Summary of the Swiss Risk Management Plan (RMP) for Jylamvo, Lösung zum Einnehmen

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Disclaimer

The Risk Management Plan (RMP) is a comprehensive document submitted as part of the application dossier for market approval of a medicine. The RMP summary contains information on the medicine's safety profile and explains the measures that are taken in order to further investigate and follow the risks as well as to prevent or minimise them.

The RMP summary of Jylamvo, Lösung zum Einnehmen is a concise document and does not claim to be exhaustive.

As the RMP is an international document, the summary might differ from the “Arzneimittelinformation / Information sur le médicament” approved and published in Switzerland, e.g. by mentioning risks occurring in populations or indications not included in the Swiss authorization.

Please note that the reference document which is valid and relevant for the effective and safe use of Jylamvo, Lösung zum Einnehmen in Switzerland is the “Arzneimittelinformation / Information sur le médicament” (see www.swissmedic.ch) approved and authorized by Swissmedic. Ideogen AG is fully responsible for the accuracy and correctness of the content of the published summary RMP of Jylamvo, Lösung zum Einnehmen.

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.