identified risks:

- Noncompliance with folic acid and vitamin B_{12} regimens manifested mainly as haematological and gastrointestinal toxicities
- Bone marrow suppression
- Gastrointestinal disorders
- Renal disorders
- Sepsis
- Bullous skin reaction including Stevens-Johnson syndrome and toxic epidermal necrolysis
- Interstitial pneumonitis
- Radiation pneumonitis
- Radiation recall

General consideration for justification of removal:

These safety concerns are already sufficiently characterised, have no additional pharmacovigilance activities or risk minimisation measures, and information in each Summary of Medicinal Product Characteristics (SmPC) is sufficient to reduce these risks.

SVII.3 Details of Important Identified Risks, Important Potential Risks, and Missing Information

SVII.3.1 Presentation of Important Identified Risks and Important Potential Risks

Not applicable.

SVII.3.2 Presentation of the Missing Information

Not applicable.

Module SVIII - Summary of the Safety Concerns

Table SVIII.1. Summary of Safety Concerns

Summary of safety concerns	
Important identified risks	None
Important potential risks	None
Missing information	None

Part III: Pharmacovigilance Plan (Including Post-Authorisation Safety Studies)

III.1 Routine Pharmacovigilance Activities

Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:

Routine follow-up will be conducted on events of special interest.

Other forms of routine pharmacovigilance activities for safety concerns:

Not applicable.

III.2 Additional Pharmacovigilance Activities

None.

III.3 Summary Table of Additional Pharmacovigilance Activities

None.

Part IV: Plans for Post-Authorisation Efficacy Studies

None.

Part V: Risk Minimisation Measures (Including Evaluation of the Effectiveness of Risk Minimisation Activities)

Risk Minimisation Plan

V.1 Routine Risk Minimisation Measures

The safety information in the proposed Product Information is aligned to the reference medicinal product.

V.2 Additional Risk Minimisation Measures

Routine risk minimisation activities as described in Part V.1 are sufficient to manage the safety concerns of the medicinal product.

V.3 Summary of Risk Minimisation Measures

The safety information in the proposed Product Information is aligned to the reference medicinal product.

Part VI: Summary of the Risk Management Plan

Summary of Risk Management Plan for ALIMTA (pemetrexed)

This is a summary of the RMP for ALIMTA. The RMP details important risks of ALIMTA and how more information will be obtained about ALIMTA's risks and uncertainties (missing information).

ALIMTA's SmPC and its package leaflet give essential information to healthcare professionals and patients on how ALIMTA should be used.

This summary of the RMP for ALIMTA should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all of which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of ALIMTA's RMP.

I - The Medicine and What It is Used for

ALIMTA is authorised for malignant pleural mesothelioma and NSCLC (see SmPC for the full indication). It contains pemetrexed as the active substance and it is given by IV infusion.

Further information about the evaluation of ALIMTA's benefits can be found in ALIMTA's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage.

https://www.ema.europa.eu/en/medicines/human/EPAR/alimta

II - Risks Associated with the Medicine and Activities to Minimise or Further Characterise the Risks

Important risks of ALIMTA, together with measures to minimise such risks and the proposed studies for learning more about ALIMTA's risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status — the way a medicine is supplied to the patient (e.g., with or without prescription) can help to minimise its risks.

Together, these measures constitute *routine risk minimisation* measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed including Periodic Safety Update Report assessment so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

II.A List of Important Risks and Missing Information

Important risks of ALIMTA are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of ALIMTA. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g., on the long-term use of the medicine).

List of important risks and missing information	
Important identified risks	None
Important potential risks	None
Missing information	None

II.B Summary of Important Risks

The safety information in the proposed Product Information is aligned to the reference medicinal product.

II.C Post-Authorisation Development Plan

II.C.1 Studies that are Conditions of the Marketing Authorisation

There are no studies that are conditions of the marketing authorisation or specific obligation of ALIMTA.

II.C.2 Other Studies in Post-Authorisation Development Plan

There are no studies required for ALIMTA.

Summary of Risk Management Plan for Pemetrexed Lilly (pemetrexed)

This is a summary of the RMP for Pemetrexed Lilly. The RMP details important risks of Pemetrexed Lilly and how more information will be obtained about Pemetrexed Lilly's risks and uncertainties (missing information).

Pemetrexed Lilly's SmPC and its package leaflet give essential information to healthcare professionals and patients on how Pemetrexed Lilly should be used.

This summary of the RMP for Pemetrexed Lilly should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all of which is part of the EPAR.

Important new concerns or changes to the current ones will be included in updates of Pemetrexed Lilly's RMP.

I - The Medicine and What It is Used for

Pemetrexed Lilly is authorised for malignant pleural mesothelioma and NSCLC (see SmPC for the full indication). It contains pemetrexed as the active substance and it is given by IV infusion.

Further information about the evaluation of Pemetrexed Lilly's benefits can be found in Pemetrexed Lilly's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage.

https://www.ema.europa.eu/en/medicines/human/EPAR/pemetrexed-lilly

II - Risks Associated with the Medicine and Activities to Minimise or Further Characterise the Risks

Important risks of Lilly Pemetrexed, together with measures to minimise such risks and the proposed studies for learning more about Pemetrexed Lilly's risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status — the way a medicine is supplied to the patient (e.g., with or without prescription) can help to minimise its risks.

Together, these measures constitute *routine risk minimisation* measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed including Periodic Safety Update Report assessment so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

II.A List of Important Risks and Missing Information

Important risks of Pemetrexed Lilly are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Pemetrexed Lilly. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g., on the long-term use of the medicine).

List of important risks and missing information	
Important identified risks	None
Important potential risks	None
Missing information	None

II.B Summary of Important Risks

The safety information in the proposed Product Information is aligned to the reference medicinal product.

II.C Post-Authorisation Development Plan

II.C.1 Studies that are Conditions of the Marketing Authorisation

There are no studies that are conditions of the marketing authorisation or specific obligation of Pemetrexed Lilly.

II.C.2 Other Studies in Post-Authorisation Development Plan

There are no studies required for Pemetrexed Lilly.

Part VII: Annexes

Annex **Page**

Annex 4 - Specific Adverse Drug Reaction Follow-Up Forms

Not applicable.

Annex 6 - Details of Proposed Additional Risk Minimisation Activities (If Applicable)

Not applicable.