EU Risk Management Plan

for

Jylamvo 2 mg/ml oral solution (methotrexate)

RMP version to be assessed as part of this application:

RMP Version number: 4.3

Data lock point for this RMP: 01 April 2019

Date of final sign off: 01 October 2019

Rationale for submitting an updated RMP: following a request from the Referral under Article 31 of Directive 2001/83/EC resulting from pharmacovigilance data for methotrexate containing medicinal products: Jylamvo 2 mg/ml oral solution (procedure number: EMEA/H/A-31/1463/C/3756/0002).

Summary of significant changes in this RMP: the format of the RMP has been updated according to the requirements from GVP Module V Revision 2. List of all parts and modules including version number and date of approval are tabulated in the table below. High level comment on the rationale for creating the update is included for significant changes to each module:

Part	Date of approval	Version	Significant changes
Part I: Product(s) Overview	12 September 2019	4.2	Updated with the latest information.
Part II: Safety specification			
Module SI - Epidemiology of the indication(s) and target population(s)	01 July 2016	2.0	
Module SII - Non-clinical part of the safety specification	12 September 2019	4.2	New format included for the first time.
Module SIII - Clinical trial exposure	01 July 2016	2.0	
Module SIV - Populations not studied in clinical trials	12 September 2019	4.2	New format included for the first time.
Module SV - Post-authorisation experience	12 September 2019	4.2	New format included for the first time.
Module SVI - Additional EU requirements for the safety specification	12 September 2019	4.2	New format included for the first time.
Module SVII - Identified and potential risks	01 October 2019	4.3	Updated with the latest information.
Module SVIII - Summary of the safety concerns	12 September 2019	4.2	Updated with the latest information.
Part III: Pharmacovigilance Plan (including post-authorisation safety studies)	12 September 2019	4.2	New format included for the first time.
Part IV: Plans for post-authorisation efficacy studies	-		Not applicable.

Part	Date of approval	Version	Significant changes
Part V: Risk minimisation measures (including evaluation of the effectiveness of risk minimisation activities)	12 September 2019	4.2	Updated with the latest information.
Part VI: Summary of the risk management plan	12 September 2019	4.2	Updated with the latest information.
Part VII: Annexes	12 September 2019	4.2	New format included for the first time.
Annex 1 – EudraVigilance Interface	12 September 2019	4.2	New format included for the first time.
Annex 2 – Tabulated summary of planned, ongoing, and completed pharmacovigilance study programme	12 September 2019	4.2	New format included for the first time.
Annex 3 - Protocols for proposed, on-going and completed studies in the pharmacovigilance plan	12 September 2019	4.2	New format included for the first time.
Annex 4 - Specific adverse drug reaction follow-up forms	12 September 2019	4.2	Updated with the latest information.
Annex 5 - Protocols for proposed and on-going studies in RMP part IV	12 September 2019	4.2	New format included for the first time.
Annex 6 - Details of proposed additional risk minimisation activities (if applicable)	01 October 2019	4.3	Updated with the latest information.
Annex 7 - Other supporting data (including referenced material)	12 September 2019	4.2	Updated with the latest information.
ANNEX 8 - Summary of changes to the risk management plan over time	12 September 2019	4.2	Updated with the latest information.

Other RMP versions under evaluation: Not applicable.

Details of the currently approved RMP

Version number: 4.0

Approved with procedure: EMEA/H/C/0003756/0000

Date of approval (opinion date): 29 March 2017

QPPV name: Dr. Olaf Schickling

QPPV signature: 

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List of Abbreviations

AAL	Acute Lymphoblastic Leukaemia
ACR	American College of Rheumatology
ADR	Adverse Drug Reaction
ATC	Anatomical Therapeutic Chemical classification
BSA	Body Surface Area
CAPA	Corrective and Preventative Action
CI	Confidence Interval
CNS	Central Nervous System
DIP	Distal Interphalangeal Predominant
DMARD	Disease-Modifying Antirheumatic Drug
DNA	Deoxyribonucleic Acid
EEA	European Economic Area
EM	Educational Material
EPAR	European Public Assessment Report
EU	European Union
FDA	Food and Drug Administration
GBD	Global Burden of Disease
HLGT	High Level Group Term (MedDRA)
HLT	High Level Term (MedDRA)
HRQOL	Health-Related Quality of Life
IHME	Institute for Health Metrics and Evaluation
JIA	Juvenile Idiopathic Arthritis
MAA	Marketing Authorisation Application
MAH	Marketing Authorisation Holder
MedDRA	Medical Dictionary for Regulatory Activities
ME	Medication Error
NCA	National Competent Authority
NSAID	Non-Steroidal Anti-Inflammatory Drug
PL	Package Leaflet
PML	Progressive Multifocal Leukoencephalopathy
PRAC	Pharmacovigilance Risk Assessment Committee

PsA	Psoriatic Arthritis
PSUR	Periodic Safety Update Report
PT	Preferred Term (MedDRA)
PUVA	Psoralen and Ultraviolet A Radiation
RA	Rheumatoid Arthritis
RMP	Risk Management Plan
ROS	Reactive Oxygen Species
RSI	Reference Safety Information
SmPC	Summary of Product Characteristics
SMQ	Standardised MedDRA Query (MedDRA)
QPPV	Qualified Person Responsible for Pharmacovigilance
TNF-α	Tumour Necrosis Factor α
UK	United Kingdom
USA	United States of America

Part I: Product(s) Overview

Table Part I.1 – Product(s) Overview

Active substance(s) (INN or common name)	Methotrexate 2 mg/ml oral solution.
Pharmacotherapeutic group(s) (ATC Code)	Pharmacotherapeutic group: Antineoplastic and immunomodulating agents; antineoplastic agents; antimetabolites; folic acid analogues. ATC code: L01BA01.
Marketing Authorisation Applicant	Therakind (Europe) Ltd., Ireland.
Medicinal products to which this RMP refers	1.
Invented name(s) in the European Economic Area (EEA)	Jylamvo 2 mg/ml oral solution.
Marketing authorisation procedure	Centralised procedure.
Brief description of the product	Chemical class Antineoplastic and immunomodulating agent.
	Summary of mode of action Methotrexate is a folic acid antagonist that, as an antimetabolite, belongs to the class of cytotoxic active substances. It acts by competitive inhibition of the enzyme dihydrofolate reductase and thus inhibits Deoxyribonucleic Acid (DNA) synthesis. It has not yet been possible to date to clarify whether the efficacy of methotrexate in the management of psoriasis, psoriatic arthritis and chronic polyarthritis is due either to an anti-inflammatory or immunosuppressive effect, or to what extent a methotrexate induced increase in extracellular adenosine concentration at inflamed sites contributes to this effect. Highly proliferating tissue such as malignant cells, bone marrow, foetal cells, skin epithelium and mucosa is generally more sensitive to this effect of methotrexate. Cell proliferation is usually greater in malignant tumours than in normal tissue and methotrexate can therefore exert a sustained effect on malignant growth without causing irreversible damage to normal tissue. In psoriasis, cell proliferation of the epithelium is markedly increased compared with normal skin. This difference in cell proliferation rate is the starting point for the use of methotrexate in particularly severe, generalised, treatment resistant psoriasis and psoriatic arthritis.

	Important information about its composition None.
Hyperlink to the Product Information	Refer to the Product Information.
Indication(s) in the EEA	Current: Jylamvo is for use in the following indications: In rheumatological and dermatological diseases: • Active rheumatoid arthritis in adult patients. • Polyarthritic forms of active, severe Juvenile Idiopathic Arthritis (JIA) in adolescents and children aged 3 years and over when the response to non-steroidal anti-inflammatory drugs has been inadequate. • Severe, treatment refractory, disabling psoriasis which does not respond sufficiently to other forms of treatment such as phototherapy, Psoralen and Ultraviolet A Radiation (PUVA) therapy and retinoids, and severe psoriatic arthritis in adult patients. In oncology: • Maintenance treatment of Acute Lymphoblastic Leukaemia (ALL) in adults, adolescents and children aged 3 years and over.
	Proposed: Not applicable.
Dosage in the EEA	Current: Methotrexate should only be prescribed by physicians with expertise in the use of methotrexate and a full understanding of the risks of methotrexate therapy. Rheumatological and dermatological diseases: **Important warning about the dosage of Jylamvo (methotrexate)** In the treatment of rheumatological or dermatological diseases, Jylamvo (methotrexate) **must only be taken once a week**. Dosage errors in the use of Jylamvo (methotrexate) can result in serious adverse reactions, including death. Please read this section of the summary of product characteristics very carefully. The prescriber should ensure that patients or their carers will be able to comply with the once weekly regimen. The prescriber should specify the day of intake on the prescription. The dose and duration of treatment are determined individually on the basis of the patient's clinical picture and the tolerability of methotrexate. Treatment of active rheumatoid arthritis, severe JIA, severe psoriasis and severe psoriatic arthritis represents a long-term treatment. A weekly dose of 25 mg (12.5 ml) should not be exceeded. Doses exceeding 20 mg (10 ml)/week can be associated with a substantial

	increase in toxicity, especially bone marrow depression. Concurrent folic acid supplementation of 5 mg twice weekly (except on the day of administration) is indicated additionally. Adult patients with rheumatoid arthritis: The recommended initial dose is 7.5 mg (3.75 ml) methotrexate once weekly. Depending on the individual activity of the disease and tolerability by the patient, the dose may be increased gradually by 2.5 mg (1.25 ml) per week. Response to treatment can be expected after approximately 4-8 weeks. After the desired treatment outcome is achieved, the dose should be reduced gradually to the lowest possible effective maintenance dose. Children and adolescents with polyarthritic forms of JIA: The recommended dose is 10-15 mg (5-7.5 ml)/m² Body Surface Area (BSA)/week. In therapy refractory cases the weekly dosage may be increased to 20 mg (10 ml)/m² BSA/week. However, an increased monitoring frequency is indicated if the dosage is increased. Adults with severe forms of psoriasis and adult patients with psoriatic arthritis: It is recommended that a test dose of 2.5-5 mg (1.25-2.5 ml) be administered one week prior to initiation of therapy, in order to detect early occurring adverse reactions. If, one week later, appropriate laboratory tests are normal, treatment may be initiated. The recommended initial dose is 7.5 mg (3.75 ml) methotrexate once weekly. The dose should be increased gradually but should not, in general, exceed a weekly dose of 25 mg of methotrexate. The usual dose is 10 mg-25 mg (5 ml-12.5 ml) taken once weekly. Doses exceeding 20 mg (10 ml) per week can be associated with significant increase in toxicity, especially bone marrow suppression. Response to treatment can generally be expected after approximately 4-8 weeks. After the desired treatment outcome is achieved, the dose should be reduced gradually to the lowest possible effective maintenance dose. Acute Lymphoblastic Leukaemia (ALL): Low dose methotrexate is used in the maintenance treatment of ALL in children aged 3 years and over, adolescents and adults within complex protocols in combination with other cytostatic medicinal products. Treatment should follow current therapy protocols. Common accepted single doses lie in the range of 20-40 mg (10-20 ml)/m² BSA. If methotrexate is administered in combination with chemotherapy regimens, the dosage should take into consideration any overlapping toxicity of the other medicinal product components. Higher dosages should be given parenterally.

	Paediatric population: Methotrexate should be used with caution in paediatric patients. Treatment should follow currently published therapy protocols for children. Doses are usually based on the patient's BSA and maintenance treatment represents a long term treatment.
	Proposed: Not applicable.
Pharmaceutical form(s) and strengths	Current: • Oral solution: 1 ml of solution contains 2 mg methotrexate
	Proposed: Not applicable.
Is/will the product be subject to additional monitoring in the EU?	No.

Part II: Safety specification

Part II: Module SI - Epidemiology of the indication(s) and target population(s)

Adult Rheumatoid Arthritis (RA)

Incidence and prevalence:

Estimating the incidence of RA is problematic due to the delay between patients experiencing symptoms and seeking medical help for these symptoms. This is a problem as the American College of Rheumatology (ACR) criteria depend on the time elapsed between symptom onset and assessment of RA criteria, and on how the criteria are applied. The use of different case definitions makes the estimates vary as widely as 25 to 115 per 100,000. The annual incidence rate of RA recorded in studies varies between 20 and 50 cases per 100,000 in Northern European countries but there are indications that it may be lower in Southern European countries. Studies of the incidence and prevalence of RA suggest variations between different populations even within the same country. Possible explanations include regional variation in behavioural factors, climate, environmental exposures, RA diagnosis, and genetic factors [Eumusc.net].

Data collected in the Global Burden of Disease project [IHME, 2013] showed that the annual incidence rate of RA for adults up to 99 years of age ranges from 22 cases per 100,000 in the United Kingdom (UK) to 35 per 100,000 in Finland. The standardised prevalence rates in studies for adults up to 99 years of age range from 0.31% in France [Guillemin, 2005] to 0.83% in the UK. The prevalence rates for females tend to be considerably higher than the rate for males [Eumusc.net]. Similar data have been released by the European Commission [European Commission].

Demographics of the population in the authorised indication – age, gender, racial and/or ethnic origin and risk factors for the disease:

The incidence of RA increases between 25 and 55 years of age, after which it plateaus until the age of 75 and then decreases. Like many other autoimmune diseases, RA occurs more commonly in females than in males, with a 2-3:1 ratio. Interestingly, studies of RA from some of the Latin American and African countries show an even greater predominance of disease in females compared to males, with ratios of 6-8:1. Given this preponderance of females, various theories have been proposed to explain the possible role of oestrogen in disease pathogenesis. Most of the theories centre on the role of oestrogens in enhancing the immune response. For example, some experimental studies have shown that oestrogen can stimulate production of Tumour Necrosis Factor α (TNF-α), a major cytokine in the pathogenesis of RA [Shah, 2015].

Regarding risk factors, it has been recognised for over 30 years that genetic factors contribute to the occurrence of RA as well as to its severity. The likelihood that a first-degree relative of a patient will share the diagnosis of RA is 2-10 times greater than in the general population. There remains, however, some uncertainty in the extent to which genetics plays a role in the causative mechanisms of RA. Although twin studies imply that genetic factors may explain up to 60% of the occurrence of RA, the more commonly stated estimate falls in the range of 10-25%.

In addition to genetic predisposition, a host of environmental factors have been implicated in the pathogenesis of RA. The most reproducible of these environmental links is cigarette smoking. Numerous cohort and case control studies have demonstrated that smoking confers a relative risk for developing RA of 1.5-3.5. In particular, women who smoke cigarettes have a nearly 2.5 times greater risk of RA, a risk that persists even 15 years after smoking cessation.

It has not been possible to directly implicate infection as a causative factor in RA [Shah, 2015].

The main existing treatment options:

Several developments during the past two decades have changed the therapeutic landscape in RA. They include (1) the emergence of methotrexate as the Disease-Modifying Antirheumatic Drug (DMARD) of first choice for the treatment of early RA; (2) the development of novel highly efficacious biologicals that can be used alone or in combination with methotrexate; and (3) the proven superiority of combination DMARD regimens over methotrexate alone [Shah, 2015].

Natural history of the indicated condition in the untreated population, including mortality and morbidity:

The natural history of RA is complex and affected by a number of factors including age of onset, gender, genotype, phenotype (i.e. extra-articular manifestations or variants of RA) and comorbid conditions, which make for a truly heterogeneous disease. There is no simple way to predict the clinical course. It is important to realise that as many as 10% of patients with inflammatory arthritis fulfilling ACR classification criteria for RA will undergo a spontaneous remission within 6 months (particularly seronegative patients). However, the vast majority of patients will exhibit a pattern of persistent and progressive disease activity that waxes and wanes in intensity over time. A minority of patients will show intermittent and recurrent explosive attacks of inflammatory arthritis interspersed with periods of disease quiescence. Finally, an aggressive form of RA may occur in an unfortunate few with inexorable progression of severe erosive joint disease [Shah, 2015].

The overall mortality rate in RA is two times greater than the general population. Median life expectancy is shortened by an average of 7 years for men and 3 years for women compared to control populations [Shah, 2015].

Important co-morbidities:

Co-morbidities may shorten the life span of patients with RA [Dougados, 2014]. This higher death rate appears to be the consequence of an increased prevalence of cardiovascular disease [van den Oever, 2013], a greater incidence of infections [Dougados, 2014], and the development of certain malignancies in patients with RA [Khan, 2013]. Also, osteoporotic fractures are more commonly observed in patients with RA and significantly affect the prognosis for functional decline. In addition, RA patients with more co-morbidities experience greater functional impairment [Dougados, 2014]. For instance, depression is highly prevalent in RA and associated with poorer RA outcomes [Matcham, 2013].

Active juvenile idiopathic arthritis

Incidence and prevalence:

Juvenile idiopathic arthritis (JIA) is one of the more common chronic diseases of childhood. Estimates for prevalence and incidence cover a wide range. With an annual incidence of 0.008-0.226 and a prevalence of 0.07-4.01/1,000 children JIA is less common than RA in adults but it is one of the most common systemic autoimmune diseases in children and adolescents [CPMP/EWP/422/04, 2006; Kahn, 2012].

Demographics of the population in the authorised indication – age, gender, racial and/or ethnic origin and risk factors for the disease:

Paediatric population. Children of all age groups may be affected although onset of disease during the first year of life is rare and is mostly seen in the "systemic" subtype [CPMP/EWP/422/04, 2006]. In some of the subgroups, girls predominate.

Regarding risk factors, JIA is a common autoimmune disease characterised by environmental influences along with several predisposing genes in the pathogenesis (see RA).

The main existing treatment options:

The goals of treatment for JIA include suppression of inflammation, achievement of remission, relief of pain, maintenance of function and doing so with minimal toxicity. Methotrexate is considered as the first-line, disease-modifying antirheumatic drug in JIA, especially as initial treatment for oligoarticular and polyarticular JIA if high disease activity and poor prognostic features are present also because of its ability to improve the Health-Related Quality Of Life (HRQOL) of children with JIA. [Gutierrez-Suarez, 2010; Beresford, 2011; Harris, 2013]

Other targeted treatments include the TNF-α inhibitors, interleukin-1 blockade, interleukin-6 blockade, selective co-stimulation modulators and selective B-cell blockade [Ruth, 2012]. The introduction of those newer biologic DMARDs has spawned optimism that treatment will increasingly lead to improved outcomes for JIA, but the evidence is insufficient to support superiority over methotrexate [Kemper, 2012].

Natural history of the indicated condition in the untreated population, including mortality and morbidity:

JIA often persists into adulthood and can result in significant long-term morbidity, including physical disability [Beukelman, 2012] and a significant increase in mortality in adults with a history of JIA compared to the general population [French, 2001]. For all children with JIA versus children without JIA, the Standardised Incidence Ratios (SIR) was 4.4 (95% confidence interval [95% CI] 1.8-9.0) for probable and highly probable malignancies. For those taking methotrexate without TNF inhibitor use, the SIR was 3.9 (95% CI 0.4-14). Following any use of TNF inhibitors, no probable or highly probable malignancies were identified (SIR 0 [95% CI 0-9.7]) [Beukelman, 2012].

Important co-morbidities:

Children with JIA appear to have an increased rate of incident malignancy compared to children without JIA [Beukelman, 2012].

Severe forms of psoriasis and psoriatic arthritis

Incidence and prevalence:

Psoriasis is one of the most common dermatologic diseases, affecting up to 2% of the world's population with an overall 1-year prevalence of 2.53%. According to the National Psoriasis Foundation, up to 30% of patients with psoriasis have Psoriatic Arthritis (PsA). There are five subtypes of PsA: symmetric, asymmetric, Distal Interphalangeal Predominant (DIP), spondylitis and arthritis mutilans. Symmetric arthritis resembles rheumatoid arthritis but is usually milder. Asymmetric arthritis can involve any joint and may present as "sausage digits." DIP is the classic form but occurs in only about 5% of patients with PsA. It may involve fingers and toes. Spondylitis also occurs in about 5% of patients with PsA. Arthritis mutilans is severe and deforming. It affects primarily the small joints of the hands and feet. It accounts for fewer than 5% of PsA cases [Lawley, 2015].

Demographics of the population in the authorised indication – age, gender, racial and/or ethnic origin and risk factors for the disease:

Important factors in the variation of the prevalence of psoriasis include age, gender, geography and ethnicity, probably due to genetic and environmental factors. The first manifestation of psoriasis may occur at any age. Two peaks of onset are frequently reported: in the second and third decades and about the age of 60. A German study, based on an insurance database and confined to those aged under 18 years, reported a much lower overall prevalence of psoriasis in children with respect to adults (0.71% (95% CI: 0.68-0.74)) and an increasing prevalence with age (0.37% for 0-9 years and 1.01% for 10-18 years) [Parisi, 2013]

Higher prevalence rates have been reported at higher latitudes, and in Caucasians compared with other ethnic groups. In addition, the wide variation in prevalence estimates may be influenced by aspects of psoriasis such as its remitting–relapsing course, diversity of clinical presentations, and variation in severity [Parisi, 2013].

Regarding risk factors, traumatised areas often develop lesions of psoriasis (the Koebner or isomorphic phenomenon). In addition, other external factors may exacerbate psoriasis, including infections, stress and medications (lithium, β-blockers and antimalarial drugs) [Lawley, 2015].

The main existing treatment options:

Various systemic agents can be used for severe, widespread psoriatic disease. Oral glucocorticoids should not be used for the treatment of psoriasis due to the potential for development of life-threatening pustular psoriasis when therapy is discontinued. Methotrexate is an effective agent, especially in patients with psoriatic arthritis. The synthetic retinoid acitretin is useful, especially when immunosuppression must be avoided; however, teratogenicity limits its use [Lawley, 2015].

Natural history of the indicated condition in the untreated population, including mortality and morbidity:

The most common variety of psoriasis is called "plaque-type". Patients with plaque-type psoriasis have stable, slowly enlarging plaques, which remain basically unchanged for long periods of time [Lawley, 2015].

Widely varying estimates of clinical outcome have been reported in PsA. At its worst, severe PsA with arthritis mutilans is potentially at least as crippling and ultimately fatal as severe RA. Unlike RA, however, many patients with PsA experience temporary remissions. Overall, erosive disease develops in the majority of patients, progressive disease with deformity and disability is common, and in some large published series, mortality was found to be significantly increased compared with the general

population. There appears to be a greater incidence of cardiovascular death in psoriatic disease [Taurog, 2015].

Important co-morbidities:

It is well established that several inflammatory-type conditions, such as arthritis, diabetes, cardiovascular disease and irritable bowel disease exist co-morbidly and at an increased incidence in patients with psoriasis. Psoriasis and other associated diseases are thought to share common inflammatory pathways [Mrowietz, 2006] An increased risk of metabolic syndrome, including increased morbidity and mortality from cardiovascular events, has been demonstrated in psoriasis patients [Lawley, 2015].

Acute Lymphoblastic Leukaemia (ALL)

Incidence and prevalence:

ALL is more common in children than adults (~6,000 total cases/year). It was estimated that 75,700 new cases of leukaemia were diagnosed in 2005 in the EU. In the paediatric population, ALL accounted for 80% of these cases. In Europe, the proportion of prevalent adult people was estimated as 38 per 100,000. The 5 years prevalence, that is the number of living people with a diagnosis of leukaemia made 5 or less years before the index date, was 20 per 100,000 [Bassan, 2004; Rodriguez-Abreu, 2007].

A more precise and updated prevalence estimate can be calculated from data provided by Orphanet, a web portal with the partnership of the French "Institut National de la Santé et de la Recherche Médicale", the French Directorate General for Health finances Orphanet's core activities, the European Commission (DG SANCO and DG RESEARCH), the WHO and other organisations. According to these data, prevalence of ALL is 1-9 cases/100,000 individuals [Orphanet, 2016].

Demographics of the population in the authorised indication – age, gender, racial and/or ethnic origin and risk factors for the disease:

Childhood ALL is the most common malignancy diagnosed in children, representing about 30% of childhood cancers and 75% of childhood acute leukaemias, which peaks between the ages of 2 and 5 years. In contrast, ALL accounts for only 15% of leukaemias in adults [Rodriguez-Abreu, 2007].

Regarding risk factors, the precise pathogenetic events leading to development of ALL are unknown.

The main existing treatment options:

Successful treatment requires intensive induction phase, Central Nervous System (CNS) prophylaxis, and maintenance chemotherapy that extends for about 2 years. Vincristine, L-asparaginase, cytarabine, daunorubicin and prednisone are particularly effective agents. Intrathecal or high-dose systemic methotrexate is effective CNS prophylaxis. Maintenance therapy comprises antimetabolite therapy with oral methotrexate and oral mercaptopurine. ALL has an overall survival of approximately 80%, with certain subsets experiencing greater than 98% cure rate. The role and timing of bone marrow transplantation in primary therapy is debated, but up to 30% of relapsed pts may be cured with salvage transplantation [Longo, 2014; Cooper, 2015].

Natural history of the indicated condition in the untreated population, including mortality and morbidity:

Age at diagnosis has a strong prognostic effect. The outcome of treatment in adults worsens with increasing age. Leucocyte count is a continuous prognostic variable, with increasing counts conferring a poorer outcome, especially in patients with B-cell precursor disease [Longo, 2014]

Important co-morbidities:

Almost 75% of ALL survivors, have a chronic health condition negatively affecting cardiovascular morbidity and mortality. Obesity can be considered one of the most important health chronic conditions in the general population, with an increasing incidence in patients treated for childhood cancers and especially in ALL survivors who are, at the same time, more at risk of experiencing precocious cardiovascular and metabolic co-morbidities. The hypothalamic-pituitary axis damage secondary to cancer therapies (cranial irradiation and chemotherapy) or to primary tumour together with lifestyle modifications and genetic factors could affect long-term outcomes [Iughetti, 2012].

Part II: Module SII - Non-clinical part of the safety specification

Jylamvo 2 mg/ml oral solution is a hybrid product. Therefore, this section is not applicable.

Part II: Module SIII - Clinical trial exposure

The Marketing Authorisation Application (MAA) for this product was submitted under the legal basis for a hybrid Application, i.e. under Article 10(3) of Council Directive 2001/83 as amended by 2004/27/EC, for a new immediate-release oral pharmaceutical form with reference to the off-patent injection authorised in Austria as the originator methotrexate product (METHOTREXAT "Lederle" 25 mg – Stechampulle; Pfizer Corporation Austria Ges.m.b.H., 1210 Wien; MA number: 17.626; date of authorisation 29 March 1984). In addition, this hybrid application refers to the oral tablet authorised in Austria as a hybrid application (under Article 10(3) with reference to the aforementioned originator product) (Ebetrexat® 10 mg tablets; EBEWE Pharma Ges.m.b.H. Nfg. KG, 4866 Unterach, Austria; MA number: 1-22272; date of authorisation 04 December 1997) to demonstrate bioequivalence and to support the indications and Summary of Product Characteristics (SmPC) details.

Since methotrexate is a well-established off-patent drug which has been used safely and effectively in humans for over 50 years in the EU and USA, and the authorised indications and doses for Jylamvo are broadly the same as those authorised for the oral reference (hybrid) product, the Applicant has conducted bioequivalence studies only – one was conducted for the original MAA submission and a further study was conducted in response to the Day 120 CHMP List of Questions.

Table SIII.1: Duration of exposure (totals)*

Total exposed population (person time should only be provided for final duration category and total)		
Duration of exposure (at least)	Persons	Person time
1 m		
3 m		
6 m		
12 m etc.		
Total person time		

* Since only two single dose bioequivalence studies have been performed, all subjects were exposed to methotrexate (test and reference formulation) for a period less than 1 month. Therefore, this table has not been populated.

Table SIII.2: Dose (totals)*

Total Population		
Dose of exposure	Persons	Person time
Dose level (10 mg per administration; total dose: 20 mg)	24	Two single doses
Dose level (2.5 mg per administration; total dose: 5 mg)	24	Two single doses
Total	48	Two single doses

Table SIII.3: Age group and gender (totals)*

Total population				
Age group	Persons		Person time	
	M	F	M	F
Age group (18-40 years)	48	-	Two single doses	-
Total	48	-	Two single doses	-

Part II: Module SIV - Populations not studied in clinical trials

Jylamvo 2 mg/ml oral solution is a hybrid product. Therefore, this section is not applicable.

Part II: Module SV - Post-authorisation experience

Jylamvo 2 mg/ml oral solution is a hybrid product. Therefore, this section is not applicable.

Part II: Module SVI - Additional EU requirements for the safety specification

Jylamvo 2 mg/ml oral solution is a hybrid product. Therefore, this section is not applicable.

Part II: Module SVII - Identified and potential risks

SVII.1 Identification of safety concerns in the initial RMP submission

Not applicable as this is an update of the RMP.

SVII.2 New safety concerns and reclassification with a submission of an updated RMP

RMP version 4.3 is an update of the previously approved RMP for Jylamvo (methotrexate) 2 mg/ml oral solution (version 4.0, dated 08 February 2017). The following table includes those safety concerns included in RMP version 4.0 and those proposed for RMP version 4.3:

Summary of safety concerns	RMP version 4.0	RMP version 4.3
Important identified risks	• Increased risk of neoplasia • Haematological toxicity • Hepatotoxicity • Pulmonary toxicity • Renal toxicity • Medication error; overdose from inadvertent daily instead of weekly dosing in e.g. non-malignant indications	• Increased risk of neoplasia • Haematological toxicity • Hepatotoxicity • Pulmonary toxicity • Renal toxicity • Medication errors due to inadvertent daily instead of once weekly dosing
Important potential risks	• Bone growth defects in the paediatric population • Medication error due to the proposed dosage form (medication errors due to incorrect use of the oral dosing syringe and confusion between mg and ml) • Progressive Multifocal Leukoencephalopathy	• Bone growth defects in the paediatric population • Medication error due to the proposed dosage form (medication errors due to incorrect use of the oral dosing syringe and confusion between mg and ml) • Progressive Multifocal Leukoencephalopathy
Missing information	• Use in children younger than 3 years	• Use in children younger than 3 years

Minor changes concerning renaming of safety concerns:

- "Medication error; overdose from inadvertent daily instead of weekly dosing in e.g. non-malignant indications" has been renamed as "Medication errors due to inadvertent daily instead of once weekly dosing", following a request from the Referral under Article 31 of Directive 2001/83/EC resulting from pharmacovigilance data for methotrexate containing medicinal products: Jylamvo 2 mg/ml oral solution (procedure number: EMEA/H/A-31/1463/C/3756/0002).

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

Important identified risk: Increased risk of neoplasia *(SMQs: Malignant lymphomas (narrow scope), Malignant or unspecified tumours (narrow scope))*

Potential mechanisms:

The mechanism has been theorised to be related to chronic cytokine release associated with autoimmunity and chronic inflammation, and reactivation of Epstein-Barr virus (a pro-oncogenic virus) by the primary disease and immunodeficiency associated with treatment with immunosuppressive drugs [Naidu, 2014; Inui, 2015]. Epstein-Barr virus is characterised mainly by tropism for B lymphocytes and their infection may result in transformation to B-cell lymphoma. Latent antigens encoded by Epstein-Barr virus interfere with important cellular pathways leading to tumorigenesis [Grywalska, 2015].

Evidence source(s) and strength of evidence:

Immunosuppressive therapy (such as methotrexate) for patients diagnosed with RA has long been implicated in the development of various neoplastic processes, including leukaemia, lymphoma, melanoma and lung cancer [Barclay, 2008; Naidu, 2014]. Among conditions, iatrogenic immunodeficiency-associated lymphoproliferative disorders due to methotrexate are particularly common [Inui, 2015].

Characterisation of the risk:

Patient prognosis is predominately driven by age and tumour stage. Patients older than ages 65 to 70 have a lower cure rate than younger patients. The difference in cure rates may be related to the frequent presence of comorbid diseases and decreased organ function in older patients, which impairs their ability to tolerate intensive chemotherapy [Chan, 2014].

- Clinical trials

Not applicable.

- Post-marketing

According to the Marketing Authorisation Holder (MAH) safety database, 12 cases involving 12 adverse events associated with the occurrence of neoplasias have been cumulatively received from post-marketing sources. Based on this information, the reporting rate for these events when calculated per 10 patients exposed is 1.09 [95% CI 0.56-1.91] and when calculated per 10 patient-years is 0.84 [95% CI 0.43-1.47].

The 12 reported events were acute myeloid leukaemia (3), juvenile chronic myelomonocytic leukaemia (2), squamous cell carcinoma of the tongue (2), neoplasm malignant (1) breast cancer (1), plasma cell myeloma (1), prostate cancer (1) and squamous cell carcinoma of lung (1). At the time of reporting, the outcome of the majority of the events was unknown (6), 4 were not resolved and 2 were fatal.

The fatal cases involved patients who experienced juvenile chronic myelomonocytic leukaemia. The patient in the first case (unknown age) was taking concomitant medication (not specified) which could have also contributed to the occurrence of this event and the patient in the second case [redacted] old) had a medical history of adenovirus infection. Based on the limited information available, it is not possible to perform an accurate assessment of the causality of these cases.

Risk factors and risk groups:

Patients with systemic rheumatic diseases, particularly rheumatoid arthritis, systemic lupus erythematosus, systemic sclerosis and idiopathic inflammatory myopathies, are at increased risk of developing malignancies. This risk is related to the pathobiology of the underlying rheumatic diseases including the inflammatory burden, immunological defects, and personal and environmental exposure such as smoking and some viral infections [Raheel, 2016]. In particular, several studies have reported that malignant lymphoma is 2-5.5 times more prevalent in patients with rheumatoid arthritis than in healthy individuals [Inui, 2015].

There is an increased risk for malignant neoplasms in patients older than 70 years who are treated with methotrexate compared to the general population and an increased risk for those who had ever used cyclophosphamide [Barclay, 2008].

Long-term methotrexate therapy is also a risk factor for developing lymphoma [Naidu, 2014].

Preventability:

Spontaneous remission has been seen after discontinuation of the methotrexate therapy [Naidu, 2014]. Watchful waiting after methotrexate cessation with observation of early lymphocyte recovery (in the two weeks following treatment discontinuation) and uninterrupted continuation of other anti-rheumatoid drugs may be an acceptable management plan for methotrexate -associated lymphoproliferative disorders [Inui, 2015].

According to the Reference Safety Information (RSI), malignant lymphomas may occur in patients receiving low-dose methotrexate, in which case therapy must be discontinued. If the lymphomas fail to regress spontaneously, cytotoxic treatment must be initiated.

Impact on the risk-benefit balance of the product:

The benefit-risk balance for the product is expected to be favourable. No additional pharmacovigilance activities or additional risk minimisation measures are deemed necessary.

Public health impact:

The potential impact on public health is expected to be low, providing that precautions and risk factors are taken into account.

Important identified risk: Haematological toxicity *(SMQ: Haematopoietic cytopenias (narrow scope))*

Potential mechanisms:

These adverse effects are caused by the inhibitory effect of methotrexate on the folate synthesis and subsequently on the transmethylation reactions and purine synthesis. They primarily affect highly replicative cells, such as mucosal tissue and blood stem cells [Gonzalez-Ibarra, 2014; Knoll, 2016].

Evidence source(s) and strength of evidence:

Exposure to methotrexate concentrations as low as 0.01 for more than 24 hours may result in bone marrow toxicity [Widemann, 2006].

Haematologic toxicity is a serious complication commonly observed with high-dose methotrexate. This complication consists of a thrombocytopenia followed by a rapidly progressive neutropenia. Leukopenia occurs from one to three weeks and marrow recovery is generally observed within approximately 3 weeks. Haematologic toxicity including thrombocytopenia, megaloblastic anaemia, leukopenia and pancytopenia with low-dose methotrexate are rare [Gaies, 2012].

Characterisation of the risk:

Side effects of methotrexate, especially myelosuppression, could cause significant morbidity and mortality [Mori, 2016].

- Clinical trials

Not applicable.

- Post-marketing

According to the MAH safety database, 23 cases involving 29 adverse events associated with haematological toxicity have been cumulatively received from post-marketing sources. Based on this information, the reporting rate for these events when calculated per 10 patients exposed is 2.64 [95% CI 1.77-3.79] and when calculated per 10 patient-years is 2.03 [95% CI 1.36-2.91].

The 29 reported events were white blood cell count decreased (7), neutrophil count decreased (5), neutropenia (5), thrombocytopenia (3), full blood count decreased (3), platelet count decreased (2), neutropenic sepsis (1), leukopenia (1), bone marrow failure (1) and pancytopenia (1). At the time of reporting, the outcome of the majority of the events was unknown (15), 5 were not resolved, 6 were resolved, 2 were resolving and 1 was fatal.

The fatal case involved a 34-year-old male patient who experienced acute kidney injury, malaise, thrombocytopenia, fatigue, meningitis pneumococcal, headache, myalgia, hepatic function abnormal, purpura, lethargy, sepsis and coagulopathy. No information is available concerning the medical history. The patient was taking concomitant medication which could be a contributory factor for these events. The Company assessed the causality of this case as possible for acute kidney injury, thrombocytopenia, fatigue, meningitis pneumococcal, headache, myalgia, hepatic function abnormal, lethargy and sepsis, due to plausible pharmacological association with the role of methotrexate. The causality was considered unassessable for malaise, purpura and coagulopathy based on the information available.

Risk factors and risk groups:

Pancytopenia due to methotrexate is attributed to the patients with renal dysfunction, presence of infection, folic acid deficiency, hypoalbuminemia, concomitant use of drugs such as trimethoprim, high doses of methotrexate and advanced age [Agarwal, 2008; Jariwala, 2014; Gonzalez-Ibarra, 2014; Knoll, 2016].

Serum albumin levels and folic acid supplementation are the important factors affecting the severity of methotrexate-related pancytopenia and neutropenia. Slow elimination of methotrexate in patients with renal insufficiency leads to prolonged exposure of bone marrow tissues to this drug. Renal insufficiency has been incriminated as the major risk factor for myelosuppression [Mori, 2016].

Preventability:

The RSI for the product recommends performing a complete blood count with differential blood count and platelets before beginning treatment with methotrexate or resuming treatment after a recovery period. In addition, this test is to be conducted weekly in the first 2 weeks, then every 2 weeks for a month. Thereafter, depending on the leucocyte count and the stability of the patient, it should be conducted at least once a month during the next 6 months and then at least every 3 months.

The RSI warns on the methotrexate-induced haematopoietic suppression that may occur abruptly and with apparently safe doses. As per the RSI, any serious decrease in leucocyte or platelet counts indicates the immediate discontinuation of treatment and appropriate supportive therapy. The RSI encourages patients to report all signs and symptoms suggestive of infection to their doctor.

According to the RSI for the product, especially strict monitoring of the patient is indicated following functional impairment of the haematopoietic system (e.g. following prior radio- or chemotherapy) and in patients simultaneously taking haematotoxic medicinal products (e.g. leflunomide). In addition, the RSI includes a warning stating that doses exceeding 20 mg (10 ml)/week can be associated with a substantial increase in toxicity, especially bone marrow depression.

Impact on the risk-benefit balance of the product:

The benefit-risk balance for the product is expected to be favourable. No additional pharmacovigilance activities or additional risk minimisation measures are deemed necessary.

Public health impact:

The potential impact on public health is expected to be low, providing that precautions and risk factors are taken into account.

Important identified risk: Hepatotoxicity *(HLTs: Hepatic and hepatobiliary disorders NEC, Hepatic failure and associated disorders, Hepatic fibrosis and cirrhosis and Hepatocellular damage and hepatitis NEC)*

Potential mechanisms:

The suggested molecular mechanism for hepatotoxicity is not well delineated. However, it is proposed that methotrexate enters the cell utilising the folate transporter and is pumped out by ATP-binding cassette family of transporters. Impaired activity of these transporters results in excess accumulation of drug in liver cells. Methotrexate is retained within the cells as polyglutamates which inhibit enzymes dihydrofolate reductase, thymidylate synthase, and 5-aminoimidazole-4-carboxamideribonucleotide transformylase, leading to impaired pyrimidine and purine synthesis. Methotrexate affects methylenetetrahydrofolate reductase and hence the generation of methionine from homocysteine. Excess homocysteine so generated lead to oxidative stress and activated pro-inflammatory cytokines leading to fatty infiltration of the liver [Moghadam, 2015; Dubey, 2016; Hagag, 2016].

Evidence source(s) and strength of evidence:

Long-term methotrexate use or its usage in high doses may cause hepatic steatosis, cholestasis, fibrosis and cirrhosis [Aslaner, 2015].

Methotrexate liver dysfunction is mostly associated with its chronic use in inflammatory disease, although acute hepatitis following high-dose administration has been described. Liver enzyme abnormalities under methotrexate treatment do not necessarily represent significant liver toxicity as they usually resolve with dose modification or drug discontinuation and may even normalise during the course of therapy [Rabinowich, 2015].

Characterisation of the risk:

Cases of hepatic atrophy, necrosis, cirrhosis, changes in lipid profile and periportal fibrosis have been reported [Osuga, 2015].

- Clinical trials

Not applicable.

- Post-marketing

According to the MAH safety database, 18 cases involving 20 adverse events associated with hepatotoxicity have been cumulatively received from post-marketing sources. Based on this information, the reporting rate for these events when calculated per 10 patients exposed is 1.82 [95% CI 1.11-2.81] and when calculated per 10 patient-years is 1.40 [95% CI 0.85-2.16].

The 20 reported events were liver disorder (7), hepatic steatosis (4), hepatotoxicity (2), liver injury (2), hepatic cirrhosis (1), granulomatous liver disease (1), hepatic failure (1), drug-induced liver injury (1) and hepatitis (1). At the time of reporting, the outcome of the majority of the events was unknown (16), 1 was not resolved, 1 was recovering, 1 was resolved and 1 was fatal.

The fatal case involved a 27-year-old male patient who experienced renal and hepatic failure with a fatal outcome. There is no information on when the patient took the product and the onset date of events or the frequency and dose administered. Concomitant medication included calcium folinate and an antiviral (aciclovir). The Company assessed the causality of this case as possible for both events, due to plausible pharmacological association with the role of methotrexate; however, temporal relationship was unclear.

Risk factors and risk groups:

Potential risk factors suggested for hepatic adverse effects in patients with rheumatoid arthritis are increased age, female gender, alcohol intake, smoking, disease duration, diabetes and obesity, hepatitis B or C infection cumulative dose of methotrexate, concomitant medications mainly Non-Steroidal Anti-Inflammatory Drugs (NSAIDs), and other DMARDs. Genetic factors may also play a role in predicting such adverse effects [Sotoudehmanesh, 2010; Issabeagloo, 2011; Weidmann, 2014; Dubey, 2016; Tang, 2016]. One major factor of methotrexate-induced hepatotoxicity, aside from the above-mentioned comorbidities, is the frequency of administration [Herfarth, 2012].

Preventability:

The RSI for the product recommends performing liver function tests before beginning treatment with methotrexate or resuming treatment after a recovery period. In addition, such tests are to be conducted weekly in the first 2 weeks, then every 2 weeks for a month. Thereafter, depending on the leucocyte count and the stability of the patient, it should be conducted at least once a month during the next 6 months and then at least every 3 months.

According to the RSI, the treatment should not be started or should be discontinued if there are any abnormalities in liver function tests or liver biopsies, or if these develop during therapy.

The RSI recommends considering a dose reduction or treatment discontinuation if liver enzymes are constantly increased. As per the RSI, additional hepatotoxic medicinal products should not be taken during treatment with methotrexate unless urgently necessary, due to methotrexate's potentially toxic effect on the liver. Likewise, alcohol consumption should be avoided or reduced.

The RSI recommends closer monitoring of liver enzymes in patients taking other hepatotoxic medicinal products concomitantly. In addition, this should be considered during simultaneous administration of haematotoxic medicinal products.

Finally, the RSI recommends increased caution in patients with insulin-dependent diabetes mellitus as hepatic cirrhosis has developed in individual cases without any elevation of transaminases during methotrexate treatment.

Impact on the risk-benefit balance of the product:

The benefit-risk balance for the product is expected to be favourable. No additional pharmacovigilance activities or additional risk minimisation measures are deemed necessary.

Public health impact:

The potential impact on public health is expected to be low, providing that precautions and risk factors are taken into account.

Important identified risk: Pulmonary toxicity *(HLGT: Lower respiratory tract disorders (excl obstruction and infection), Respiratory disorders NEC)*

Potential mechanisms:

Although the reasons for methotrexate toxicity in the lungs are unclear, some explanations have been proposed. Methotrexate -induced immune suppression causes recurrent viral or bacterial infections and hypersensitivity reactions. Methotrexate may also have a direct toxic effect on the alveolar epithelial walls. Furthermore, methotrexate causes toxicity by increasing apoptosis and fibrosis of lung tissue. Although no human studies have been conducted, experimental studies have shown that methotrexate may cause acute pulmonary toxicity by increasing secretion of cytokines such as TNF-α, interleukin-1, interleukin-8, and monocyte chemotactic protein-1. In addition, overdose of methotrexate can lead to pro-inflammatory cytokine release due to the increase in oxidative stress and Reactive Oxygen Species (ROS) formation. Overdose also leads to pulmonary tissue damage by increasing the caspase enzyme system and activating ROS formation [Kurt, 2015].

Evidence source(s) and strength of evidence:

Long-term use at therapeutic doses or overdose of methotrexate can cause significant dose-dependent pulmonary side effects, such as acute and subacute respiratory failure, non-productive cough, dyspnoea, fever, pneumonitis, interstitial lung disease and pulmonary fibrosis [Kurt, 2015]. In addition, pulmonary alveolar haemorrhage has been reported for methotrexate used in rheumatologic and related indications [EMA/PRAC/8429/2018 Corr, 2018].

Characterisation of the risk:

Methotrexate -induced lung diseases such as pneumonitis can occur acutely and are not always completely reversible. Acute or chronic interstitial pneumonia, often in association with blood eosinophilia, may occur and deaths have been reported.

Lung disease is a major contributor to morbidity and mortality in patients with rheumatoid arthritis. Prognosis varies depending on the type and severity of involvement [Shaw, 2015]. Some types of rheumatoid arthritis-associated lung disease are steroid responsive, but some patients have a progressive course leading to end-stage fibrosis and death [Kahlenberg, 2011].

- Clinical trials

Not applicable.

- Post-marketing

According to the MAH safety database, 33 cases involving 46 adverse events associated with pulmonary toxicity have been cumulatively received from post-marketing sources. Based on this information, the reporting rate for these events when calculated per 10 patients exposed is 4.18 [95% CI 3.06-5.58] and when calculated per 10 patient-years is 3.22 [95% CI 2.35-4.30].

The 46 reported events were dyspnoea (12), cough (11), pulmonary fibrosis (6), pneumonitis (3), acute interstitial pneumonitis (2), dyspnoea exertional (2), interstitial lung disease (2), lung disorder (2), productive cough (1), respiratory disorder (1), respiratory failure (1), haemoptysis (1), tachypnoea (1) and hypoxia (1). At the time of reporting, the outcome of the majority of the events was unknown (27), 4 resolved, 3 were resolving, 5 were not resolved and 7 were fatal.

The events with fatal outcome were reported in 2 cases. The first fatal case involved a 72-year-old female patient who experienced cough, acute interstitial pneumonitis, dyspnoea, influenza like illness and hypoxia. The cause of death was acute interstitial pneumonitis. The Company assessed the causality of this case as possible for dry cough, acute interstitial pneumonitis, dyspnoea and hypoxia,

due to plausible pharmacological association with the role of methotrexate. The causality was considered unassessable for influenza like illness based on the information available. The second fatal case involved another 72-year-old female patient who experienced pulmonary embolism, dyspnoea, acute interstitial pneumonitis and cough. Due to plausible pharmacological association with the role of methotrexate, the Company assessed the causality of these events as possible.

Risk factors and risk groups:

Multicentre case-control studies have been performed which may predict the possibility of methotrexate lung injury and the following risk factors have been identified: diabetes, rheumatoid pulmonary involvement, previous use of DMARDs, older age (>60 years), pre-existing lung disease [Hlaing, 2007], smoking, acetylsalicylic acid use and renal insufficiency [Liu, 2015].

The factors found to be associated with the higher risk for development of interstitial lung disease in rheumatoid arthritis were male gender, age, presence of inflammatory arthritis, disease activity, history of smoking, high titre rheumatoid factor and anti-cyclic citrullinated protein antibodies [Anand, 2014].

Preventability:

The RSI for the product recommends performing a chest X-ray before beginning treatment with methotrexate or resuming treatment after a recovery period. In addition, patients must be monitored for symptoms of a lung function disorder and lung function tests should be performed if necessary. As per the RSI, lung-related symptoms (particularly a dry, non-productive cough) or non-specific pneumonitis that occurs during treatment with methotrexate can be a sign of potentially dangerous damage and require the discontinuation of treatment and careful monitoring. In these cases, a chest X-ray must be taken in order to be able to exclude an infection and tumours. The RSI recommends informing patients of the risk of pneumonia and advising them to contact their doctor immediately if they develop a persistent cough or persistent dyspnoea.

In addition, the RSI suggests considering prompt investigation when pulmonary alveolar haemorrhage is suspected to confirm the diagnosis.

According to the RSI, particular caution is required in patients with impaired pulmonary function, in patients with inactive chronic infections (e.g. herpes zoster, tuberculosis, hepatitis B or C) as it is possible that activation of these infections may occur.

Impact on the risk-benefit balance of the product:

The benefit-risk balance for the product is expected to be favourable. No additional pharmacovigilance activities or additional risk minimisation measures are deemed necessary.

Public health impact:

The potential impact on public health is expected to be low, providing that precautions and risk factors are taken into account.

Important identified risk: Renal toxicity *(HLGT: Nephropathies; HLTs: Renal disorders NEC, Renal failure and impairment)*

Potential mechanisms:

Methotrexate is nephrotoxic due to precipitation of methotrexate or its metabolites in the renal tubules causing obstruction and diminution of renal clearance with a consequent prolongation of methotrexate high levels, which further worsen renal function and exacerbate non-renal adverse events. Also, methotrexate and its metabolites are relatively insoluble in acid urine [Hagag, 2016; Howard, 2016].

Evidence source(s) and strength of evidence:

It is well known that renal clearance is the principal pathway of methotrexate elimination, and its elimination appears to be related to renal function. On the other hand, nephrotoxicity is one of the most frequently reported side effects of high-dose methotrexate infusion, especially in patients with delayed methotrexate elimination [Yang, 2015].

Methotrexate-induced renal dysfunction results in sustained, elevated plasma methotrexate concentrations, which in turn may lead to ineffective rescue by leucovorin and a marked enhancement of methotrexate's other toxicities, especially myelosuppression, mucositis, hepatitis and dermatitis [Widemann, 2006].

Characterisation of the risk:

Manifestations include glomerulonephritis, amyloidosis, tubulointerstitial nephritis and drug toxicity [Muthukumar, 2017; Sakthirajan, 2017]. These renal adverse effects may affect significantly morbidity and even mortality in cases of severe reactions.

- Clinical trials

Not applicable.

- Post-marketing

According to the MAH safety database, 7 cases involving 8 adverse events associated with renal toxicity have been cumulatively received from post-marketing sources. Based on this information, the reporting rate for these events when calculated per 10 patients exposed is 0.73 [95% CI 0.31-1.43] and when calculated per 10 patient-years is 0.56 [95% CI 0.24-1.10].

The 8 reported events were acute kidney injury (3), renal failure (2), renal impairment (1), nephritis (1) and renal disorder (1). At the time of reporting, the outcome of the majority of the events was unknown (4), 2 was resolved and 2 were fatal.

The events with fatal outcome were reported in 2 cases. The first fatal case involved a 34-year-old male patient who experienced acute kidney injury, malaise, thrombocytopenia, fatigue, meningitis pneumococcal, headache, myalgia, hepatic function abnormal, purpura, lethargy, sepsis and coagulopathy. No information is available concerning the medical history. The patient was taking concomitant medication which could be a contributory factor for these events. The Company assessed the causality of this case as possible for acute kidney injury, thrombocytopenia, fatigue, meningitis pneumococcal, headache, myalgia, hepatic function abnormal, lethargy and sepsis, due to plausible pharmacological association with the role of methotrexate. The causality was considered unassessable for malaise, purpura and coagulopathy based on the information available. The second case involved a 27-year-old male patient who experienced renal and hepatic failure with a fatal outcome. There is no information on when the patient took the product and the onset date of events or the frequency and dose administered. Concomitant medication included calcium folinate and an antiviral (aciclovir). The Company assessed the causality of this case as possible for both events, due to plausible pharmacological association with the role of methotrexate; however, temporal relationship was unclear.

Risk factors and risk groups:

Risk factors for methotrexate-associated toxicity include a history of renal dysfunction, volume depletion, acidic urine and drug interactions [Howard, 2016].

Preventability:

Renal function should be monitored by renal function tests and urinalyses. The RSI for the product recommends performing renal function tests before beginning treatment with methotrexate or resuming treatment after a recovery period. In addition, these tests are to be conducted weekly in the first 2 weeks, then every 2 weeks for a month. Thereafter, depending on the leucocyte count and the stability of the patient, it should be conducted at least once a month during the next 6 months and then at least every 3 months.

According to the RSI, if serum creatinine levels are increased, the dose should be reduced and if creatinine clearance is less than 30 ml/min, treatment with methotrexate should not be given.

Impact on the risk-benefit balance of the product:

The benefit-risk balance for the product is expected to be favourable. No additional pharmacovigilance activities or additional risk minimisation measures are deemed necessary.

Public health impact:

The potential impact on public health is expected to be low, providing that precautions and risk factors are taken into account.

Important identified risk: Medication errors due to inadvertent daily instead of once weekly dosing *(PTs: Overdose, Intentional overdose, Accidental overdose, Medication error, Dose calculation error, Extra dose administered, Incorrect dose administered, Wrong dose, Inappropriate schedule of drug administration, Wrong schedule, Toxicity to various agents)*

Potential mechanisms:

Not applicable.

Evidence source(s) and strength of evidence:

Oral methotrexate is indicated in the treatment of active rheumatoid arthritis, adult psoriasis, severe JIA in adolescents and children over 3 years of age, and in a number of oncological indications such as ALL. Compared to dosing for antineoplastic indications, methotrexate for rheumatological and dermatological diseases is administered once weekly as low-dose therapy. Harmful or fatal errors with low-dose oral methotrexate have been reported; most errors involved accidental daily dosing of oral methotrexate that was intended for weekly administration [EMA/215649/2018, 2018; Grissinger, 2018].

The risk of dosing errors with methotrexate has been recognised for many years and several measures are already in place in some EU countries to reduce this risk, including the use of visual reminders on the medicine packs.

Characterisation of the risk:

Some of the most common toxic effects with a low-dose regimen of methotrexate are gastrointestinal, hematologic and hepatic. Severe adverse effects are more common with the higher doses of methotrexate used for antineoplastic indications. However, haematologic toxicity is reported to occur in up to 3% of patients treated with long-term, low-dose methotrexate for rheumatoid arthritis and other auto immune disorders. Severe toxic effects, such as myelosuppression, pulmonary complications, central nervous system toxicity, hepatotoxicity, and mucositis, have led to hospital admissions and even death [Grissinger, 2018].

- Clinical trials

Not applicable.

- Post-marketing

According to the MAH safety database, 1 case involving overdose and 4 cases involving inappropriate schedule of drug administration have been cumulatively received from post-marketing sources. However, the overdose case was associated with a concomitant medication that the patient was taking (clozapine), not with methotrexate; and the cases reporting inappropriate schedule of drug administration did not involve a daily administration of methotrexate.

Risk factors and risk groups:

A range of factors contribute to these adverse events, including patients not being given sufficient information on how often to take the drug (once weekly and not once daily), lack of clear packaging and variations in patient monitoring and treatment reviews [Mayor, 2003].

Preventability:

The RSI clearly warns about the dosage of methotrexate when used for rheumatological and dermatological diseases. It also states that methotrexate should only be prescribed by physicians with expertise in the use of methotrexate and a full understanding of the risks of methotrexate therapy. When used for these indications, the product must only be taken once a week and the RSI states that the prescriber should specify the day of intake on the prescription. The prescriber should ensure that patients or their carers will be able to comply with the once weekly regimen. The RSI also advises to read very carefully the section regarding posology of the product and warns on the serious adverse reaction (including death) that can result when dosage errors occur.

In order to minimise this risk, educational material (including a guide for health care professionals and a patient card) and a Direct Healthcare Professional Communication (DHPC) will be distributed. In addition, targeted questionnaires to collect further information on medication errors are used.

Impact on the risk-benefit balance of the product:

Of the 397 total of all case reports received for Methotrexate 2 mg/ml oral solution, 1 case involving overdose and 4 cases involving inappropriate schedule of drug administration have been cumulatively received from post-marketing sources. However, the overdose case was associated with a concomitant medication that the patient was taking (clozapine), not with methotrexate; and the cases reporting inappropriate schedule of drug administration did not involve a daily administration of methotrexate. Taking into account the educational material (including a guide for health care professionals and a patient card) and the DHPC, it is expected that the risk-benefit balance of the product will be favourable.

Public health impact:

The potential impact on public health is expected to be low, providing that precautions and risk factors are taken into account.

Important potential risk: Bone growth defects in the paediatric population *(HLGT: Fractures; HLTs: Bone disorders NEC, Metabolic bone disorders, Fractures and dislocations NEC, Limb fractures and dislocations, Pelvic fractures and dislocations, Skull fractures, facial bone fractures and dislocations, Spinal fractures and dislocations, Thoracic cage fractures and dislocations)*

Potential mechanisms:

Although the mechanism for chemotherapy-induced bone damage is multifactorial, research has revealed that chemotherapeutic agents can directly impair bone growth. In particular, rat studies have confirmed that methotrexate can directly disrupt the growth plate structure and function by inducing chondrocyte apoptosis, reducing chondrocyte proliferation and cartilage protein synthesis. Dysfunction

of the growth plate, therefore, reduces formation of primary woven bone. Direct damage to osteoblasts by decreasing osteoblast activity/formation (possibly through inducing the switch in the bone marrow stromal cells towards adipogenic differentiation at the expense of osteogenesis) and bone marrow osteoprogenitor cells also contributes to reduced bone formation. In addition, methotrexate chemotherapy has also been shown to increase osteoclast formation and cause aggravated bone resorption, contributing to the associated bone loss [Fan, 2011].

Evidence source(s) and strength of evidence:

Typically, bone metabolism in children with ALL (the predominant childhood cancer) is known to be disturbed after chemotherapy, resulting in reduced bone lengthening and bone loss. Bone growth defects or bone loss during childhood may predispose to osteopenia and osteoporosis in later life. While many studies have examined effects of long-term low-dose methotrexate on bone metabolism and have reported no significant adverse effects on bone mineral density, long-term intensive chemotherapy with methotrexate has been shown to cause serious damage to bone development in paediatric patients [Fan, 2012].

Characterisation of the risk:

- Clinical trials

Not applicable.

- Post-marketing

According to the MAH safety database, 5 cases involving 6 adverse events associated with bone disorders have been cumulatively received from post-marketing sources. However, these cases did not involve the paediatric population.

Risk factors and risk groups:

Longitudinal bone growth is mainly regulated by genetic and hormonal factors such as growth hormone, insulin-like growth factors, thyroid hormone and glucocorticoids, sex steroids, fibroblast growth factors, epidermal growth factor and related ligands transforming growth factor β and bone morphogenic protein. In addition, environmental factors such as nutrition and medical treatments including chemotherapy have also been shown to be important determinants for bone growth in children, influencing the final height and bone mass of an individual [Fan, 2011].

Preventability:

Folinic acid supplementation during chronic methotrexate treatment can alleviate growth plate and metaphyseal damage and therefore may be potentially useful in paediatric patients who are at risk of skeletal growth suppression due to chronic methotrexate chemotherapy [Fan, 2012].

Impact on the risk-benefit balance of the product:

The benefit-risk balance for the product is expected to be favourable. No additional pharmacovigilance activities or additional risk minimisation measures are deemed necessary.

Public health impact:

The potential impact on public health is expected to be low, providing that precautions and risk factors are taken into account.

Important potential risk: Medication error due to the proposed dosage form (medication errors due to incorrect use of the oral dosing syringe and confusion between mg and ml) *(PTs: Accidental overdose, Accidental underdose, Dose calculation error, Extra dose administered,*

Incorrect dose administered, Intentional overdose, Intentional underdose, Overdose, Underdose, Wrong dose, Medication error, Syringe issue, Wrong technique in product usage process)

Potential mechanisms:

Not applicable.

Evidence source(s) and strength of evidence:

Overdose of methotrexate may cause important cutaneous, oral mucosa and systemic side effects. In case of acute intoxication by methotrexate, skin signs and symptoms are a toxicity alert sign and may precede more serious hematologic alterations [Souza, 2016].

Characterisation of the risk:

Methotrexate overdose leads to toxic undesirable effects and therefore may result in high mortality and morbidity or cause permanent sequelae.

- Clinical trials

Not applicable.

- Post-marketing

According to the MAH safety database, 1 case involving overdose and 1 case involving wrong technique in product usage process have been cumulatively received from post-marketing sources. However, the overdose was associated with a concomitant medication that the patient was taking (clozapine), not with methotrexate; and the case reporting wrong technique in product usage process did not involve an incorrect use of the oral dosing syringe and confusion between mg and ml.

Risk factors and risk groups:

Patients not being given sufficient information on how to take the product are at higher risk.

Preventability:

The RSI for the product clearly states how to take the product and the recommended dose (both in mg and ml) for each indication and special populations. Furthermore, the RSI indicates that the oral solution contains 2 mg of methotrexate in each ml of solution and informs that the scaling of the dosing syringe is in ml and not mg. According to the RSI, care should be taken that the correct dosing volume is prescribed.

In order to minimise this risk, educational material will be distributed. In addition, targeted questionnaires to collect further information on medication errors are used.

Impact on the risk-benefit balance of the product:

Of the 397 total of all case reports received for Methotrexate 2 mg/ml oral solution, 1 case involving overdose and 1 case involving wrong technique in product usage process have been cumulatively received from post-marketing sources. However, the overdose was associated with a concomitant medication that the patient was taking (clozapine), not with methotrexate; and the case reporting wrong technique in product usage process did not involve an incorrect use of the oral dosing syringe and confusion between mg and ml. Taking into account the educational material, it is expected that the risk-benefit balance of the product will be favourable.

Public health impact:

The potential impact on public health is expected to be low, providing that precautions and risk factors are taken into account.

Important potential risk: Progressive Multifocal Leukoencephalopathy (PML) *(PT: Progressive multifocal leukoencephalopathy)*

Potential mechanisms:

The kidneys, bone marrow and B lymphocytes may serve as sites for latency of the archetype variant of the virus, but the mechanism by which the pathogenic variant of the virus arises is unclear. Immunosuppression (e.g. caused by methotrexate) may play a role in leading to changes in the JC virus regulatory region, producing the tandem repeat variant of the virus that leads to PML [Lach, 2014; Sammut, 2016].

Evidence source(s) and strength of evidence:

PML is a rare and serious infection caused by the John Cunningham virus and characterised by progressive inflammation and demyelination of the white matter of the brain at multiple locations. Following initial infection, the virus remains latent in multiple tissues in healthy individuals, with reactivation and clinical disease occurring in severely immunosuppressed states [Bharat, 2012].

PML has been most commonly observed among patients infected with human immunodeficiency virus, those with malignancies, and in organ transplant recipients. PML has also been reported rarely in patients with inflammatory autoimmune disorders including rheumatoid arthritis and other rheumatic conditions, particularly in those using cytotoxic and biologic therapies [Bharat, 2012].

Characterisation of the risk:

The frequency of PML with methotrexate use is very low; however, given the almost uniformly fatal consequences of this infection [Lach, 2014] it may result in high mortality and morbidity or cause permanent sequelae.

- Clinical trials

Not applicable.

- Post-marketing

According to the MAH safety database, no cases involving progressive multifocal leukoencephalopathy have been cumulatively received from post-marketing sources.

Risk factors and risk groups:

Previous history of other cytotoxic drugs, other biologics or documented cancer [Bharat, 2012].

Preventability:

Early recognition of the condition and withdrawal of the drug lead to a better prognosis [González-Suárez, 2014].

According to the RSI, since cases of encephalopathy/leukoencephalopathy have occurred in cancer patients treated with methotrexate, this cannot be ruled out either for patients with non-cancer indications.

Impact on the risk-benefit balance of the product:

The benefit-risk balance for the product is expected to be favourable. No additional pharmacovigilance activities or additional risk minimisation measures are deemed necessary.

Public health impact:

The potential impact on public health is expected to be low, providing that precautions and risk factors are taken into account.

SVII.3.2. Presentation of the missing information

Missing information: Use in children younger than 3 years *(Paediatric population under 3 years of age)*

Evidence source:

Use in children under 3 years of age is not recommended as insufficient data on efficacy and safety are available for this population group.

Population in need of further characterisation:

Since there is scarce experience with the use of methotrexate in children below 3 years of age, this population needs to be further studied.

Part II: Module SVIII - Summary of the safety concerns

Table SVIII.1: Summary of safety concerns

Summary of safety concerns	
Important identified risks	• Increased risk of neoplasia • Haematological toxicity • Hepatotoxicity • Pulmonary toxicity • Renal toxicity • Medication errors due to inadvertent daily instead of once weekly dosing
Important potential risks	• Bone growth defects in the paediatric population • Medication error due to the proposed dosage form (medication errors due to incorrect use of the oral dosing syringe and confusion between mg and ml) • Progressive Multifocal Leukoencephalopathy
Missing information	• Use in children younger than 3 years

Part III: Pharmacovigilance Plan (including post-authorisation safety studies)

III.1 Routine pharmacovigilance activities

Routine pharmacovigilance including analysis of adverse drug reaction reports to assess compliance with the authorised SmPC recommendations will allow assessing and judging the success of the risk minimisation.

Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection include:

- Specific adverse reaction follow-up questionnaire for medication errors:
  - Medication errors due to inadvertent daily instead of once weekly dosing.
  - Medication error due to the proposed dosage form (medication errors due to incorrect use of the oral dosing syringe and confusion between mg and ml).

This specific adverse reaction follow-up questionnaire was created to collect further information on medication errors.

Cases of medication errors that do not result in an adverse drug reaction and which are not reported to EudraVigilance (medication errors without harm, intercepted medication errors and potential medication errors) will also be further substantiated by using the follow-up questionnaire and will be reported through the PSURs.

The targeted follow-up questionnaire is appended in Annex 4 of the RMP.

III.2 Additional pharmacovigilance activities

No additional pharmacovigilance activities are in place.

III.3 Summary Table of additional Pharmacovigilance activities

There are no ongoing or planned categories 1-3 safety studies.

Part IV: Plans for post-authorisation efficacy studies

Not applicable as no imposed post-authorisation efficacy studies are planned or ongoing.

Part V: Risk minimisation measures (including evaluation of the effectiveness of risk minimisation activities)

Risk Minimisation Plan

V.1 Routine Risk Minimisation Measures

Table Part V.1: Description of routine risk minimisation measures by safety concern

Safety concern	Routine risk minimisation activities
Increased risk of neoplasia	Routine risk communication: SmPC section 4.8. Package Leaflet (PL) section 4. Routine risk minimisation activities recommending specific clinical measures to address the risk: Section 4.4 of the SmPC states that malignant lymphomas may occur in patients receiving low-dose methotrexate, in which case therapy must be discontinued. If the lymphomas fail to regress spontaneously, cytotoxic treatment must be initiated. Section 2 of the PL states that enlarged lymph nodes (lymphoma) may occur in patients receiving low dose methotrexate and if this is the case, therapy must be stopped. Other routine risk minimisation measures beyond the Product Information: Pack size. Restricted medical prescription.
Haematological toxicity	Routine risk communication: SmPC section 4.8. PL section 4. Routine risk minimisation activities recommending specific clinical measures to address the risk: According to section 4.3 of the SmPC, Jylamvo is contraindicated in patients with pre-existing blood disorders such as bone marrow hypoplasia, leukopenia, thrombocytopenia or significant anaemia; in patients with immunodeficiency or severe, acute or chronic infections such as tuberculosis and HIV. Concurrent vaccination with live vaccines is also contraindicated. There is a warning in section 4.4 of the SmPC recommending performing a complete blood count with differential blood count and platelets before beginning treatment with methotrexate or resuming treatment after a recovery period. In addition, this test is to be conducted weekly in the first 2 weeks, then every 2 weeks for a month. Thereafter, depending on the leucocyte count and the stability of the patient, it should be conducted at least once a month during the next 6 months and then at least every 3 months. Section 4.4 of the SmPC also warns on the methotrexate-induced

Safety concern	Routine risk minimisation activities
	haematopoietic suppression that may occur abruptly and with apparently safe doses. Any serious decrease in leucocyte or platelet counts indicates the immediate discontinuation of treatment and appropriate supportive therapy. Patients should be encouraged to report all signs and symptoms suggestive of infection to their doctor. According to section 4.4 of the SmPC, especially strict monitoring of the patient is indicated following functional impairment of the haematopoietic system (e.g. following prior radio- or chemotherapy) and in patients simultaneously taking haematotoxic medicinal products (e.g. leflunomide). In addition, this section of the SmPC includes a warning stating that doses exceeding 20 mg (10 ml)/week can be associated with a substantial increase in toxicity, especially bone marrow depression. Furthermore, there is a warning in section 4.4 of the SmPC stating that concurrent vaccination using live vaccines should not be given since, due to its effect on the immune system, methotrexate may impair the response to vaccinations and affect the results of immunological tests. Section 4.5 of the SmPC includes interactions between methotrexate and several medicinal products that have been associated with haematological toxicity. According to section 2 of the PL, Jylamvo should not be taken in patients with blood disorders such as bone marrow hypoplasia, leukopenia, thrombocytopenia or significant anaemia; in patients with a weakened immune system or suffering from a serious infection such as tuberculosis or HIV. The product should also not be taken with concurrent vaccination with live vaccines. Section 2 of the PL also warns that laboratory tests should be performed in order to detect side effects. Section 2 of the PL includes interactions between methotrexate and several medicinal products that have been associated with haematological toxicity. In addition, section 4 of the PL encourages patients to report all signs and symptoms suggestive of infection to their doctor. Other routine risk minimisation measures beyond the Product Information: Pack size. Restricted medical prescription.
Hepatotoxicity	Routine risk communication: SmPC section 4.8. PL section 4. Routine risk minimisation activities recommending specific clinical measures to address the risk: Section 4.2 of the SmPC states that methotrexate should be administered only with the greatest caution, if at all, in patients with significant existing or previous liver disease, especially if due to alcohol. According to section 4.3 of the SmPC, Jylamvo is contraindicated in patients with hepatic impairment (bilirubin levels >5 mg/dl (85.5 µmol/l)) and in patients with alcohol abuse.

Safety concern	Routine risk minimisation activities
	Section 4.4 of the SmPC states that methotrexate should be used only with great caution, if at all, in patients who have a significant liver disease, particularly if this is/was alcohol related. There is a warning in section 4.4 of the SmPC recommending performing liver function tests before beginning treatment with methotrexate or resuming treatment after a recovery period. In addition, such tests are to be conducted weekly in the first 2 weeks, then every 2 weeks for a month. Thereafter, depending on the leucocyte count and the stability of the patient, it should be conducted at least once a month during the next 6 months and then at least every 3 months. According to the section 4.4 of the SmPC, the treatment should not be started or should be discontinued if there are any abnormalities in liver function tests or liver biopsies, or if these develop during therapy. If liver enzymes are constantly increased, a dose reduction or treatment discontinuation should be considered. This section of the SmPC also states that additional hepatotoxic medicinal products should not be taken during treatment with methotrexate unless urgently necessary, due to methotrexate's potentially toxic effect on the liver. Likewise, alcohol consumption should be avoided or reduced. Section 4.4 of the SmPC recommends closer monitoring of liver enzymes in patients taking other hepatotoxic medicinal products concomitantly. In addition, this should be considered during simultaneous administration of haematotoxic medicinal products. Finally, it recommends increased caution in patients with insulin-dependent diabetes mellitus as hepatic cirrhosis has developed in individual cases without any elevation of transaminases during methotrexate treatment. Section 4.5 of the SmPC includes interactions between methotrexate and several medicinal products that have been associated with hepatic toxicity. According to section 2 of the PL, Jylamvo should not be taken in patients with liver impairment or in case of alcohol abuse. A doctor or pharmacist should be consulted before treatment if the patient has ever had any liver disease. Section 2 of the PL also warns that blood tests should be performed before the beginning of the treatment to check how well the liver is working. If the results of any test are abnormal, the treatment will not be restarted until all the values have returned to normal. Section 2 of the PL includes interactions between methotrexate and several medicinal products that have been associated with hepatic toxicity. Other routine risk minimisation measures beyond the Product Information: Pack size. Restricted medical prescription.
Pulmonary toxicity	Routine risk communication: SmPC section 4.8. PL section 4. Routine risk minimisation activities recommending specific clinical measures to address the risk: There is a warning in section 4.4 of the SmPC recommending performing a

Safety concern	Routine risk minimisation activities
	chest X-ray before beginning treatment with methotrexate or resuming treatment after a recovery period. In addition, patients must be monitored for symptoms of a lung function disorder and lung function tests should be performed if necessary. Lung-related symptoms (particularly a dry, non-productive cough) or non-specific pneumonitis that occurs during treatment with methotrexate can be a sign of potentially dangerous damage and require the discontinuation of treatment and careful monitoring. In these cases, a chest X-ray must be taken in order to be able to exclude an infection and tumours. Patients should be informed of the risk of pneumonia and advised to contact their doctor immediately if they develop a persistent cough or persistent dyspnoea. Pulmonary symptoms require a rapid diagnosis and discontinuation of methotrexate therapy. In addition, section 4.4 of the SmPC suggests considering prompt investigation when pulmonary alveolar haemorrhage is suspected to confirm the diagnosis. According to this section, opportunistic infections can occur during treatment with methotrexate, including *Pneumocystis jiroveci pneumonia*, which can also have a fatal outcome. If a patient develops pulmonary symptoms, the possibility *of Pneumocystis jiroveci pneumonia* should be considered. Particular caution is also required in patients with impaired pulmonary function, in patients with inactive chronic infections (e.g. herpes zoster, tuberculosis, hepatitis B or C) as it is possible that activation of these infections may occur. Section 2 of the PL recommends consulting a doctor or pharmacist before beginning treatment with Jylamvo if the patient has problems with the lung function or if the patient has an abnormal build-up of fluid in the abdomen (ascites) or around the lungs (pleural effusions). Acute bleeding from the lungs in patients with underlying rheumatologic disease has been reported with methotrexate. If case of experiencing symptoms of spitting or coughing up blood, a doctor should be consulted immediately. Section 2 of the PL also warns that an X-ray may be performed before the beginning of the treatment. If the results are abnormal, the treatment will not be restarted until the values have returned to normal. Other routine risk minimisation measures beyond the Product Information: Pack size. Restricted medical prescription.
Renal toxicity	Routine risk communication: SmPC section 4.8. PL section 4. Routine risk minimisation activities recommending specific clinical measures to address the risk: Section 4.2 of the SmPC states that methotrexate should be used with caution in patients with impaired renal function and that the dose should be adjusted for patients with rheumatoid arthritis, juvenile arthritis, psoriasis and psoriatic arthritis. For the oncology indication

Safety concern	Routine risk minimisation activities
	recommendations in published protocols should also apply. According to section 4.3 of the SmPC, Methotrexate 2 mg/ml oral solution is contraindicated in patients with severe renal impairment (creatinine clearance less than 30 ml/min). Section 4.4 of the SmPC states that because of the delayed excretion of methotrexate in patients with impaired kidney function, they should be treated with particular caution and only with low doses of methotrexate. There is a warning in section 4.4 of the SmPC recommending performing renal function tests before beginning treatment with methotrexate or resuming treatment after a recovery period. In addition, these tests are to be conducted weekly in the first 2 weeks, then every 2 weeks for a month. Thereafter, depending on the leucocyte count and the stability of the patient, it should be conducted at least once a month during the next 6 months and then at least every 3 months. Renal function should be monitored by renal function tests and urinalyses. If serum creatinine levels are increased, the dose should be reduced and if creatinine clearance is less than 30 ml/min, treatment with methotrexate should not be given. Treatment with moderately high and high doses of methotrexate should not be initiated at urinary pH values of less than 7.0. Alkalinisation of the urine must be tested by repeated pH monitoring (value greater than or equal to 6.8) for at least the first 24 hours after the administration of methotrexate is started. In addition, this section 4.4 includes a warming stating that as methotrexate is eliminated mainly via the kidneys, increased concentrations are to be expected in the presence of renal impairment, which may result in severe adverse reactions. If there is the possibility of renal impairment (e.g. in elderly subjects), monitoring should take place at shorter intervals. This applies in particular when medicinal products that affect the elimination of methotrexate, or that cause kidney damage (e.g. NSAIDs) or that can potentially lead to impairment of haematopoiesis, are administered concomitantly. If risk factors such as renal function disorders, including mild renal impairment, are present, combined administration with NSAIDs is not recommended. Dehydration may also intensify the toxicity of methotrexate. Section 4.5 of the SmPC includes interactions between methotrexate and several medicinal products that have been associated with renal toxicity. According to section 2 of the PL, Jylamvo should not be taken in patients with severe kidney impairment (or the doctor classes the impairment as severe). A doctor or pharmacist should be consulted before treatment if the patient has ever had any kidney disease. Section 2 of the PL also warns that blood tests should be performed before the beginning of the treatment to check how well the kidney is working. If the results of any test are abnormal, the treatment will not be restarted until all the values have returned to normal. Section 2 of the PL includes interactions between methotrexate and several medicinal products that have been associated with kidney toxicity.

Safety concern	Routine risk minimisation activities
	Other routine risk minimisation measures beyond the Product Information: Pack size. Restricted medical prescription.
Medication errors due to inadvertent daily instead of once weekly dosing	Routine risk communication: None. Routine risk minimisation activities recommending specific clinical measures to address the risk: Section 4.2 of the SmPC states that methotrexate should only be prescribed by physicians with expertise in the use of methotrexate and a full understanding of the risks of methotrexate therapy. In addition, section 4.2 of the SmPC includes a boxed warning stating that in the treatment of rheumatological or dermatological diseases, Jylamvo (methotrexate) must only be taken once a week. Dosage errors in the use of Jylamvo (methotrexate) can result in serious adverse reactions, including death. It advises to read very carefully the section regarding posology of the product. Section 4.2 of the SmPC also states that the prescriber should specify the day of intake on the prescription and that the prescriber should ensure that patients or their carers will be able to comply with the once weekly regimen. There is a warning in section 4.4 of the SmPC stating that the prescriber should make sure patients understand that methotrexate should only be taken once a week. The prescriber should specify the day of intake on the prescription and patients should be instructed on the importance of adhering to the once weekly intakes. In addition, this section includes a boxed warning regarding patients with rheumatological or dermatological diseases, who must be informed unequivocally that treatment is to be taken just once a week and not daily. Incorrect use of methotrexate can result in severe and even fatal adverse reactions. Section 4.9 of the SmPC states that cases of overdose have been reported, sometimes fatal, due to erroneous daily intake instead of weekly intake of oral methotrexate. Section 2 of the PL includes boxed information about the dosage of methotrexate when used for rheumatological and dermatological diseases and advises to read very carefully the section regarding posology of the product. When used for these indications, the product must only be taken once a week. Taking too much methotrexate may be fatal. Section 3 of the PL indicates that the doctor will decide what dose of methotrexate is needed according to the condition the patient is being treated for, how severe it is and the general health of the patient. This dose should be kept to exactly and the doctor's instructions on when to take the medicine should be followed. This section also includes information about the dosage of methotrexate when used for rheumatological and dermatological diseases and indicates that when used for these indications, the product must only be taken once a week. In addition, section 3 of the PL includes a warning stating that if the patient takes more methotrexate than he should, the recommendations made by

Safety concern	Routine risk minimisation activities
	the doctor should be followed. The dose is never to be changed based on the decision of the patient. It also advises on the symptoms of an overdose and that the doctor or hospital casualty department should be contacted if it is suspected that too much has been taken. Other routine risk minimisation measures beyond the Product Information: Labelling: warning on outer and inner packaging. Pack size. Restricted medical prescription.
Bone growth defects in the paediatric population	Routine risk communication: None. Routine risk minimisation activities recommending specific clinical measures to address the risk: None. Other routine risk minimisation measures beyond the Product Information: Pack size. Restricted medical prescription.
Medication error due to the proposed dosage form (medication errors due to incorrect use of the oral dosing syringe and confusion between mg and ml)	Routine risk communication: None. Routine risk minimisation activities recommending specific clinical measures to address the risk: Section 4.2 of the SmPC clearly states how to take the product and the recommended dose (both in mg and ml) for each indication and special populations. There is a boxed warning in section 4.4 of the SmPC stating that the oral solution contains 2 mg of methotrexate in each ml of solution and informs that the scaling of the dosing syringe is in ml and not mg. Incorrect use of methotrexate can result in severe and even fatal adverse reactions. Section 6.6 of the SmPC lists detailed instructions on the use of the syringe. Section 2 of the PL includes a boxed warning stating that the oral solution contains 2 mg of methotrexate in each ml of solution and informs that the scaling of the dosing syringe is in ml and not mg; and advises to read very carefully the section regarding posology of the product. Section 3 of the PL also includes a warning stating that the oral solution contains 2 mg of methotrexate in each ml of solution and informs that the scaling of the dosing syringe is in ml and not mg. This section also lists detailed instructions on the use of the syringe. Other routine risk minimisation measures beyond the Product Information: Pack size. Restricted medical prescription.
Progressive Multifocal Leukoencephalopathy	Routine risk communication: SmPC section 4.8.

Safety concern	Routine risk minimisation activities
	PL section 4. Routine risk minimisation activities recommending specific clinical measures to address the risk: According to section 4.4 of the SmPC, since cases of encephalopathy/leukoencephalopathy have occurred in cancer patients treated with methotrexate, this cannot be ruled out either for patients with non-cancer indications. Section 2 of the PL states that certain brain disorders (encephalopathy/leukoencephalopathy) have been reported in cancer patients receiving methotrexate. Such side effects cannot be excluded when methotrexate is used to treat other diseases. Other routine risk minimisation measures beyond the Product Information: Pack size. Restricted medical prescription.
Use in children younger than 3 years	Routine risk communication: None. Routine risk minimisation activities recommending specific clinical measures to address the risk: Section 4.2 of the SmPC states that use in children under 3 years of age is not recommended as insufficient data on efficacy and safety are available for this patient group. Section 2 of the PL states that methotrexate is not recommended in children under 3 years of age as there is insufficient experience in this age group. Other routine risk minimisation measures beyond the Product Information: Pack size. Restricted medical prescription.

V.2 Additional Risk Minimisation Measures

Educational material

Objectives:

Regarding the identified risk "Medication errors due to inadvertent daily instead of once weekly dosing" and the potential risk "Medication error due to the proposed dosage form (medication errors due to incorrect use of the oral dosing syringe and confusion between mg and ml)", educational material (including a guide for healthcare professionals, a patient card, the SmPC and the PL) are necessary in order to increase the awareness of healthcare professionals and patients of the risk of medication errors with methotrexate for oral use and their possible consequences.

Prior to launch of Jylamvo 2 mg/ml oral solution in each Member State, the MAH must agree about the content and format of the educational material, including communication media, distribution modalities, and any other aspects of the programme, with the National Competent Authority (NCA). Educational materials were already a requirement for Jylamvo and so those already agreed were based on the

current requirements. These educational materials will be updated to reflect the amended educational material requirements and agreed at the national level.

Rationale for the additional risk minimisation activity:

The Pharmacovigilance Risk Assessment Committee (PRAC) noted that despite the introduction of educational material, cases of medication errors continued to be reported. For this reason, the PRAC agreed that educational material should be distributed/updated [EMA/PRAC/360022/2019, 2019].

The main objective is to help mitigate the potential risk of medication errors. Potential causes for medication errors with this product include:

- Inadvertent daily dosing (in arthritis and psoriasis indications).
- Overdose due to confusing mg and ml.

Target audience and planned distribution path:

The MAH shall ensure that, in each Member State where Jylamvo is marketed, all healthcare professionals who are expected to prescribe, or dispense and patients who receive Jylamvo 2 mg/ml oral solution have access to their respective educational material.

Plans to evaluate the effectiveness of the interventions and criteria for success:

The effectiveness of the educational material and its Communication Plan will be assessed as defined in the Communication and Effectiveness Evaluation and Oversight Plans agreed at the national level; it is evaluated as part of the annual full review of the Risk Management Plan by Therakind and the EEA QPPV. This broadly involves a review of:

- Annual and cumulative incidence rates of overdose.
- Compliance with the requirements of the Communication Plan.

The conclusions of this review and any recommendations for strengthening the process are documented. Any compliance issues are addressed through the appropriate deviation/CAPA (Corrective and Preventative Action) system. If the educational material or its Communication Plan are believed to be less than effective, recommendations to strengthen it are generated and approvals sought from the Regulatory Authority of each Member State as appropriate.

Direct Healthcare Professional Communication (DHPC)

Objectives:

Regarding the identified risk "Medication errors due to inadvertent daily instead of once weekly dosing", a DHPC has been agreed upon to raise awareness of the new recommendations and other risk minimisation measures regarding medication errors.

Rationale for the additional risk minimisation activity:

The PRAC noted that despite the introduction of educational material, cases of medication errors continued to be reported. For this reason, the PRAC agreed that a DHPC should be distributed to inform healthcare professionals of recommendations to avoid potentially fatal dosing errors when using methotrexate for autoimmune diseases [EMA/PRAC/360022/2019, 2019].

Target audience and planned distribution path:

The MAH shall ensure that, in each Member State where Jylamvo is marketed, DHPCs are distributed to all healthcare professionals involved in prescribing, dispensing and handling of methotrexate-

containing products (e.g. physicians and pharmacists). Target groups should be further defined at national level, depending on national health care systems.

Plans to evaluate the effectiveness of the interventions and criteria for success:

The effectiveness of the DHPC broadly involves a review of:

- Effectiveness of distribution (% of documented deliveries to target population).
- Comparison of 12-months and cumulative incidence rates of overdose before and after distribution.

The conclusions of this review and any recommendations for strengthening the process are documented. Any compliance issues are addressed through the appropriate deviation/CAPA (Corrective and Preventative Action) system. If the DHPC or its distribution are believed to be less than effective, recommendations to strengthen it are generated and approvals sought from the Regulatory Authority of each Member State as appropriate.

V.3 Summary of risk minimisation measures

Table Part V.3: Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Increased risk of neoplasia	Routine risk minimisation measures: SmPC section 4.8. PL section 4. Section 4.4 of the SmPC states that malignant lymphomas may occur in patients receiving low-dose methotrexate, in which case therapy must be discontinued. If the lymphomas fail to regress spontaneously, cytotoxic treatment must be initiated. Section 2 of the PL states that enlarged lymph nodes (lymphoma) may occur in patients receiving low dose methotrexate and if this is the case, therapy must be stopped. Pack size. Restricted medical prescription. Additional risk minimisation measures: None.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None. Additional pharmacovigilance activities: None.
Haematological toxicity	Routine risk minimisation measures: SmPC section 4.8. PL section 4. According to section 4.3 of the SmPC, Jylamvo is contraindicated in patients with pre-existing blood disorders such as bone marrow hypoplasia, leukopenia, thrombocytopenia or significant anaemia; in patients with immunodeficiency or severe, acute or	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None. Additional

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	chronic infections such as tuberculosis and HIV. Concurrent vaccination with live vaccines is also contraindicated. There is a warning in section 4.4 of the SmPC recommending performing a complete blood count with differential blood count and platelets before beginning treatment with methotrexate or resuming treatment after a recovery period. In addition, this test is to be conducted weekly in the first 2 weeks, then every 2 weeks for a month. Thereafter, depending on the leucocyte count and the stability of the patient, it should be conducted at least once a month during the next 6 months and then at least every 3 months. Section 4.4 of the SmPC also warns on the methotrexate-induced haematopoietic suppression that may occur abruptly and with apparently safe doses. Any serious decrease in leucocyte or platelet counts indicates the immediate discontinuation of treatment and appropriate supportive therapy. Patients should be encouraged to report all signs and symptoms suggestive of infection to their doctor. According to section 4.4 of the SmPC, especially strict monitoring of the patient is indicated following functional impairment of the haematopoietic system (e.g. following prior radio- or chemotherapy) and in patients simultaneously taking haematotoxic medicinal products (e.g. leflunomide). In addition, this section of the SmPC includes a warning stating that doses exceeding 20 mg (10 ml)/week can be associated with a substantial increase in toxicity, especially bone marrow depression. Furthermore, there is a warning in section 4.4 of the SmPC stating that concurrent vaccination using live vaccines should not be given since, due to its effect on the immune system, methotrexate may impair the response to vaccinations and affect the results of immunological tests. Section 4.5 of the SmPC includes interactions between methotrexate and several medicinal products that have been associated with haematological toxicity. According to section 2 of the PL, Jylamvo should not be taken in patients with blood disorders such as bone marrow hypoplasia, leukopenia, thrombocytopenia or significant anaemia; in patients	pharmacovigilance activities: None.

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	with a weakened immune system or suffering from a serious infection such as tuberculosis or HIV. The product should also not be taken with concurrent vaccination with live vaccines. Section 2 of the PL also warns that laboratory tests should be performed in order to detect side effects. Section 2 of the PL includes interactions between methotrexate and several medicinal products that have been associated with haematological toxicity. In addition, section 4 of the PL encourages patients to report all signs and symptoms suggestive of infection to their doctor. Pack size. Restricted medical prescription. Additional risk minimisation measures: None.	
Hepatotoxicity	Routine risk minimisation measures: SmPC section 4.8. PL section 4. Section 4.2 of the SmPC states that methotrexate should be administered only with the greatest caution, if at all, in patients with significant existing or previous liver disease, especially if due to alcohol. According to section 4.3 of the SmPC, Jylamvo is contraindicated in patients with hepatic impairment (bilirubin levels >5 mg/dl (85.5 µmol/l)) and in patients with alcohol abuse. Section 4.4 of the SmPC states that methotrexate should be used only with great caution, if at all, in patients who have a significant liver disease, particularly if this is/was alcohol related. There is a warning in section 4.4 of the SmPC recommending performing liver function tests before beginning treatment with methotrexate or resuming treatment after a recovery period. In addition, such tests are to be conducted weekly in the first 2 weeks, then every 2 weeks for a month. Thereafter, depending on the leucocyte count and the stability of the patient, it should be conducted at least once a month during the next 6 months and then at least every 3 months. According to the section 4.4 of the SmPC, the treatment should not be started or should be discontinued if there are any abnormalities in liver function tests or liver biopsies, or if these develop	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None. Additional pharmacovigilance activities: None.

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	during therapy. If liver enzymes are constantly increased, a dose reduction or treatment discontinuation should be considered. This section of the SmPC also states that additional hepatotoxic medicinal products should not be taken during treatment with methotrexate unless urgently necessary, due to methotrexate's potentially toxic effect on the liver. Likewise, alcohol consumption should be avoided or reduced. Section 4.4 of the SmPC recommends closer monitoring of liver enzymes in patients taking other hepatotoxic medicinal products concomitantly. In addition, this should be considered during simultaneous administration of haematotoxic medicinal products. Finally, it recommends increased caution in patients with insulin-dependent diabetes mellitus as hepatic cirrhosis has developed in individual cases without any elevation of transaminases during methotrexate treatment. Section 4.5 of the SmPC includes interactions between methotrexate and several medicinal products that have been associated with hepatic toxicity. According to section 2 of the PL, Jylamvo should not be taken in patients with liver impairment or in case of alcohol abuse. A doctor or pharmacist should be consulted before treatment if the patient has ever had any liver disease. Section 2 of the PL also warns that blood tests should be performed before the beginning of the treatment to check how well the liver is working. If the results of any test are abnormal, the treatment will not be restarted until all the values have returned to normal. Section 2 of the PL includes interactions between methotrexate and several medicinal products that have been associated with hepatic toxicity. Pack size. Restricted medical prescription. Additional risk minimisation measures: None.	
Pulmonary toxicity	Routine risk minimisation measures: SmPC section 4.8. PL section 4. There is a warning in section 4.4 of the SmPC recommending performing a chest X-ray before	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	beginning treatment with methotrexate or resuming treatment after a recovery period. In addition, patients must be monitored for symptoms of a lung function disorder and lung function tests should be performed if necessary. Lung-related symptoms (particularly a dry, non-productive cough) or non-specific pneumonitis that occurs during treatment with methotrexate can be a sign of potentially dangerous damage and require the discontinuation of treatment and careful monitoring. In these cases, a chest X-ray must be taken in order to be able to exclude an infection and tumours. Patients should be informed of the risk of pneumonia and advised to contact their doctor immediately if they develop a persistent cough or persistent dyspnoea. Pulmonary symptoms require a rapid diagnosis and discontinuation of methotrexate therapy. In addition, section 4.4 of the SmPC suggests considering prompt investigation when pulmonary alveolar haemorrhage is suspected to confirm the diagnosis. According to this section, opportunistic infections can occur during treatment with methotrexate, including *Pneumocystis jiroveci pneumonia*, which can also have a fatal outcome. If a patient develops pulmonary symptoms, the possibility of *Pneumocystis jiroveci pneumonia* should be considered. Particular caution is also required in patients with impaired pulmonary function, in patients with inactive chronic infections (e.g. herpes zoster, tuberculosis, hepatitis B or C) as it is possible that activation of these infections may occur. Section 2 of the PL recommends consulting a doctor or pharmacist before beginning treatment with Jylamvo if the patient has problems with the lung function or if the patient has an abnormal build-up of fluid in the abdomen (ascites) or around the lungs (pleural effusions). Acute bleeding from the lungs in patients with underlying rheumatologic disease has been reported with methotrexate. If case of experiencing symptoms of spitting or coughing up blood, a doctor should be consulted immediately. Section 2 of the PL also warns that an X-ray may be performed before the beginning of the treatment. If the results are abnormal, the treatment will not be restarted until the values have returned to normal. Pack size.	None. Additional pharmacovigilance activities: None.

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	Restricted medical prescription. Additional risk minimisation measures: None.	
Renal toxicity	Routine risk minimisation measures: SmPC section 4.8. PL section 4. Section 4.2 of the SmPC states that methotrexate should be used with caution in patients with impaired renal function and that the dose should be adjusted for patients with rheumatoid arthritis, juvenile arthritis, psoriasis and psoriatic arthritis. For the oncology indication recommendations in published protocols should also apply. According to section 4.3 of the SmPC, Methotrexate 2 mg/ml oral solution is contraindicated in patients with severe renal impairment (creatinine clearance less than 30 ml/min). Section 4.4 of the SmPC states that because of the delayed excretion of methotrexate in patients with impaired kidney function, they should be treated with particular caution and only with low doses of methotrexate. There is a warning in section 4.4 of the SmPC recommending performing renal function tests before beginning treatment with methotrexate or resuming treatment after a recovery period. In addition, these tests are to be conducted weekly in the first 2 weeks, then every 2 weeks for a month. Thereafter, depending on the leucocyte count and the stability of the patient, it should be conducted at least once a month during the next 6 months and then at least every 3 months. Renal function should be monitored by renal function tests and urinalyses. If serum creatinine levels are increased, the dose should be reduced and if creatinine clearance is less than 30 ml/min, treatment with methotrexate should not be given. Treatment with moderately high and high doses of methotrexate should not be initiated at urinary pH values of less than 7.0. Alkalinisation of the urine must be tested by repeated pH monitoring (value greater than or equal to 6.8) for at least the first 24 hours after the administration of methotrexate is started. In addition, this section 4.4 includes a warming	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None. Additional pharmacovigilance activities: None.

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	stating that as methotrexate is eliminated mainly via the kidneys, increased concentrations are to be expected in the presence of renal impairment, which may result in severe adverse reactions. If there is the possibility of renal impairment (e.g. in elderly subjects), monitoring should take place at shorter intervals. This applies in particular when medicinal products that affect the elimination of methotrexate, or that cause kidney damage (e.g. NSAIDs) or that can potentially lead to impairment of haematopoiesis, are administered concomitantly. If risk factors such as renal function disorders, including mild renal impairment, are present, combined administration with NSAIDs is not recommended. Dehydration may also intensify the toxicity of methotrexate. Section 4.5 of the SmPC includes interactions between methotrexate and several medicinal products that have been associated with renal toxicity. According to section 2 of the PL, Jylamvo should not be taken in patients with severe kidney impairment (or the doctor classes the impairment as severe). A doctor or pharmacist should be consulted before treatment if the patient has ever had any kidney disease. Section 2 of the PL also warns that blood tests should be performed before the beginning of the treatment to check how well the kidney is working. If the results of any test are abnormal, the treatment will not be restarted until all the values have returned to normal. Section 2 of the PL includes interactions between methotrexate and several medicinal products that have been associated with kidney toxicity. Pack size. Restricted medical prescription. Additional risk minimisation measures: None.	
Medication errors due to inadvertent daily instead of once weekly dosing	Routine risk minimisation measures: Section 4.2 of the SmPC states that methotrexate should only be prescribed by physicians with expertise in the use of methotrexate and a full understanding of the risks of methotrexate therapy. In addition, section 4.2 of the SmPC includes a boxed warning stating that in the treatment of rheumatological or dermatological diseases, Jylamvo (methotrexate) must only be taken once a week.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Specific adverse reaction follow-up questionnaire for

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	Dosage errors in the use of Jylamvo (methotrexate) can result in serious adverse reactions, including death. It advises to read very carefully the section regarding posology of the product. Section 4.2 of the SmPC also states that the prescriber should specify the day of intake on the prescription and that the prescriber should ensure that patients or their carers will be able to comply with the once weekly regimen. There is a warning in section 4.4 of the SmPC stating that the prescriber should make sure patients understand that methotrexate should only be taken once a week. The prescriber should specify the day of intake on the prescription and patients should be instructed on the importance of adhering to the once weekly intakes. In addition, this section includes a boxed warning regarding patients with rheumatological or dermatological diseases, who must be informed unequivocally that treatment is to be taken just once a week and not daily. Incorrect use of methotrexate can result in severe and even fatal adverse reactions. Section 4.9 of the SmPC states that cases of overdose have been reported, sometimes fatal, due to erroneous daily intake instead of weekly intake of oral methotrexate. Section 2 of the PL includes boxed information about the dosage of methotrexate when used for rheumatological and dermatological diseases and advises to read very carefully the section regarding posology of the product. When used for these indications, the product must only be taken once a week. Taking too much methotrexate may be fatal. Section 3 of the PL indicates that the doctor will decide what dose of methotrexate is needed according to the condition the patient is being treated for, how severe it is and the general health of the patient. This dose should be kept exactly and the doctor's instructions on when to take the medicine should be followed. This section also includes information about the dosage of methotrexate when used for rheumatological and dermatological diseases and indicates that when used for these indications, the product must only be taken once a week. In addition, section 3 of the PL includes a warning stating that if the patient takes more methotrexate than he should, the recommendations made by the	medication errors. Additional pharmacovigilance activities: None.

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	doctor should be followed. The dose is never to be changed based on the decision of the patient. It also advises on the symptoms of an overdose and that the doctor or hospital casualty department should be contacted if it is suspected that too much has been taken. Labelling: warning on outer and inner packaging. Pack size. Restricted medical prescription. Additional risk minimisation measures: Educational material (including a guide for health care professionals and a patient card). DHPC.	
Bone growth defects in the paediatric population	Routine risk minimisation measures: Pack size. Restricted medical prescription. Additional risk minimisation measures: None.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None. Additional pharmacovigilance activities: None.
Medication error due to the proposed dosage form (medication errors due to incorrect use of the oral dosing syringe and confusion between mg and ml)	Routine risk minimisation measures: Section 4.2 of the SmPC clearly states how to take the product and the recommended dose (both in mg and ml) for each indication and special populations. There is a boxed warning in section 4.4 of the SmPC stating that the oral solution contains 2 mg of methotrexate in each ml of solution and informs that the scaling of the dosing syringe is in ml and not mg. Incorrect use of methotrexate can result in severe and even fatal adverse reactions. Section 6.6 of the SmPC lists detailed instructions on the use of the syringe. Section 2 of the PL includes a boxed warning stating that the oral solution contains 2 mg of methotrexate in each ml of solution and informs that the scaling of the dosing syringe is in ml and not mg; and advises to read very carefully the section regarding posology of the product. Section 3 of the PL also includes a warning stating	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Specific adverse reaction follow-up questionnaire for medication errors. Additional pharmacovigilance activities: None.

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	that the oral solution contains 2 mg of methotrexate in each ml of solution and informs that the scaling of the dosing syringe is in ml and not mg. This section also lists detailed instructions on the use of the syringe. Pack size. Restricted medical prescription. Additional risk minimisation measures: Educational Material.	
Progressive Multifocal Leukoencephalopathy	Routine risk minimisation measures: SmPC section 4.8. PL section 4. According to section 4.4 of the SmPC, since cases of encephalopathy/leukoencephalopathy have occurred in cancer patients treated with methotrexate, this cannot be ruled out either for patients with non-cancer indications. Section 2 of the PL states that certain brain disorders (encephalopathy/leukoencephalopathy) have been reported in cancer patients receiving methotrexate. Such side effects cannot be excluded when methotrexate is used to treat other diseases. Pack size. Restricted medical prescription. Additional risk minimisation measures: None.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None. Additional pharmacovigilance activities: None.
Use in children younger than 3 years	Routine risk minimisation measures: Section 4.2 of the SmPC states that use in children under 3 years of age is not recommended as insufficient data on efficacy and safety are available for this patient group. Section 2 of the PL states that methotrexate is not recommended in children under 3 years of age as there is insufficient experience in this age group. Pack size. Restricted medical prescription. Additional risk minimisation measures: None.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None. Additional pharmacovigilance activities: None.

Part VI: Summary of the risk management plan

Summary of risk management plan for Jylamvo 2 mg/ml oral solution (methotrexate)

This is a summary of the risk management plan (RMP) for Jylamvo 2 mg/ml oral solution. The RMP details important risks of Jylamvo 2 mg/ml oral solution, how these risks can be minimised, and how more information will be obtained about Jylamvo 2 mg/ml oral solution's risks and uncertainties (missing information).

Jylamvo 2 mg/ml oral solution's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how Jylamvo 2 mg/ml oral solution should be used.

This summary of the RMP for Jylamvo 2 mg/ml oral solution should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all 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 Jylamvo 2 mg/ml oral solution's RMP.

I. The medicine and what it is used for

Jylamvo 2 mg/ml oral solution is authorised for use in the following indications: in rheumatological and dermatological diseases (active rheumatoid arthritis in adult patients; polyarthritic forms of active, severe Juvenile Idiopathic Arthritis (JIA) in adolescents and children aged 3 years and over when the response to NSAIDs has been inadequate; and in severe, treatment-refractory, disabling psoriasis which does not respond sufficiently to other forms of treatment such as phototherapy, Psoralen and Ultraviolet A radiation therapy and retinoids, and severe psoriatic arthritis in adult patients). It is also indicated in oncology (maintenance treatment of Acute Lymphoblastic Leukaemia in adults, adolescents and children aged 3 years and over) (see SmPC for the full indication).

It contains methotrexate as the active substance and it is given by the oral route of administration.

Further information about the evaluation of Jylamvo 2 mg/ml oral solution's benefits can be found in Jylamvo 2 mg/ml oral solution'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/jylamvo

II. Risks associated with the medicine and activities to minimise or further characterise the risks

Important risks of Jylamvo 2 mg/ml oral solution, together with measures to minimise such risks and the proposed studies for learning more about Jylamvo 2 mg/ml oral solution'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 the case of Jylamvo 2 mg/ml oral solution, these measures are supplemented with *additional risk minimisation measures* mentioned under relevant important risks, below.

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

If important information that may affect the safe use of Jylamvo 2 mg/ml oral solution is not yet available, it is listed under 'missing information' below.

II.A List of important risks and missing information

Important risks of Jylamvo 2 mg/ml oral solution are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely taken. 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 Jylamvo 2 mg/ml oral solution. 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	• Increased risk of neoplasia • Haematological toxicity • Hepatotoxicity • Pulmonary toxicity • Renal toxicity • Medication errors due to inadvertent daily instead of once weekly dosing
Important potential risks	• Bone growth defects in the paediatric population • Medication error due to the proposed dosage form (medication errors due to incorrect use of the oral dosing syringe and confusion between mg and ml) • Progressive Multifocal Leukoencephalopathy
Missing information	• Use in children younger than 3 years

II.B Summary of important risks

Important identified risk: Increased risk of neoplasia	
Evidence for linking the risk to the medicine	Immunosuppressive therapy (such as methotrexate) for patients diagnosed with RA has long been implicated in the development of various neoplastic processes, including leukaemia, lymphoma, melanoma and lung cancer [Barclay, 2008; Naidu, 2014]. Among conditions, iatrogenic immunodeficiency-associated lymphoproliferative disorders due to methotrexate are particularly common [Inui, 2015].
Risk factors and risk groups	Patients with systemic rheumatic diseases, particularly rheumatoid arthritis, systemic lupus erythematosus, systemic sclerosis and idiopathic inflammatory myopathies, are at increased risk of developing malignancies. This risk is related to the pathobiology of the underlying rheumatic diseases including the inflammatory burden, immunological defects, and personal and environmental exposure such as smoking and some viral infections [Raheel, 2016]. In particular, several studies have reported that malignant lymphoma is 2-5.5 times more prevalent in patients with rheumatoid arthritis than in healthy individuals [Inui, 2015]. There is an increased risk for malignant neoplasms in patients older than 70 years who are treated with methotrexate compared to the general population and an increased risk for those who had ever used cyclophosphamide [Barclay, 2008]. Long-term methotrexate therapy is also a risk factor for developing lymphoma [Naidu, 2014].
Risk minimisation measures	Routine risk minimisation measures: SmPC section 4.8. PL section 4. Section 4.4 of the SmPC states that malignant lymphomas may occur in patients receiving low-dose methotrexate, in which case therapy must be discontinued. If the lymphomas fail to regress spontaneously, cytotoxic treatment must be initiated. Section 2 of the PL states that enlarged lymph nodes (lymphoma) may occur in patients receiving low dose methotrexate and if this is the case, therapy must be stopped. Pack size. Restricted medical prescription. Additional risk minimisation measures: None.

Important identified risk: Haematological toxicity	
Evidence for linking the risk to the medicine	Exposure to methotrexate concentrations as low as 0.01 for more than 24 hours may result in bone marrow toxicity [Widemann, 2006]. Haematologic toxicity is a serious complication commonly observed with high-dose methotrexate. This complication consists of a thrombocytopenia followed by a rapidly progressive neutropenia. Leukopenia occurs from one to three weeks and marrow recovery is generally observed within approximately 3 weeks. Haematologic toxicity including thrombocytopenia, megaloblastic anaemia, leukopenia and pancytopenia with low-dose methotrexate are rare [Gaies, 2012].
Risk factors and risk groups	Pancytopenia due to methotrexate is attributed to the patients with renal dysfunction, presence of infection, folic acid deficiency, hypoalbuminemia, concomitant use of drugs such as trimethoprim, high doses of methotrexate and advanced age [Agarwal, 2008; Jariwala, 2014; Gonzalez-Ibarra, 2014; Knoll, 2016]. Serum albumin levels and folic acid supplementation are the important factors affecting the severity of methotrexate-related pancytopenia and neutropenia. Slow elimination of methotrexate in patients with renal insufficiency leads to prolonged exposure of bone marrow tissues to this drug. Renal insufficiency has been incriminated as the major risk factor for myelosuppression [Mori, 2016].
Risk minimisation measures	Routine risk minimisation measures: SmPC section 4.8. PL section 4. According to section 4.3 of the SmPC, Jylamvo is contraindicated in patients with pre-existing blood disorders such as bone marrow hypoplasia, leukopenia, thrombocytopenia or significant anaemia; in patients with immunodeficiency or severe, acute or chronic infections such as tuberculosis and HIV. Concurrent vaccination with live vaccines is also contraindicated. There is a warning in section 4.4 of the SmPC recommending performing a complete blood count with differential blood count and platelets before beginning treatment with methotrexate or resuming treatment after a recovery period. In addition, this test is to be conducted weekly in the first 2 weeks, then every 2 weeks for a month. Thereafter, depending on the leucocyte count and the stability of the patient, it should be conducted at least once a month during the next 6 months and then at least every 3 months. Section 4.4 of the SmPC also warns on the methotrexate-induced haematopoietic suppression that may occur abruptly and with apparently safe doses. Any serious decrease in leucocyte or platelet counts indicates the immediate discontinuation of

Important identified risk: Haematological toxicity	
	treatment and appropriate supportive therapy. Patients should be encouraged to report all signs and symptoms suggestive of infection to their doctor. According to section 4.4 of the SmPC, especially strict monitoring of the patient is indicated following functional impairment of the haematopoietic system (e.g. following prior radio- or chemotherapy) and in patients simultaneously taking haematotoxic medicinal products (e.g. leflunomide). In addition, this section of the SmPC includes a warning stating that doses exceeding 20 mg (10 ml)/week can be associated with a substantial increase in toxicity, especially bone marrow depression. Furthermore, there is a warning in section 4.4 of the SmPC stating that concurrent vaccination using live vaccines should not be given since, due to its effect on the immune system, methotrexate may impair the response to vaccinations and affect the results of immunological tests. Section 4.5 of the SmPC includes interactions between methotrexate and several medicinal products that have been associated with haematological toxicity. According to section 2 of the PL, Jylamvo should not be taken in patients with blood disorders such as bone marrow hypoplasia, leukopenia, thrombocytopenia or significant anaemia; in patients with a weakened immune system or suffering from a serious infection such as tuberculosis or HIV. The product should also not be taken with concurrent vaccination with live vaccines. Section 2 of the PL also warns that laboratory tests should be performed in order to detect side effects. Section 2 of the PL includes interactions between methotrexate and several medicinal products that have been associated with haematological toxicity. In addition, section 4 of the PL encourages patients to report all signs and symptoms suggestive of infection to their doctor. Pack size. Restricted medical prescription. Additional risk minimisation measures: None.

Important identified risk: Hepatotoxicity	
Evidence for linking the risk to the medicine	Long-term methotrexate use or its usage in high doses may cause hepatic steatosis, cholestasis, fibrosis and cirrhosis [Aslaner, 2015]. Methotrexate liver dysfunction is mostly associated with its chronic use in inflammatory disease, although acute hepatitis following high-dose administration has been described. Liver enzyme abnormalities under methotrexate treatment do not necessarily

Important identified risk: Hepatotoxicity	
	represent significant liver toxicity as they usually resolve with dose modification or drug discontinuation and may even normalise during the course of therapy [Rabinowich, 2015].
Risk factors and risk groups	Potential risk factors suggested for hepatic adverse effects in patients with rheumatoid arthritis are increased age, female gender, alcohol intake, smoking, disease duration, diabetes and obesity, hepatitis B or C infection cumulative dose of methotrexate, concomitant medications mainly NSAIDs, and other DMARDs. Genetic factors may also play a role in predicting such adverse effects [Sotoudehmanesh, 2010; Issabeagloo, 2011; Weidmann, 2014; Dubey, 2016; Tang, 2016]. One major factor of methotrexate-induced hepatotoxicity, aside from the above-mentioned comorbidities, is the frequency of administration [Herfarth, 2012].
Risk minimisation measures	Routine risk minimisation measures: SmPC section 4.8. PL section 4. Section 4.2 of the SmPC states that methotrexate should be administered only with the greatest caution, if at all, in patients with significant existing or previous liver disease, especially if due to alcohol. According to section 4.3 of the SmPC, Jylamvo is contraindicated in patients with hepatic impairment (bilirubin levels >5 mg/dl (85.5 µmol/l)) and in patients with alcohol abuse. Section 4.4 of the SmPC states that methotrexate should be used only with great caution, if at all, in patients who have a significant liver disease, particularly if this is/was alcohol related. There is a warning in section 4.4 of the SmPC recommending performing liver function tests before beginning treatment with methotrexate or resuming treatment after a recovery period. In addition, such tests are to be conducted weekly in the first 2 weeks, then every 2 weeks for a month. Thereafter, depending on the leucocyte count and the stability of the patient, it should be conducted at least once a month during the next 6 months and then at least every 3 months. According to the section 4.4 of the SmPC, the treatment should not be started or should be discontinued if there are any abnormalities in liver function tests or liver biopsies, or if these develop during therapy. If liver enzymes are constantly increased, a dose reduction or treatment discontinuation should be considered. This section of the SmPC also states that additional hepatotoxic medicinal products should not be taken during treatment with methotrexate unless urgently necessary, due to methotrexate's potentially toxic effect on the liver. Likewise, alcohol consumption should be avoided or reduced.

Important identified risk: Hepatotoxicity	
	Section 4.4 of the SmPC recommends closer monitoring of liver enzymes in patients taking other hepatotoxic medicinal products concomitantly. In addition, this should be considered during simultaneous administration of haematotoxic medicinal products. Finally, it recommends increased caution in patients with insulin-dependent diabetes mellitus as hepatic cirrhosis has developed in individual cases without any elevation of transaminases during methotrexate treatment. Section 4.5 of the SmPC includes interactions between methotrexate and several medicinal products that have been associated with hepatic toxicity. According to section 2 of the PL, Jylamvo should not be taken in patients with liver impairment or in case of alcohol abuse. A doctor or pharmacist should be consulted before treatment if the patient has ever had any liver disease. Section 2 of the PL also warns that blood tests should be performed before the beginning of the treatment to check how well the liver is working. If the results of any test are abnormal, the treatment will not be restarted until all the values have returned to normal. Section 2 of the PL includes interactions between methotrexate and several medicinal products that have been associated with hepatic toxicity. Pack size. Restricted medical prescription. Additional risk minimisation measures: None.

Important identified risk: Pulmonary toxicity	
Evidence for linking the risk to the medicine	Long-term use at therapeutic doses or overdose of methotrexate can cause significant dose-dependent pulmonary side effects, such as acute and subacute respiratory failure, non-productive cough, dyspnoea, fever, pneumonitis, interstitial lung disease and pulmonary fibrosis [Kurt, 2015]. In addition, pulmonary alveolar haemorrhage has been reported for methotrexate used in rheumatologic and related indications [EMA/PRAC/8429/2018 Corr, 2018].
Risk factors and risk groups	Multicentre case-control studies have been performed which may predict the possibility of methotrexate lung injury and the following risk factors have been identified: diabetes, rheumatoid pulmonary involvement, previous use of DMARDs, older age (>60 years), pre-existing lung disease [Hlaing, 2007], smoking, acetylsalicylic acid use and renal insufficiency [Liu, 2015]. The factors found to be associated with the higher risk for development of interstitial lung disease in rheumatoid arthritis were

Important identified risk: Pulmonary toxicity	
	male gender, age, presence of inflammatory arthritis, disease activity, history of smoking, high titre rheumatoid factor and anti-cyclic citrullinated protein antibodies [Anand, 2014].
Risk minimisation measures	Routine risk minimisation measures: SmPC section 4.8. PL section 4. There is a warning in section 4.4 of the SmPC recommending performing a chest X-ray before beginning treatment with methotrexate or resuming treatment after a recovery period. In addition, patients must be monitored for symptoms of a lung function disorder and lung function tests should be performed if necessary. Lung-related symptoms (particularly a dry, non-productive cough) or non-specific pneumonitis that occurs during treatment with methotrexate can be a sign of potentially dangerous damage and require the discontinuation of treatment and careful monitoring. In these cases, a chest X-ray must be taken in order to be able to exclude an infection and tumours. Patients should be informed of the risk of pneumonia and advising them to contact their doctor immediately if they develop a persistent cough or persistent dyspnoea. Pulmonary symptoms require a rapid diagnosis and discontinuation of methotrexate therapy. In addition, section 4.4 of the SmPC suggests considering prompt investigation when pulmonary alveolar haemorrhage is suspected to confirm the diagnosis. According to this section, opportunistic infections can occur during treatment with methotrexate, including *Pneumocystis jiroveci pneumonia*, which can also have a fatal outcome. If a patient develops pulmonary symptoms, the possibility of *Pneumocystis jiroveci pneumonia* should be considered. Particular caution is also required in patients with impaired pulmonary function, in patients with inactive chronic infections (e.g. herpes zoster, tuberculosis, hepatitis B or C) as it is possible that activation of these infections may occur. Section 2 of the PL recommends consulting a doctor or pharmacist before beginning treatment with Jylamvo if the patient has problems with the lung function or if the patient has an abnormal build-up of fluid in the abdomen (ascites) or around the lungs (pleural effusions). Acute bleeding from the lungs in patients with underlying rheumatologic disease has been reported with methotrexate. If case of experiencing symptoms of spitting or coughing up blood, a doctor should be consulted immediately. Section 2 of the PL also warns that an X-ray may be performed before the beginning of the treatment. If the results are abnormal, the treatment will not be restarted until the values have returned to normal. Pack size.

Important identified risk: Pulmonary toxicity	
	Restricted medical prescription. Additional risk minimisation measures: None.

Important identified risk: Renal toxicity	
Evidence for linking the risk to the medicine	It is well known that renal clearance is the principal pathway of methotrexate elimination, and its elimination appears to be related to renal function. On the other hand, nephrotoxicity is one of the most frequently reported side effects of high-dose methotrexate infusion, especially in patients with delayed methotrexate elimination [Yang, 2015]. Methotrexate-induced renal dysfunction results in sustained, elevated plasma methotrexate concentrations, which in turn may lead to ineffective rescue by leucovorin and a marked enhancement of methotrexate's other toxicities, especially myelosuppression, mucositis, hepatitis and dermatitis [Widemann, 2006].
Risk factors and risk groups	Risk factors for methotrexate-associated toxicity include a history of renal dysfunction, volume depletion, acidic urine and drug interactions [Howard, 2016].
Risk minimisation measures	Routine risk minimisation measures: SmPC section 4.8. PL section 4. Section 4.2 of the SmPC states that methotrexate should be used with caution in patients with impaired renal function and that the dose should be adjusted for patients with rheumatoid arthritis, juvenile arthritis, psoriasis and psoriatic arthritis. For the oncology indication recommendations in published protocols should also apply. According to section 4.3 of the SmPC, Methotrexate 2 mg/ml oral solution is contraindicated in patients with severe renal impairment (creatinine clearance less than 30 ml/min). Section 4.4 of the SmPC states that because of the delayed excretion of methotrexate in patients with impaired kidney function, they should be treated with particular caution and only with low doses of methotrexate. There is a warning in section 4.4 of the SmPC recommending performing renal function tests before beginning treatment with methotrexate or resuming treatment after a recovery period. In addition, these tests are to be conducted weekly in the first 2 weeks, then every 2 weeks for a month. Thereafter, depending on the leucocyte count and the stability of the patient, it should be conducted at least once a month during the next 6 months and then at least every 3 months. Renal function should be

Important identified risk: Renal toxicity	
	monitored by renal function tests and urinalyses. If serum creatinine levels are increased, the dose should be reduced and if creatinine clearance is less than 30 ml/min, treatment with methotrexate should not be given. Treatment with moderately high and high doses of methotrexate should not be initiated at urinary pH values of less than 7.0. Alkalinisation of the urine must be tested by repeated pH monitoring (value greater than or equal to 6.8) for at least the first 24 hours after the administration of methotrexate is started. In addition, this section 4.4 includes a warming stating that as methotrexate is eliminated mainly via the kidneys, increased concentrations are to be expected in the presence of renal impairment, which may result in severe adverse reactions. If there is the possibility of renal impairment (e.g. in elderly subjects), monitoring should take place at shorter intervals. This applies in particular when medicinal products that affect the elimination of methotrexate, or that cause kidney damage (e.g. NSAIDs) or that can potentially lead to impairment of haematopoiesis, are administered concomitantly. If risk factors such as renal function disorders, including mild renal impairment, are present, combined administration with NSAIDs is not recommended. Dehydration may also intensify the toxicity of methotrexate. Section 4.5 of the SmPC includes interactions between methotrexate and several medicinal products that have been associated with renal toxicity. According to section 2 of the PL, Jylamvo should not be taken in patients with severe kidney impairment (or the doctor classes the impairment as severe). A doctor or pharmacist should be consulted before treatment if the patient has ever had any kidney disease. Section 2 of the PL also warns that blood tests should be performed before the beginning of the treatment to check how well the kidney is working. If the results of any test are abnormal, the treatment will not be restarted until all the values have returned to normal. Section 2 of the PL includes interactions between methotrexate and several medicinal products that have been associated with kidney toxicity. Pack size. Restricted medical prescription. Additional risk minimisation measures: None.

Important identified risk: Medication errors due to inadvertent daily instead of once weekly dosing	
Evidence for linking the risk to the medicine	Oral methotrexate is indicated in the treatment of active rheumatoid arthritis, adult psoriasis, severe JIA in adolescents and children over 3 years of age, and in a number of oncological indications such as ALL. Compared to dosing for antineoplastic indications, methotrexate for rheumatological and dermatological diseases is administered once weekly as low-dose therapy. Harmful or fatal errors with low-dose oral methotrexate have been reported; most errors involved accidental daily dosing of oral methotrexate that was intended for weekly administration [EMA/215649/2018, 2018; Grissinger, 2018]. The risk of dosing errors with methotrexate has been recognised for many years and several measures are already in place in some EU countries to reduce this risk, including the use of visual reminders on the medicine packs.
Risk factors and risk groups	A range of factors contribute to these adverse events, including patients not being given sufficient information on how often to take the drug (once weekly and not once daily), lack of clear packaging and variations in patient monitoring and treatment reviews [Mayor, 2003].
Risk minimisation measures	Routine risk minimisation measures: Section 4.2 of the SmPC states that methotrexate should only be prescribed by physicians with expertise in the use of methotrexate and a full understanding of the risks of methotrexate therapy. In addition, section 4.2 of the SmPC includes a boxed warning stating that in the treatment of rheumatological or dermatological diseases, Jylamvo (methotrexate) must only be taken once a week. Dosage errors in the use of Jylamvo (methotrexate) can result in serious adverse reactions, including death. It advises to read very carefully the section regarding posology of the product. Section 4.2 of the SmPC also states that the prescriber should specify the day of intake on the prescription and that the prescriber should ensure that patients or their carers will be able to comply with the once weekly regimen. There is a warning in section 4.4 of the SmPC stating that the prescriber should make sure patients understand that methotrexate should only be taken once a week. The prescriber should specify the day of intake on the prescription and patients should be instructed on the importance of adhering to the once weekly intakes. In addition, this section includes a boxed warning regarding patients with rheumatological or dermatological diseases, who must be informed unequivocally that treatment is to be taken just once a week and not daily. Incorrect use of methotrexate can result in severe and even fatal adverse reactions.

Important identified risk: Medication errors due to inadvertent daily instead of once weekly dosing	
	Section 4.9 of the SmPC states that cases of overdose have been reported, sometimes fatal, due to erroneous daily intake instead of weekly intake of oral methotrexate. Section 2 of the PL includes boxed information about the dosage of methotrexate when used for rheumatological and dermatological diseases and advises to read very carefully the section regarding posology of the product. When used for these indications, the product must only be taken once a week. Taking too much methotrexate may be fatal. Section 3 of the PL indicates that the doctor will decide what dose of methotrexate is needed according to the condition the patient is being treated for, how severe it is and the general health of the patient. This dose should be kept to exactly and the doctor's instructions on when to take the medicine should be followed. This section also includes information about the dosage of methotrexate when used for rheumatological and dermatological diseases and indicates that when used for these indications, the product must only be taken once a week. In addition, section 3 of the PL includes a warning stating that if the patient takes more methotrexate than he should, the recommendations made by the doctor should be followed. The dose is never to be changed based on the decision of the patient. It also advises on the symptoms of an overdose and that the doctor or hospital casualty department should be contacted if it is suspected that too much has been taken. Labelling: warning on outer and inner packaging. Pack size. Restricted medical prescription. Additional risk minimisation measures: Educational material (including a guide for health care professionals and a patient card). DHPC.

Important potential risk: Bone growth defects in the paediatric population	
Evidence for linking the risk to the medicine	Typically, bone metabolism in children with acute lymphoblastic leukaemia (the predominant childhood cancer) is known to be disturbed after chemotherapy, resulting in reduced bone lengthening and bone loss. Bone growth defects or bone loss during childhood may predispose to osteopenia and osteoporosis in later life. While many studies have examined effects of long-term low-dose methotrexate on bone metabolism and have reported no significant adverse effects on bone mineral density, long-term intensive chemotherapy with methotrexate has been shown to cause serious damage to bone development in paediatric patients

Important potential risk: Bone growth defects in the paediatric population	
	[Fan, 2012].
Risk factors and risk groups	Longitudinal bone growth is mainly regulated by genetic and hormonal factors such as growth hormone, insulin-like growth factors, thyroid hormone and glucocorticoids, sex steroids, fibroblast growth factors, epidermal growth factor and related ligands transforming growth factor β and bone morphogenic protein. In addition, environmental factors such as nutrition and medical treatments including chemotherapy have also been shown to be important determinants for bone growth in children, influencing the final height and bone mass of an individual [Fan, 2011].
Risk minimisation measures	Routine risk minimisation measures: Pack size. Restricted medical prescription. Additional risk minimisation measures: None.

Important potential risk: Medication error due to the proposed dosage form (medication errors due to incorrect use of the oral dosing syringe and confusion between mg and ml)	
Evidence for linking the risk to the medicine	Overdose of methotrexate may cause important cutaneous, oral mucosa and systemic side effects. In case of acute intoxication by methotrexate, skin signs and symptoms are a toxicity alert sign and may precede more serious hematologic alterations [Souza, 2016].
Risk factors and risk groups	Patients not being given sufficient information on how to take the product are at higher risk.
Risk minimisation measures	Routine risk minimisation measures: Section 4.2 of the SmPC clearly states how to take the product and the recommended dose (both in mg and ml) for each indication and special populations. There is a boxed warning in section 4.4 of the SmPC stating that the oral solution contains 2 mg of methotrexate in each ml of solution and informs that the scaling of the dosing syringe is in ml and not mg. Incorrect use of methotrexate can result in severe and even fatal adverse reactions. Section 6.6 of the SmPC lists detailed instructions on the use of the syringe. Section 2 of the PL includes a boxed warning stating that the oral solution contains 2 mg of methotrexate in each ml of solution and informs that the scaling of the dosing syringe is in ml and not mg; and advises to read very carefully the section regarding posology of the product. Section 3 of the PL also includes a warning stating that the oral

Important potential risk: Medication error due to the proposed dosage form (medication errors due to incorrect use of the oral dosing syringe and confusion between mg and ml)	
	solution contains 2 mg of methotrexate in each ml of solution and informs that the scaling of the dosing syringe is in ml and not mg. This section also lists detailed instructions on the use of the syringe. Pack size. Restricted medical prescription. Additional risk minimisation measures: Educational Material.

Important potential risk: Progressive Multifocal Leukoencephalopathy	
Evidence for linking the risk to the medicine	Progressive Multifocal Leukoencephalopathy (PML) is a rare and serious infection caused by the John Cunningham (JC) virus and characterised by progressive inflammation and demyelination of the white matter of the brain at multiple locations. Following initial infection, the virus remains latent in multiple tissues in healthy individuals, with reactivation and clinical disease occurring in severely immunosuppressed states [Bharat, 2012].
Risk factors and risk groups	Previous history of other cytotoxic drugs, other biologics or documented cancer [Bharat, 2012].
Risk minimisation measures	Routine risk minimisation measures: SmPC section 4.8. PL section 4. According to section 4.4 of the SmPC, since cases of encephalopathy/leukoencephalopathy have occurred in cancer patients treated with methotrexate, this cannot be ruled out either for patients with non-cancer indications. Section 2 of the PL states that certain brain disorders (encephalopathy/leukoencephalopathy) have been reported in cancer patients receiving methotrexate. Such side effects cannot be excluded when methotrexate is used to treat other diseases. Pack size. Restricted medical prescription. Additional risk minimisation measures: None.

Missing information: Use in children younger than 3 years	
Risk minimisation measures	Routine risk minimisation measures: Section 4.2 of the SmPC states that use in children under 3 years of age is not recommended as insufficient data on efficacy and safety are available for this patient group.

Missing information: Use in children younger than 3 years	
	Section 2 of the PL states that methotrexate is not recommended in children under 3 years of age as there is insufficient experience in this age group. Pack size. Restricted medical prescription. Additional risk minimisation measures: None.

II.C Post-authorisation development plan

II.C.1 Studies which are conditions of the marketing authorisation

There are no studies which are conditions of the marketing authorisation or specific obligation of Jylamvo 2 mg/ml oral solution.

II.C.2 Other studies in post-authorisation development plan

There are no studies required for Jylamvo 2 mg/ml oral solution.

Annex 4 - Specific adverse drug reaction follow-up forms

Targeted Follow-up Questionnaire for Medication Errors related to Overdose

Jylamvo 2 mg/ml oral solution
(methotrexate)

Please complete the following questions, as appropriate, during follow-up assessments of patients reporting Medication Errors. Complete the form as fully as possible and return to the Marketing Authorisation Holder to enable assessment and assurance of the adequacy of the existing patient risk minimization measures.

Therakind Unique Id Number for the original Medication Error report for this patient:
.....

A. Patient Details:

Initials:		Age (at the time of medication error):	
Sex M / F		Weight (if known) (kg):	

B. Suspect Drug Details

Suspect drug:		Indication:	
Prescribed dose:	_____mg once daily ☐ once weekly ☐ other ☐, please specify: _____	Dosage form	oral solution ☐ tablets ☐ parenteral ☐
Dose actually used:	_____mg once daily ☐ once weekly ☐ other ☐, please specify: _____	Treatment dates:	From: _____ To: _____ Or ongoing: ☐

C. Details of Medication Error

1. Classification of medication error:

Error did reach the patient and led to an overdose ☐
Error was noticed before medication was taken by the patient and there was no actual overdose ☐
Unknown ☐

2. Which stage of the medication process did the medication error occur?

Prescribing ☐ Dispensing ☐ Transcription ☐ Preparation for administration ☐
Administration ☐ Unknown ☐ Other ☐, please specify:

_____

3. Please provide start and stop dates of the occurrence of the medication error:

Start date: _____ _____Stop date: _____

Cumulative dose: _____in _____days

4. Where did the error occur?
Hospital ☐ Rehabilitation hospital ☐ Care Home ☐ Outpatient care ☐ At patient's home ☐
Other ☐, please specify:

_____

5. Were there any contributing factors that may have played a part in the origin or the development of the medication error?

a. Patient factors (e.g. poor adherence, cognitive decline, impaired vision, polymedication, first-users) ☐
Please specify:

_____

b. Healthcare professional factors (e.g. not accustomed to Methotrexate use in once weekly indications) ☐
- Human factor: Mix up with other products (e.g. identification incidents due to similarity of appearance of folic acid and methotrexate) ☐
- Organisational (prepared tablet boxes/solution, transition of patient care) ☐
- External factors beyond the control of the healthcare professional or patient (e.g. IT software issues) ☐
- Other ☐
Please specify:

_____

Unknown ☐

D. Details of any Adverse Reaction(s) (side effects) – only complete this section if an adverse reaction (side effect) was experienced

Was there an adverse drug reaction (side effect) experienced as a consequence of the medication error?
Yes ☐ No ☐ Unknown ☐; please specify:

_____

If Yes:
Outcome: Recovered ☐ Recovering ☐ Continuing ☐ Resolved with sequelae ☐
Fatal ☐ Unknown ☐

Do you consider the reaction to be serious? Yes ☐ No ☐
If Yes, please indicate why (tick all that apply):
Patient died due to reaction ☐
Involved or prolonged an inpatient hospitalisation ☐
Life threatening ☐
Involved persistent or significant disability ☐
Congenital anomaly/birth defect ☐
Medically significant/Required intervention to prevent one of the above ☐; please specify:
_____
_____

Action taken with the medicinal product as a result of the medication error:
Drug Withdrawn ☐ Dose Reduced ☐ Dose not changed ☐ Other ☐ please specify:

Unknown ☐

Was the reaction related to the suspect drug?
Yes ☐ No ☐

E. Short narrative with (additional) relevant information (including concurrent medical conditions and test results):

Reporter Details:

Name: _____ _____

Address:

Email: _____

Phone: _____

Fax: _____

Once completed, please send this form to vigicare-therakind@pharmalex.com

[Only those questions from the form should be sent to the reporter which ask for information not yet provided in the initial report. Alternatively, the reporter should be provided with a pre-filled form already including the information initially provided.]

Annex 6 - Details of proposed additional risk minimisation activities (if applicable)

Approved key messages of the additional risk minimisation measures

- **Educational material**

Prior to launch of Jylamvo in each Member State, the Marketing Authorisation Holder (MAH) must agree about the content and format of the educational material, including communication media, distribution modalities, and any other aspects of the programme, with the National Competent Authority.

The MAH shall ensure that, in each Member State where Jylamvo is marketed, all healthcare professionals who are expected to prescribe or dispense Jylamvo have access to the following educational package:

- The Summary of Product Characteristics
- The Patient Leaflet
- Guide for healthcare professionals
- Patient card (for full-text details please refer to PI referred to in Part I Table I.1)

The **Guide for healthcare professionals** shall contain the following key elements:

- Remarks on the importance of reporting ADRs.
- A statement about the responsibility of the prescribing physician to determine which patients may be suitable for home or self-administration of Jylamvo. With every prescription, healthcare professionals should advise the patient and/or caregiver on how to measure the prescribed dose.
- Detailed description regarding strength of the solution and the dose volumes to help clarify the appropriate dose of the oral solution.
- Information on treatment with Jylamvo, administration and posology.
- Information on the importance to fill in prescriptions with clear instructions about once weekly dosing, defined day of intake, and to not use abbreviations; in addition the dose should always be prescribed in mg with ml equivalence based on the correct age of the patient.
- The need to inform patients and relatives/carers about the once weekly dosing.
- The pharmacist should counsel the patient about the inadvertent daily instead of once-weekly dosing.
- The potential for fatal overdose due to Medication Errors (ME), including daily instead of once weekly use.
- Causes of ME, severity and outcomes.
- Recommendation to monitor patients for signs and symptoms of overdose (these predominantly affect the haematopoietic and gastrointestinal systems).
- Management of overdose (including the use of calcium folinate and dose interruption).

The **Patient card** shall contain the following key elements:

- Reminder that patients who use methotrexate for an indication requiring a weekly dosing schedule to take the product only once weekly and to write the day of the week for intake on the card.
- Inform on serious adverse effects that may be fatal and on the symptoms of overdose and steps to be taken should symptoms arise to enable the patient to seek medical help in time.
- Recommendation to always show the card to and alert new HCPs about the once weekly dosing of the patient's methotrexate (e.g. on hospital admission, change of carer, etc.).

For full-text of the patient card please refer to PI referred to in Part I Table I.1.

- **Direct Healthcare Professional Communication (DHPC)**

The DHPC wording has been agreed by PRAC within Article 31 Referral EMA/PRAC/360022/2019 (Enclosure 2 of PRAC final report).

Summary:

- Dosing errors with serious consequences, including fatalities, have been reported when methotrexate intended for once weekly use in autoimmune diseases was taken daily.
- Only physicians with expertise in using methotrexate-containing medicines should prescribe them.
- Healthcare professionals who prescribe or dispense methotrexate for autoimmune diseases should:
    - Provide to the patient/carer complete and clear dosing instructions on the once weekly dosing.
    - Check carefully at every new prescription /dispensation that the patient/carer understands that the medicine must be used once weekly.
    - Decide together with the patient/carer on which day of the week the patient uses methotrexate.
    - Inform the patient/carer of signs of overdose and instruct them to promptly seek medical advice in case of suspected overdose.

Background on the safety concern:

Methotrexate is authorised in the EU for two different groups of indications, each of them with a different administration schedule:

- For the treatment of cancer in which frequency depends on the regimen and can require daily administration of methotrexate.
- For the treatment of autoimmune diseases including rheumatoid arthritis, psoriasis and Crohn's disease, which require once weekly use.

Despite measures already taken to prevent dosing errors, serious, sometimes fatal, cases continue to be reported, in which patients being treated for autoimmune diseases have taken methotrexate daily instead of once weekly. A safety review performed at EU level found that these errors can occur at all stages of the medication process.

Therefore, further measures to prevent dosing errors will be introduced, including prominent warnings on outer and inner packaging and updates to the SmPC and package leaflet. For oral formulations,

there will be educational material for healthcare professionals and a patient card will be provided with each package. In addition, tablets will only be available in blister packs.

Call for reporting:

Suspected adverse reactions and any medication error should be reported in accordance with the national spontaneous reporting system <to be filled nationally>.

Company contacts

Annexes:

<To be populated after referral outcome with measure that will be implemented>.