ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Jylamvo 2 mg/ml oral solution

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One ml of solution contains 2 mg methotrexate.

Excipients with known effect
One ml of solution contains 2 mg methyl hydroxybenzoate (as the sodium salt), and 0.2 mg ethyl hydroxybenzoate.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Oral solution.
Clear yellow solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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 (NSAIDs) 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

4.2 Posology and method of administration

Methotrexate should only be prescribed by physicians with expertise in the use of methotrexate and a full understanding of the risks of methotrexate therapy.

Posology

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.

Dosage in 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.
Symptoms may return after treatment discontinuation.

Dosage in children and adolescents with polyarthritic forms of juvenile idiopathic arthritis

Patients with JIA should always be referred to a rheumatology unit specialising in the treatment of children/adolescents.

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.

Dosage in 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.

Oncology

Dosage in acute lymphoblastic leukaemia

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 body surface area.

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 (see section 4.4).

Doses are usually based on the patient's BSA and maintenance treatment represents a long-term treatment.

Special populations

Renal impairment
Methotrexate should be used with caution in patients with impaired renal function (see section 4.4).

The dose should be adjusted as follows for patients with rheumatoid arthritis, juvenile arthritis, psoriasis and psoriatic arthritis. For the oncology indication recommendations in published protocols should also apply.

Creatinine clearance (ml/min)	**% of dose to be administered**
>60	100
30- 59	50
<30	Jylamvo must not be administered.

Hepatic impairment
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. If bilirubin levels are >5 mg/dl (85.5 µmol/l), methotrexate is contraindicated (see sections 4.3 and 4.4).

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

Elderly
Dose reduction should be considered in elderly patients (65 years and over) due to reduced liver and kidney function as well as low folic acid reserves which occur with increased age. In addition, close monitoring of patients for possible early signs of toxicity is recommended (see sections 4.4, 4.5, 4.8 and 5.2).

Patients with pathological fluid accumulations (pleural effusion, ascites)
As the half-life of methotrexate can be prolonged four-fold in patients with pathological fluid accumulations, it may be necessary to reduce the dose and in some cases even to discontinue methotrexate (see sections 4.4 and 5.2). The amount of dose reduction should be decided on a case by case basis.

Method of administration

Jylamvo is for oral use only.

The medicinal product can be taken with or without food.
The solution is provided ready for use, and it must be swallowed with some water to remove any methotrexate residue from the oral cavity.
A 10 ml oral dosing syringe is provided for accurate measurement of the prescribed dose (see Package Leaflet).

If the oral route is ineffective, a change to a parenteral dosage form is indicated. This can be done with methotrexate as an intramuscular or subcutaneous administration and is recommended for patients who exhibit inadequate absorption of the oral form of methotrexate or who do not tolerate oral administration well.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1
- Hepatic impairment (bilirubin levels are >5 mg/dl [85.5 µmol/l], see section 4.2)
- Alcohol abuse
- Severe renal impairment (creatinine clearance less than 30 ml/min, see section 4.2)
- Pre-existing blood disorders such as bone marrow hypoplasia, leukopenia, thrombocytopenia or significant anaemia
- Immunodeficiency
- Severe, acute or chronic infections such as tuberculosis and HIV
- Stomatitis, ulcers of the oral cavity and known active gastrointestinal ulcers
- Breast-feeding (see section 4.6)
- Concurrent vaccination with live vaccines

Additionally for non-oncological indications
- Pregnancy (see section 4.6)

4.4 Special warnings and precautions for use

The oral solution contains 2 mg of methotrexate in each ml of solution; the scaling of the dosing syringe is in ml and not mg; care should be taken that the correct dosing volume is prescribed.
Patients with rheumatological or dermatological diseases 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. Medical staff and patients must be clearly instructed.

The prescriber should specify the day of intake on the prescription.
The prescriber should make sure patients understand that Jylamvo (methotrexate) should only be taken once a week.
Patients should be instructed on the importance of adhering to the once-weekly intakes.

Patients must be appropriately monitored during treatment so that signs of possible toxic effects or adverse reactions can be detected and evaluated with minimal delay.
Therefore, methotrexate should only be administered by, or under the supervision of, doctors whose knowledge and experience includes treatment with antimetabolites.
Especially strict monitoring of the patient is indicated following prior radiotherapy (especially of the pelvis), functional impairment of the haematopoietic system (e.g., following prior radio- or chemotherapy), impaired general condition as well as advanced age and in very young children.
Because of the possibility of severe or even fatal toxic reactions, patients should be extensively informed by the treating doctor of the risks involved (including early signs and symptoms of toxicity) and the recommended safety measures. Patients should be informed that they must notify the doctor immediately if any symptoms of an overdose occur and that the symptoms of the overdose need to be monitored (including regular laboratory tests).
Doses exceeding 20 mg (10 ml)/week can be associated with a substantial increase in toxicity,

especially bone marrow depression.

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 (see section 4.2).

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.

Fertility
Methotrexate has been reported to cause impairment of fertility, oligospermia, menstrual dysfunction and amenorrhoea in humans during and for a short period after the discontinuation of treatment, affecting spermatogenesis and oogenesis during the period of its administration - effects that appear to be reversible on discontinuing therapy.

Teratogenicity – Reproductive risk
Methotrexate causes embryotoxicity, abortion and foetal malformations in humans. Therefore, the possible effects on reproduction, pregnancy loss and congenital malformations should be discussed with female patients of childbearing age (see section 4.6).
In non-oncologic indications, the absence of pregnancy must be confirmed before Jylamvo is used. If women of a sexually mature age are treated, effective contraception must be used during treatment and for at least six months after.

For contraception advice for men see section 4.6.

Recommended examinations and safety measures

Before beginning treatment or resuming treatment after a recovery period
Complete blood count with differential blood count and platelets, liver enzymes, bilirubin, serum albumin, chest X-ray and renal function tests. If clinically indicated, tuberculosis and hepatitis B and C should be excluded.

During treatment
The tests below must be conducted weekly in the first two weeks, then every two weeks for a month; thereafter, depending on the leucocyte count and the stability of the patient, at least once a month during the next six months and then at least every three months.

An increased monitoring frequency should be considered when the dose is increased. In particular, elderly patients should be monitored at short intervals for early signs of toxicity (see section 4.2).

- Examination of the mouth and throat for *mucosal changes.*

- *Complete blood count* with differential blood count and platelets. Methotrexate-induced haematopoietic suppression may occur abruptly and with apparently safe dosages. 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. In patients simultaneously taking haematotoxic medicinal products (e.g. leflunomide), blood count and platelets should be closely monitored.

- *Liver function tests* - particular attention should be given to the appearance of liver toxicity. Treatment should not be initiated or should be discontinued if there are any abnormalities in liver function tests or liver biopsies, or if these develop during therapy. Such abnormalities should return to normal within two weeks, after which, treatment may be resumed at the discretion of the doctor.
  Testing of serum liver enzymes Transient increases in transaminases to twice or three times normal occur in 13-20% of patients. Persistent abnormalities of liver enzymes and/or a decrease in serum albumin can indicate severe hepatotoxicity. In rheumatological indications, there is no

evidence to support use of liver biopsies in monitoring hepatotoxicity. For psoriasis patients the need of a liver biopsy prior to and during therapy is controversial.

Further research is needed to establish whether serial liver function tests or determinations of propeptide of type III collagen are appropriate for detecting hepatotoxicity. This evaluation should differentiate between patients with no risk factors and patients with risk factors, such as excessive prior alcohol consumption, persistent elevation of liver enzymes, history of liver disease, family history of a hereditary liver disease, diabetes mellitus, obesity and history of significant exposure to hepatotoxic medicinal product or chemicals, as well as prolonged methotrexate treatment or a cumulative total dose of 1.5 g or more.

If liver enzymes are constantly increased, a dose reduction or treatment discontinuation should be considered.

Due to its potentially toxic effects on the liver, additional hepatotoxic medicinal products should not be taken during treatment with methotrexate unless *urgently necessary* and the consumption of alcohol should be avoided or reduced (see section 4.5). Closer monitoring of liver enzymes should be undertaken in patients taking other hepatotoxic medicinal products concomitantly (e.g. leflunomide). This should also be considered during simultaneous administration of haematotoxic medicinal products.

Increased caution is required in patients with insulin-dependent diabetes mellitus as hepatic cirrhosis has developed in individual cases without any elevation of transaminases during methotrexate treatment.

- *Renal function* should be monitored by renal function tests and urinalyses. If serum creatinine levels are increased, the dose should be reduced. If creatinine clearance is less than 30 ml/min, treatment with methotrexate should not be given (see sections 4.2 and 4.3).

  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.

- *Respiratory tract examination* - patients must be monitored for symptoms of a lung function disorder and lung function tests 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. Although the clinical presentation is variable, patients with methotrexate-induced lung diseases typically suffer from fever, cough, dyspnoea or hypoxaemia. A chest X-ray must be taken in order to be able to exclude an infection. Acute or chronic interstitial pneumonia, often in association with blood eosinophilia, may occur and deaths have been reported. Patients should be informed of the risks of pneumonia and advised to contact their doctor immediately if they develop a persistent cough or persistent dyspnoea.

  In addition, pulmonary alveolar haemorrhage has been reported with methotrexate used in rheumatologic and related indications. This event may also be associated with vasculitis and other comorbidities. Prompt investigations should be considered when pulmonary alveolar haemorrhage is suspected to confirm the diagnosis.

  Methotrexate should be discontinued in patients with pulmonary symptoms and an immediate examination (including chest X-ray) should be performed to exclude infection and tumours. If methotrexate-induced lung disease is suspected, treatment with corticosteroids should be initiated and treatment with methotrexate should not be restarted.

  Pulmonary symptoms require a rapid diagnosis and discontinuation of methotrexate therapy. Methotrexate-induced lung diseases such as pneumonitis can occur acutely and at any time

during treatment, are not always completely reversible and have already been observed at all doses (including low doses of 7.5 mg (3.75 ml)/week).

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 required in patients with impaired pulmonary function.

Particular caution is also required in the presence of inactive chronic infections (e.g. herpes zoster, tuberculosis, hepatitis B or C) as it is possible that activation of these infections may occur.

Renal impairment and patients at risk of renal impairment
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.
(See renal function monitoring)

Immune system
Due to its effect on the immune system, methotrexate may impair the response to vaccinations and affect the results of immunological tests. Concurrent vaccination using live vaccines should not be given.

Malignant lymphomas
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.

Pleural effusions or ascites
Pleural effusions and ascites should be drained prior to initiation of methotrexate treatment (see section 4.2).

Conditions that cause dehydration such as vomiting, diarrhoea or stomatitis
Conditions that cause dehydration such as vomiting, diarrhoea or stomatitis can increase toxicity as a result of raised active substance levels. In this case, treatment with methotrexate must be discontinued until the symptoms have disappeared.

It is important to determine any increase in active substance levels within 48 hours of therapy, otherwise irreversible methotrexate toxicity may occur.

Diarrhoea and ulcerative stomatitis may be signs of toxic effects and require the discontinuation of treatment, otherwise haemorrhagic enteritis and death from intestinal perforation may occur.
Following the occurrence of haematemesis, black-coloured stools or blood in the stools, treatment must be discontinued.

Folic acid supplementation
If acute methotrexate toxicity occurs, patients may require treatment with folinic acid. In patients with rheumatoid arthritis or psoriasis, folic acid or folinic acid supplementation may reduce methotrexate toxicity, such as gastrointestinal symptoms, stomatitis, alopecia and elevated liver enzymes.

It is recommended to check levels of vitamin B12 prior to initiating folic acid supplementation, particularly in adults aged over 50 years, as folic acid intake may mask a vitamin B12 deficiency.

Vitamin products
Vitamin preparations or other products containing folic acid, folinic acid or their derivatives may decrease the effectiveness of methotrexate (see sections 4.2 and 4.5).

Dermatitis and sunburn
Radiation-induced dermatitis and sunburn can reappear during methotrexate therapy (recall reactions). Psoriatic lesions can worsen during UV radiation and co-administration of methotrexate.

Skin toxicity
Severe, occasionally fatal, dermatologic reactions, including toxic epidermal necrolysis (Lyell's syndrome) or Stevens-Johnson syndrome have been reported after single or multiple doses of methotrexate.

Encephalopathy/leukoencephalopathy
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.

Excipient warnings
This medicinal product contains sodium methyl parahydroxybenzoate (E219) and ethyl parahydroxybenzoate (E214). It may cause allergic reactions (possibly delayed).

4.5 Interaction with other medicinal products and other forms of interaction

The risk of an interaction between NSAIDs and methotrexate should be considered in patients with a low methotrexate dose, particularly in the case of impaired kidney function. If combined treatment is required, the blood count and renal function should be monitored. Caution should be exercised if NSAIDs and methotrexate are administered within 24 hours, since in this case methotrexate plasma levels can rise and toxicity be increased as a result. Animal studies showed that the administration of NSAIDs including salicylic acid resulted in reduced tubular methotrexate secretion and accordingly potentiated its toxic effects. However, in clinical trials in which NSAIDs and salicylic acid were administered adjuvantly to patients with rheumatoid arthritis, no increase in adverse reactions was observed. Treatment of rheumatoid arthritis with such medicinal products can be continued during therapy with low-dose methotrexate, but only under close medical supervision.

Patients taking potentially hepatotoxic medicinal products during treatment with methotrexate (e.g. leflunomide, azathioprine, sulfasalazine and retinoids) should be monitored closely for increased hepatotoxicity. The consumption of alcohol should be avoided during treatment with methotrexate (see section 4.4). Regular alcohol consumption and administration of additional hepatotoxic medicinal products increase the likelihood of hepatotoxic adverse reactions to methotrexate.
Administration of additional haematotoxic medicinal products (e.g. metamizole) increases the likelihood of severe haematotoxic adverse reactions to methotrexate.

Pharmacokinetic interactions between methotrexate, anticonvulsants (reduced serum methotrexate levels) and 5-fluoruracil (increased half-life of 5-fluoruracil) must be borne in mind.

Salicylates, phenylbutazone, diphenylhydantoin (= phenytoin), barbiturates, tranquillisers, oral contraceptives, tetracyclines, amidopyrine derivatives, sulphonamides, thiazide diuretics, oral hypoglycaemics, doxorubicin and p-aminobenzoic acid displace methotrexate from serum albumin binding and thus increase bioavailability and hence toxicity (indirect dose increase).

Probenecid and weak organic acids can also reduce the tubular secretion of methotrexate and thus likewise cause an indirect increase in dose.

Antibiotics such as penicillins, glycopeptides, sulphonamides, ciprofloxacin and cefalotin can in

individual cases reduce the renal clearance of methotrexate, so that increased serum methotrexate concentrations can occur, accompanied by haematological and gastrointestinal toxicity.
Oral antibiotics such as tetracyclines, chloramphenicol and non-absorbable broad-spectrum antibiotics may reduce intestinal absorption of methotrexate or interfere with the enterohepatic circulation by inhibiting intestinal flora or suppressing bacterial metabolism.

In the event of (prior) treatment with medicinal products that can have adverse reactions on bone marrow (e.g. sulphonamides, trimethoprim/sulphamethoxazole, chloramphenicol, pyrimethamine), the possibility of haematopoietic disorders must be considered.

Concomitant therapy with medicinal products that can cause folic acid deficiency (e.g. sulphonamides, trimethoprim/sulphamethoxazole) can result in increased methotrexate toxicity. Accordingly, particular caution should be exercised in patients with pre-existing folic acid deficiency.

Conversely, co-administration of medicinal products containing folinic acid or vitamin preparations containing folic acid or derivatives may impair the efficacy of methotrexate.

The combination of methotrexate and sulfasalazine can enhance the effect of methotrexate, as sulfasalazine causes inhibition of folic acid synthesis. This can result in an increased risk of adverse reactions, although in several studies this was only observed in individual patients.

Ciclosporin may potentiate methotrexate efficacy and toxicity. There is a risk of excessive immunosuppression with risk of lymphoproliferation when the combination is used.

The use of nitrous oxide potentiates the effect of methotrexate on folate metabolism, yielding increased toxicity such as severe, unpredictable myelosuppression, stomatitis and neurotoxicity with intrathecal administration. Whilst this effect can be reduced by administering calcium folinate, the concomitant use should be avoided.

Co-administration of proton pump inhibitors such as omeprazole or pantoprazole can result in interactions: co-administration of methotrexate and omeprazole has resulted in delayed renal elimination of methotrexate. In one case in which methotrexate was combined with pantoprazole, renal elimination of the metabolite 7-hydroxymethotrexate was inhibited and myalgia and shivering occurred.

The application of procarbazine during high-dose methotrexate therapy increases the risk of impairment or renal function

Excessive consumption of caffeine- or theophylline-containing beverages (coffee, caffeinated beverages, black tea) should be avoided during methotrexate therapy as the effect of methotrexate may be reduced by the possible interaction between methotrexate and methylxanthines at the adenosine receptors.

Combination therapy with methotrexate and leflunomide may increase the risk for pancytopenia.

Particularly in the case of orthopaedic surgery where the risk of infection is high, combination therapy with methotrexate and immunomodulatory medicinal products must be used with caution.

Cholestyramine can increase the non-renal elimination of methotrexate by interfering with the enterohepatic circulation.

The possibility of delayed methotrexate clearance should be considered in combination with other cytostatic medicinal products.

Radiotherapy during the use of methotrexate can increase the risk for soft tissue or bone necrosis.

Methotrexate can reduce the clearance of theophylline. During concomitant therapy with

methotrexate, therefore, serum theophylline levels should be monitored.

Combined administration of mercaptopurine and methotrexate can increase the bioavailability of mercaptopurine, possibly as a result of inhibition of the metabolism of mercaptopurine.

In view of its possible effects on the immune system, methotrexate can falsify vaccinal and test results (immunological procedures to assess the immune reaction). During methotrexate therapy, concurrent vaccination with live vaccines should be avoided (see sections 4.3 and 4.4).

4.6 Fertility, pregnancy and lactation

Women of childbearing potential/Contraception in females
Women must not get pregnant during methotrexate therapy, and effective contraception must be used during treatment with methotrexate and at least 6 months thereafter (see section 4.4). Prior to initiating therapy, women of childbearing potential must be informed of the risk of malformations associated with methotrexate and any existing pregnancy must be excluded with certainty by taking appropriate measures, e.g. a pregnancy test. During treatment pregnancy tests should be repeated as clinically required (e.g. after any gap of contraception). Female patients of reproductive potential must be counselled regarding pregnancy prevention and planning.

Contraception in males
It is not known if methotrexate is present in semen. Methotrexate has been shown to be genotoxic in animal studies, such that the risk of genotoxic effects on sperm cells cannot completely be excluded. Limited clinical evidence does not indicate an increased risk of malformations or miscarriage following paternal exposure to low-dose methotrexate (less than 30 mg [15 ml]/week). For higher doses, there is insufficient data to estimate the risks of malformations or miscarriage following paternal exposure.

As precautionary measures, sexually active male patients or their female partners are recommended to use reliable contraception during treatment of the male patient and for at least 6 months after cessation of methotrexate. Men should not donate semen during therapy or for 6 months following discontinuation of methotrexate.

Pregnancy
Methotrexate is contraindicated during pregnancy in non-oncological indications (see section 4.3). If pregnancy occurs during treatment with methotrexate and up to six months thereafter, medical advice should be given regarding the risk of harmful effects on the child associated with treatment and ultrasonography examinations should be performed to confirm normal foetal development. In animal studies, methotrexate has shown reproductive toxicity, especially during the first trimester (see section 5.3). Methotrexate has been shown to be teratogenic to humans; it has been reported to cause foetal death, miscarriages and/or congenital abnormalities (e.g. craniofacial, cardiovascular, central nervous system and extremity-related).

Methotrexate is a powerful human teratogen, with an increased risk of spontaneous abortions, intrauterine growth restriction and congenital malformations in case of exposure during pregnancy.

- Spontaneous abortions have been reported in 42.5% of pregnant women exposed to low-dose methotrexate treatment (less than 30 mg [15 ml]/week), compared to a reported rate of 22.5% in disease-matched patients treated with drugs other than methotrexate.

- Major birth defects occurred in 6.6% of live births in women exposed to low-dose methotrexate treatment (less than 30 mg [15 ml]/week) during pregnancy, compared to approximately 4% of live births in disease-matched patients treated with drugs other than methotrexate.

Insufficient data is available for methotrexate exposure during pregnancy higher than 30 mg (15 ml)/week, but higher rates of spontaneous abortions and congenital malformations are expected, in particular at doses commonly used in oncologic indications

When methotrexate was discontinued prior to conception, normal pregnancies have been reported.

When used in oncological indications, methotrexate should not be administered during pregnancy in particular during the first trimester of pregnancy. In each individual case the benefit of treatment must be weighed up against the possible risk to the foetus. If the drug is used during pregnancy or if the patient becomes pregnant while taking methotrexate the patient should be informed of the potential risk to the foetus.

Breast-feeding
As methotrexate passes into breast milk and may cause toxicity in breast-fed children, treatment is contraindicated during the lactation period (see section 4.3). If use during the lactation period should become necessary, breast-feeding is to be stopped prior to treatment.

Fertility
Methotrexate affects spermatogenesis and oogenesis and may decrease fertility. In humans, methotrexate has been reported to cause oligospermia, menstrual dysfunction and amenorrhoea. These effects appear to be reversible after discontinuation of therapy in most cases. In oncologic indications, women who are planning to become pregnant are advised to consult a genetic counselling centre, if possible, prior to therapy and men should seek advice about the possibility of sperm preservation before starting therapy as methotrexate can be genotoxic at higher doses (see section 4.4).

4.7 Effects on ability to drive and use machines

Methotrexate has moderate influence on the ability to drive and use machines, since central nervous system disorders such as tiredness, dizzy spells or drowsiness can occur during treatment.

4.8 Undesirable effects

Summary of the safety profile
In general, the incidence and severity of side effects are considered to be dose-related.

In the antineoplastic treatment, myelosuppression and mucositis are the predominant dose-limiting toxic effects of methotrexate. The severity of these reactions depends on the dose, mode and duration of application of methotrexate. Mucositis generally appears about 3 to 7 days after methotrexate application, leucopenia and thrombocytopenia follow a few days later. In patients with unimpaired elimination mechanisms, myelosuppression and mucositis are generally reversible within 14 to 28 days.

Most serious adverse reactions of methotrexate include bone marrow suppression, pulmonary toxicity, hepatotoxicity, renal toxicity, neurotoxicity, thromboembolic events, anaphylactic shock and Stevens-Johnson syndrome.

Most frequently (very common) observed adverse reactions of methotrexate include gastrointestinal disorders (e.g. stomatitis, dyspepsia, abdominal pain, nausea, loss of appetite) and abnormal liver function tests (e.g. increased alanine aminotransferase (ALAT), aspartate aminotransferase (ASAT), bilirubin, alkaline phosphatase). Other frequently (common) occurring adverse reactions are leukopenia, anaemia, thrombopenia, headache, tiredness, drowsiness, pneumonia, interstitial alveolitis/pneumonitis often associated with eosinophilia, oral ulcers, diarrhoea, exanthema, erythema and pruritus.

The occurrence and severity of adverse reactions depend on dosage level and frequency of administration of methotrexate. However, as severe adverse reactions may occur even at low doses, it is essential for the treating physician to monitor patients closely (see section 4.4).

Most adverse reactions are reversible if they are detected early. If such adverse reactions occur, the dose should either be reduced or treatment discontinued and appropriate countermeasures taken (see

section 4.9). Methotrexate therapy should only be resumed with particular caution, after careful consideration of the need for treatment and with increased vigilance for the possible recurrence of toxicity.

Tabulated list of adverse reactions
Frequencies in the table are defined according to the MedDRA convention:

Very common (≥1/10)
Common (≥ 1/100 to <1/10)
Uncommon (≥1/1,000 to < 1/100)
Rare (≥1/10,000 to <1/1,000)
Very rare (<1/10,000)
Not known (cannot be estimated from the available data)

Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

System organ class	Very common	Common	Uncommon	Rare	Very rare	Not known
Infections and infestations		Infections	Opportunistic infections (sometimes fatal)	Herpes zoster	Sepsis Cytomegalovirus-induced infections.	Nocardiosis, Histoplasma and cryptococcus mycosis, Disseminated herpes simplex
Neoplasms benign, malignant and unspecified (including cysts and polyps)			Lymphoma[1]			
Blood and lymphatic system disorders		Leucocytopenia, Thrombo-cytopenia, Anaemia	Pancytopenia, Agranulocytosis, Haematopoietic disorders	Megaloblastic anaemia	Bone marrow depression (severe courses), Aplastic anaemia, Lymphoproliferative disorder[2], Eosinophilia, Neutropenia, Lymphadenopathy	Haemorrhages
Immune system disorders			Allergic reactions, Anaphylactic shock, Fever, Chills		Immuno-suppression, Allergic vasculitis (severe toxic symptom), Hypogamma-globulinaemia	
Metabolism and nutrition disorders			Diabetes mellitus			
Psychiatric disorders			Depression	Mood swings	Insomnia	
Nervous system disorders		Headache, Fatigue, Drowsiness	Convulsions, Vertigo, Confusion	Hemiparesis, Paresis	Cerebral oedema, Acute aseptic meningitis with meningism (paralysis, vomiting), Lethargy, Transient subtle cognitive dysfunction, Psychoses, Aphasia, Pain,	Encephalop-athy/ Leukoenceph-alopathy

					Muscular asthenia or paraesthesia of the extremities, Taste changes (metallic taste), Irritation, Dysarthria, Unusual cranial sensations, Tinnitus	
Eye disorders				Severe visual disturbances	Retinopathy, Conjunctivitis	
Cardiac disorders				Pericarditis, Pericardial effusion, Pericardial tamponade		
Vascular disorders				Thromboembolic reactions (including arterial and cerebral thrombosis, thrombophlebitis, deep leg vein thrombosis, retinal vein thrombosis, pulmonary embolism), Hypotension		
Respiratory, thoracic and mediastinal disorders		Interstitial alveolitis/ pneumonia (can be fatal)	Pulmonary fibrosis	Respiratory paralysis, Bronchial asthma-like reactions such as cough, dyspnoea and pathological changes in lung function tests, Pharyngitis	Pneumocystis jiroveci pneumonia and other lung infections, Chronic obstructive pulmonary disease, Pleural effusion	Pulmonary alveolar haemorrhage[3]
Gastrointestinal disorders	Loss of appetite, Nausea, Vomiting, Abdominal pain, Inflammation and ulceration of mucosa of mouth and throat, Stomatitis, Dyspepsia	Diarrhoea	Ulceration and bleeding of gastrointestinal tract	Pancreatitis, Enteritis, Malabsorption, Melaena, Gingivitis	Toxic megacolon, Haematemesis	
Hepatobiliary disorders	Increase in liver-related enzymes (ALAT [GPT], ASAT [GOT], alkaline phosphatase and bilirubin)		Hepatic steatosis, fibrosis and cirrhosis, Decrease in serum albumin	Acute hepatitis and hepatotoxicity	Acute liver degeneration, Liver failure, Reactivation of chronic hepatitis,	Hepatitis and liver failure[4]
Skin and subcutaneous		Erythema, Exanthema,	Severe toxic manifestations:	Increased nail pigment changes,	Acute paronychia, Furunculosis,	

tissue disorders		Pruritus	vasculitis, herpetiform skin eruptions, Stevens-Johnson syndrome, toxic epidermal necrolysis (Lyell's syndrome), Increased rheumatic nodules, Painful erosions of psoriatic plaque, Photosensitivity, Increased skin pigmentation, Hair loss, Impaired wound healing, Urticaria	Onycholysis, Acne, Petechiae, Bruising, Erythema multiforme, Cutaneous erythematous eruptions, Lesions of psoriasis may worsen with concomitant UV therapy, Radiation dermatitis and sunburn may be "recalled"	Telangiectasis, Hidradenitis	
Musculoskeletal and connective tissue disorders			Osteoporosis, Arthralgia, Myalgia,	Stress fracture		Osteonecrosis of jaw (secondary to lymphoprolifer -ative disorders)
Renal and urinary disorders			Nephropathy Inflammation and ulceration of urinary bladder (possibly with haematuria), Dysuria	Renal failure, Oliguria, Anuria, Azotaemia	Proteinuria	
Reproductive system and breast disorders			Vaginal Inflammation and ulceration	Oligospermia, Menstrual dysfunction	Infertility, Loss of libido, Impotence, Vaginal discharge, Gynaecomastia	
General disorders and administration site conditions					Fever	

[1] can be reversible - see 4.4
[2] Lymphoma/Lymphoproliferative disorders: there have been reports of individual cases of lymphoma and other lymphoproliferative disorders which subsided in a number of cases once treatment with methotrexate had been discontinued.
[3] has been reported for methotrexate used in rheumatologic and related indications
[4] see remarks on liver biopsy in section 4.4

Paediatric population
Frequency, type and severity of adverse reactions in children and adolescents are expected to be the same as in adults.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

Symptoms of overdose
The symptoms following oral overdose predominantly affect the haematopoietic and gastrointestinal

systems.
Symptoms include leucocytopenia, thrombocytopenia, anaemia, pancytopenia, neutropenia, myelosuppression, mucositis, stomatitis, oral ulceration, nausea, vomiting, gastrointestinal ulceration and bleeding.
Cases of overdose have been reported, sometimes fatal, due to erroneous daily intake instead of weekly intake of oral methotrexate. In these cases, symptoms that have been commonly reported are hematological and gastrointestinal reactions.

There are reports of deaths from sepsis, septic shock, renal failure and aplastic anaemia.

Therapeutic management of overdose
Calcium folinate is the specific antidote for neutralising the adverse toxic effects of methotrexate. In the event of accidental overdose, a dose of calcium folinate equal to or higher than the offending dose of methotrexate should be administered intravenously or intramuscularly within 1 hour, and dosing continued until serum level of methotrexate are below 10^{-7} mol/L.

In the event of a massive overdose, hydration and alkalinisation of the urine may be required to prevent precipitation of methotrexate and/or its metabolites in the renal tubules. Neither haemodialysis nor peritoneal dialysis has been shown to improve the elimination of methotrexate. Effective clearance of methotrexate is reported to be achieved with acute intermittent haemodialysis using a high-flux dialyser.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antineoplastic and immunomodulating agents, antimetabolites, folic acid analogues, ATC code: L01BA01

Mechanism 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 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.

5.2 Pharmacokinetic properties

Absorption
After oral administration, methotrexate is absorbed from the gastrointestinal tract. When administered in low doses (7.5 mg/m^2 to 80 mg/m^2 body surface area), the mean bioavailability of methotrexate is approximately 70%, but considerable inter- and intra-individual variations are possible (25-100%). Peak serum concentrations are attained within 1-2 hours.

Data from a randomised trial in patients with juvenile rheumatoid arthritis (aged 2.8 to 15.1 years) indicated greater oral bioavailability of methotrexate in the fasting state. In children with JIA, the dose normalized area under the plasma concentration versus time-curve (AUC) of methotrexate increased with the age of the children and was lower than that found in adults. The dose normalized AUC of the metabolite 7-hydroxymethotrexate was not dependent on age.

Distribution
Methotrexate is approximately 50% bound to serum proteins. After distribution, it collects predominantly in the liver, kidneys and spleen in the form of polyglutamates, which can be retained for weeks or months.

The mean terminal half-life is 6-7 hours and demonstrates considerable variations (3-17 hours). The half-life may be prolonged up to four-fold in patients with a third distribution compartment (pleural effusion, ascites).

Biotransformation
Approximately 10% of the administered methotrexate dose is metabolised in the liver. The main metabolite is 7-hydroxymethotrexate.

Elimination
Excretion occurs predominantly in the unchanged form by glomerular filtration and active secretion in the proximal tubule via the kidneys.
Approximately 5-20% of methotrexate and 1-5% of 7-hydroxymethotrexate is eliminated in the bile. There is a pronounced enterohepatic circulation.

Elimination in patients with impaired renal function is markedly delayed. Impaired elimination in patients with hepatic impairment is not known at present.

Methotrexate crosses the placental barrier in rats and monkeys.

5.3 Preclinical safety data

Chronic toxicity
In chronic toxicity studies in mice, rats and dogs, toxic effects were seen in the form of gastrointestinal lesions, myelosuppression and hepatotoxicity.

Mutagenic and carcinogenic potential
Long-term studies in rats, mice and hamsters revealed no evidence of a tumorigenic potential of methotrexate. Methotrexate induces gene and chromosomal mutations *in vitro* and *in vivo*. There is a suspected mutagenic effect in humans.

Reproductive toxicology
Teratogenic effects have been observed in four species (rats, mice, rabbits, cats). In rhesus monkeys, no malformations comparable to those seen in humans occurred.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Macrogol 400
Glycerol
Orange flavour
Sucralose
Ethyl parahydroxybenzoate (E214)
Sodium methyl parahydroxybenzoate (E219)
Citric acid monohydrate

Tri-sodium citrate
Purified water

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

Unopened bottle
15 months.

After first opening
3 months.

6.4 Special precautions for storage

Do not store above 25ºC.

Keep the bottle tightly closed (see section 6.6).

6.5 Nature and contents of container

75 ml amber type III glass bottle with tamper evident child-resistant closure (polypropylene with expanded polyethylene liner) containing 60 ml of oral solution.

Each pack contains one bottle, an LDPE bottle adaptor and a 10 ml white polypropylene dosing syringe (with major graduations at every 1 ml and minor graduations at every 0.25 ml).

6.6 Special precautions for disposal and other handling

Safe handling

Anyone handling methotrexate should wash their hands before and after administering a dose. To decrease the risk of exposure, parents and care givers should wear disposable gloves when handling methotrexate.
Contact with the skin or mucous membrane must be avoided. If methotrexate comes into contact with skin or mucosa, it should be washed immediately and thoroughly with soap and water.

Spillages must be wiped immediately.

Women who are pregnant, planning to be or breast-feeding should not handle methotrexate.

Parents, care givers and patients should be advised to keep methotrexate out of the reach of children, preferably in a locked cupboard.

Accidental ingestion can be lethal for children.

Keep the bottle tightly closed to protect the integrity of the product and minimise the risk of accidental spillage.
The usual caution should be exercised in handling cytostatics.

Instructions for use of the syringe provided in the pack

1. Put on disposable gloves before handling.
2. Shake the bottle.
3. Remove the bottle cap and push the adaptor firmly into the top of the bottle.

4. Push the tip of the dosing syringe into the hole in the adaptor.
5. Turn the bottle upside down.
6. Pull the syringe plunger back SLOWLY so that the medicine is drawn from the bottle into the syringe until the WIDEST part of the white syringe plunger is lined up to the black syringe marking of the dose required. DO NOT measure to the narrow tip of the plunger. If there are air bubbles in the syringe, repeat until bubbles are eliminated.
7. Turn the bottle back the right way up and carefully remove the syringe from the adaptor, holding the syringe by the barrel rather than the plunger.
8. Confirm that the dose in the syringe is correct.
9. Ensure that the patient is sitting up or standing before giving the medicine.
10 Gently place the tip of the syringe into the patient's mouth and direct it to the inside of the cheek.
11. Slowly and gently push the plunger down to gently squirt the medicine into the inside of the cheek. DO NOT push down the plunger too hard or squirt the medicine to the back of the mouth or throat as this may cause choking. The plunger should be pushed back gently to the seated position until it clicks into place.
12. Remove the syringe from the patient's mouth.
13. Ask the patient to swallow the medicine and then to drink some water, making sure no medicine is left in the mouth.
14. Put the cap back on the bottle with the adaptor left in place. Ensure that the cap is tightly closed.
15. Wash the syringe immediately after use with fresh warm, soapy water and rinse well. The syringe should be held under water and the plunger drawn in and out several times until all traces of medicine are removed from inside the syringe including the tip. The plunger and barrel should then be separated and both washed thoroughly in the warm soapy water. They should then be rinsed thoroughly under COLD water and excess water shaken off before wiping dry with a clean paper towel. The plunger and barrel should be stored in a clean dry container with the medicine and reassembled before next use. All parts of the syringe should be completely dry before using it for the next dose.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements for cytotoxic products.

7. MARKETING AUTHORISATION HOLDER

Therakind (Europe) Limited
3 Inn's Quay
Dublin 7
D07 PW4F
Ireland

8. MARKETING AUTHORISATION NUMBER

EU/1/17/1172/001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 29 March 2017

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency (http://www.ema.europa.eu)

ANNEX II

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer responsible for batch release
Quay Pharmaceuticals Limited
Quay House, 28 Parkway
Deeside Industrial Park, Flintshire, CH5 2NS
United Kingdom

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports**

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:
- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

- **Additional risk minimisation measures**

Prior to launch of Jylamvo in each Member State, the Marketing Authorisation Holder (MAH) must agree about the content and format of the educational materials, 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

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.)

- **Obligation to conduct post-authorisation measures**

The MAH shall complete, within the stated timeframe, the below measures:

Description	**Due date**
The MAH should implement the agreed targeted follow-up questionnaires for all medication errors resulting in overdose.	From the date of notification of the Commission Decision*

*Referral EMEA/H/A-31/1463

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON

1. NAME OF THE MEDICINAL PRODUCT

Jylamvo 2 mg/ml oral solution
methotrexate

2. STATEMENT OF ACTIVE SUBSTANCE(S)

One ml of solution contains 2 mg methotrexate.

3. LIST OF EXCIPIENTS

Contains E214 and E219.
See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Oral solution

60 ml bottle
Bottle adaptor
10 ml dosing syringe

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use
Take as prescribed by your doctor using the dosing syringe provided.
Shake before use.
Read the package leaflet before use.
For arthritis and psoriasis take only once a week on ……. (include weekday of intake in full).

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Cytotoxic: Handle with caution

8. EXPIRY DATE

EXP:
Discard 3 months after first opening.

9. SPECIAL STORAGE CONDITIONS

Do not store above 25ºC.
Keep the bottle tightly closed.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Dispose of in accordance with local requirements.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Therakind (Europe) Limited
3 Inn's Quay
Dublin 7
D07 PW4F
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/17/1172/001

13. BATCH NUMBER

Lot:

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Jylamvo 2 mg/ml

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC:
SN:
NN:

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

BOTTLE LABEL

1. NAME OF THE MEDICINAL PRODUCT

Jylamvo 2 mg/ml oral solution
methotrexate

2. STATEMENT OF ACTIVE SUBSTANCE(S)

One ml of solution contains 2 mg methotrexate.

3. LIST OF EXCIPIENTS

Contains E214 and E219.
See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Oral solution.

60 ml

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use
Take as prescribed by your doctor using the dosing syringe provided.
Shake before use.
Read the package leaflet before use.
For arthritis and psoriasis take only once a week.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Cytotoxic

8. EXPIRY DATE

EXP:
Discard 3 months after first opening.
Open date:

9. SPECIAL STORAGE CONDITIONS

Do not store above 25ºC.
Keep the bottle tightly closed.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Dispose of in accordance with local requirements.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Therakind (Europe) Limited

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/17/1172/001

13. BATCH NUMBER

Lot:

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

17. UNIQUE IDENTIFIER – 2D BARCODE

Not applicable

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

Not applicable

PATIENT CARD TEXT

THIS PATIENT CARD IS ONLY INTENDED FOR PATIENTS WHO USE A METHOTREXATE-CONTAINING MEDICINE FOR ARTHRITIS AND PSORIASIS.

IF YOU USE METHOTREXATE FOR ONE OF THE ABOVE MENTIONED INDICATIONS, YOU SHOULD ONLY TAKE METHOTREXATE ONCE A WEEK

Write here in full the day of the week for intake: _____

Do not take more than the prescribed dose.

Overdose could lead to serious adverse effects and may be fatal. Symptoms of overdose are e.g. sore throat, fever, mouth ulcers, diarrhoea, vomiting, skin rashes, bleeding or unusual weakness. If you think you have taken more than the prescribed dose, consult a physician immediately.

Always show this card to health care professionals not familiar with your methotrexate treatment to alert them about your once weekly use (e.g. on hospital admission, change of care).

For more information, please read the patient leaflet inserted in the package.

B. PACKAGE LEAFLET

Package leaflet: Information for the user

Jylamvo 2 mg/ml oral solution
methotrexate

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Jylamvo is and what it is used for
2. What you need to know before you take Jylamvo
3. How to take Jylamvo
4. Possible side effects
5. How to store Jylamvo
6. Contents of the pack and other information

1. What Jylamvo is and what it is used for

Jylamvo is a medicine that:
- suppresses the growth of certain cells in the body that multiply rapidly (an anticancer medicine)
- reduces unwanted reactions by the body's own defense mechanisms (an immunosuppressive agent)
- has an anti-inflammatory effect

Jylamvo is used in patients with:
- the following rheumatic and skin diseases:
    - active rheumatoid arthritis (RA) in adults
    - polyarthritic forms (when five or more joints are affected) 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 (NSAIDs) has been inadequate
    - severe, treatment-resistant, disabling psoriasis that does not respond sufficiently to other forms of treatment such as phototherapy, psoralen and ultraviolet A radiation (PUVA) therapy and retinoids, as well as in severe psoriasis that also affects the joints (psoriatic arthritis) in adult patients
- acute lymphoblastic leukaemia (ALL) in adults, adolescents and children aged 3 years and over

You must talk to a doctor if you do not feel better or if you feel worse

2. What you need to know before you take Jylamvo

Do not take Jylamvo
- if you are allergic to methotrexate or any of the other ingredients of this medicine (listed in section 6)
- if you have a severe kidney impairment (or your doctor classes the impairment as severe)
- if you have a liver impairment
- if you have blood disorders such as bone marrow hypoplasia, leukopenia, thrombocytopenia or significant anaemia
- if you drink alcohol excessively

- if you have a weakened immune system
- if you are suffering from a serious infection such as tuberculosis or HIV
- if you have ulcers in the stomach or in the intestines
- if you have an inflammation of the mucous membrane of the mouth or mouth ulcers
- if you are pregnant or breast-feeding (see section “Pregnancy, breast-feeding and fertility”)
- if you have had a live vaccine recently or are about to have one

Warnings and precautions

Important warning about the dose of Jylamvo (methotrexate):
This oral solution contains 2 mg methotrexate in 1 ml solution and the scaling of the dosing syringe is in ml and not mg.
Take Jylamvo **only once a week** for the treatment of rheumatic or skin diseases (RA, JIA and psoriasis or psoriatic arthritis).
Taking too much of Jylamvo (methotrexate) may be fatal.
Please read section 3 of this leaflet very carefully.
If you have any questions, please talk to your doctor or pharmacist before you take this medicine.

Talk to your doctor or pharmacist before taking Jylamvo:
- if you have diabetes mellitus treated with insulin
- if you are suffering from inactive, chronic infections (e.g. tuberculosis, hepatitis B or C, shingles [herpes zoster]) as they may flare up
- if you have ever had any liver or kidney disease
- if you have problems with your lung function
- if you are particularly overweight
- if you have an abnormal build-up of fluid in the abdomen (ascites) or around the lungs (pleural effusions)
- if you are dried out (dehydrated) or suffer from conditions that result in dehydration (vomiting, diarrhoea, constipation, inflammation of the mucous membrane of the mouth)

If you had skin problems after radiotherapy (radiation dermatitis) or sunburn, these reactions can recur after methotrexate therapy (recall reaction).

Enlarged lymph nodes (lymphoma) may occur in patients receiving low dose methotrexate and if this is the case, therapy must be stopped.

Acute bleeding from the lungs in patients with underlying rheumatologic disease has been reported with methotrexate. If you experience symptoms of spitting or coughing up blood you should contact your doctor immediately.

Diarrhoea can be a possible side effect of Jylamvo and requires an interruption of therapy. If you suffer from diarrhoea please speak to your doctor.

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.

Psoriasis skin changes can become worse during treatment with methotrexate if you are under UV light.

Methotrexate temporarily affects sperm and egg production. Methotrexate can cause miscarriage and severe birth defects. You and your partner should avoid having a baby if you are being given methotrexate at the time and for at least 6 months after the end of your treatment with methotrexate. See also section “Pregnancy, breast-feeding and fertility”.

<u>Recommended follow-up examinations and precautions</u>

Severe side effects can occur even when methotrexate is used at low doses. Your doctor must carry out investigations and laboratory tests in order to detect these effects as early as possible.

Before the beginning of treatment
Your doctor should perform blood tests before the beginning of treatment to check how well your kidneys and liver are working. You will possibly also have an X-ray of your chest. Other tests may possibly be performed before and after treatment. Do not miss your blood test appointments.

If the results of any test are abnormal, the treatment will not be restarted until all the values have returned to normal.

Children, adolescents and elderly
Children, adolescents and the elderly treated with methotrexate should have particularly careful medical monitoring in order to detect important side effects quickly.

This medicine is not recommended in children under 3 years of age as there is insufficient experience in this age group

Other medicines and Jylamvo
Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines, including medicines obtained without a prescription and herbal or natural medicinal products.
Remember to inform your doctor about the treatment with Jylamvo if you are prescribed another medicine during treatment.

It is particularly important to tell your doctor if you are using the following medicines:
- other medicines for rheumatoid arthritis or psoriasis, such as leflunomide, azathioprine (also used to prevent rejection after an organ transplant), sulfasalazine (also used for ulcerative colitis)
- ciclosporin (for supressing the immune system)
- non-steroidal anti-inflammatory drugs or salicylates (medicines against pain and/or inflammation such as acetylsalicylic acid, diclofenac and ibuprofen or pyrazole)
- live vaccines
- diuretics, that reduce fluid retention
- medicines for lowering blood sugar levels such as metformin
- retinoids (for the treatment of psoriasis and other skin diseases)
- antiepileptic medicines (prevention of seizures)
- barbiturates (sleeping medicines)
- sedatives
- oral contraceptives
- probenecid (for gout)
- antibiotics
- pyrimethamine (for the prevention and treatment of malaria)
- vitamin preparations containing folic acid
- proton pump inhibitors (for the treatment of heartburn, ulcers and some other stomach complaints)
- theophylline (for breathing problems)
- mercaptopurine (for the treatment of certain types of leukaemia).
- cancer treatments (such as doxorubicin and procarbazine during high-dose methotrexate therapy)

Jylamvo with food, drink and alcohol
This medicine can be taken with or without food. When you have taken your dose, drink some water and swallow it to ensure you have taken your full dose and there is no methotrexate left in your mouth. You should not drink alcohol during treatment with Jylamvo and should avoid drinking excessive amounts of coffee, caffeinated drinks and black leaf tea. Ensure that you drink a lot of fluids during treatment with Jylamvo because dehydration (the reduction of body water) can increase the side effects

of methotrexate.

Pregnancy
Do not use Jylamvo during pregnancy except if your doctor has prescribed it for oncology treatment. Methotrexate can cause birth defects, harm the unborn child or cause miscarriage. It is associated with malformations of the skull, face, heart and blood vessels, brain, and limbs. It is therefore very important that methotrexate is not given to pregnant women or to women who are planning to become pregnant unless used for oncology treatment.

For non-oncological indications, in women of child-bearing age the possibility of a pregnancy must be ruled out, e.g. by pregnancy tests, before treatment is started.

Do not use Jylamvo if you are trying to become pregnant. You must avoid becoming pregnant during treatment with methotrexate and for at least 6 months after the end of treatment. Therefore you must ensure that you are taking effective contraception for the whole of this period (see also section "Warnings and precautions").

If you become pregnant during treatment or suspect you might be pregnant, speak to your doctor as soon as possible. If you do become pregnant during treatment, you should be offered advice regarding the risk of harmful effects on the child through treatment.

If you want to become pregnant, you should speak with your doctor, who may refer you for specialist advice before the planned start of treatment.

Breast-feeding
Do not breast-feed during treatment as methotrexate passes into the breast milk. If your doctor considers that continuing treatment with methotrexate is essential, you must stop breast-feeding.

Male Fertility
The available evidence does not indicate an increased risk of malformations or miscarriage if the father takes methotrexate less than 30 mg (15 ml)/week. However, a risk cannot be completely excluded and there is no information regarding higher methotrexate doses. Methotrexate can have a genotoxic effect. This means that the medicine can cause genetic mutations. Methotrexate can affect the production of sperm, which is associated with the possibility of birth defects.

You should avoid fathering a child or to donate semen during treatment with methotrexate and for at least 6 months after the end of treatment. As treatment with methotrexate at higher doses commonly used in cancer treatment can cause infertility and genetic mutations, it may be advisable for male patients treated with methotrexate doses higher than 30 mg (15 ml)/week to consider sperm preservation before the beginning of treatment (see also section "Warnings and precautions").

Driving and using machines

Caution: This medicine can affect your capacity to react and your ability to drive.

Side effects affecting the central nervous system such as tiredness or dizziness can occur during treatment with Jylamvo. In some cases the ability to drive or use machines may be affected. If you feel tired or dizzy, you should not drive a vehicle or use machines.

Jylamvo contains ethyl parahydroxybenzoate and sodium methyl parahydroxybenzoate
Ethyl parahydroxybenzoate (E214) and sodium methyl parahydroxybenzoate (E219) may cause allergic reactions (possibly delayed).

3. How to take Jylamvo

Jylamvo should be prescribed only by doctors who are familiar with the properties of the medicine and

how it works.

Always take this medicine exactly as your doctor has told you. Check with your doctor or pharmacist if you are not sure.

Taking Jylamvo incorrectly can result in severe side effects and even death.

The duration of the treatment is determined by the treating physician. Treatment of rheumatoid arthritis, severe juvenile idiopathic arthritis, severe psoriasis and severe psoriatic arthritis with Jylamvo is a long-term treatment.

Recommended dose
Your doctor will decide what dose of Jylamvo you should take according to the condition you are being treated for, how severe it is and your general health. Keep to the dose exactly and follow your doctor's instructions exactly on when to take the medicine.

Dose in rheumatic and skin diseases (RA, JIA and psoriasis or psoriatic arthritis)
Take Jylamvo **only once a week**. Decide with your doctor the most suitable day of the week to take the medicine.

Dosage in adult rheumatoid arthritis:
The usual initial dose is 7.5 mg (3.75 ml), once a week.

Dosage for psoriasis and psoriatic arthritis:
The usual initial dose is 7.5 mg (3.75 ml), once a week.

The doctor may increase the dose if the used dose is not effective but tolerated well.
Your doctor may adjust the dose to suit you according to your response to treatment and side effects.

Dose in acute lymphoblastic leukaemia (ALL)
Your doctor will tell you what dose you should take for your condition and when you should take the dose. Keep to this dose exactly.

Use in children and adolescents
The doctor will calculate the dose required from the child's body surface area (m^2), and the dose is expressed as mg/m^2.

Elderly
Because of the reduced liver and kidney function and the lower folate reserves in elderly patients, a relatively low dosage should be chosen for them.

How to take the medicine
Your pack of Jylamvo contains a bottle of medicine with a cap, a bottle adaptor and a white dosing syringe. Always use the syringe provided to take your medicine.

If you are a parent or caregiver giving the medicine, wash your hands before and after giving a dose. Wipe up spillages immediately. For protection, you should wear disposable gloves when handling Jylamvo.

Women who are pregnant, planning to be or breast-feeding should not handle methotrexate.

If Jylamvo comes into contact with skin, eyes or nose, you should wash the affected area with water and soap.

Jylamvo is for oral use and provided ready for use.

Please note that this oral solution contains 2 mg methotrexate in 1 ml solution and that the

scaling of the dosing syringe is in ml and not mg.

Methotrexate can be taken with or without food. When you have taken your dose, drink some water and swallow it to ensure you have taken your full dose and there is no methotrexate left in your mouth.

When you use the medicine follow the instructions below:

1. Put on disposable gloves before handling.
2. Shake the bottle.
3. Remove the bottle cap and push the adaptor firmly into the top of the bottle.
4. Push the tip of the dosing syringe into the hole in the adaptor.
5. Turn the bottle upside down.
6. Pull the syringe plunger back SLOWLY so that the medicine is drawn from the bottle into the syringe until the WIDEST part of the white syringe plunger is lined up to the black syringe marking of the dose required. DO NOT measure to the narrow tip of the plunger. If there are air bubbles in the syringe, repeat until bubbles are eliminated.
7. Turn the bottle back the right way up and carefully remove the syringe from the adaptor, holding the syringe by the barrel rather than the plunger.
8. Confirm that the dose in the syringe is correct.
9. Ensure that the patient is sitting up or standing before giving the medicine.
10 Gently place the tip of the syringe into the patient's mouth and direct it to the inside of the cheek.
11. Slowly and gently push the plunger down to gently squirt the medicine into the inside of the cheek. DO NOT push down the plunger too hard or squirt the medicine to the back of the mouth or throat as this may cause choking. The plunger should be pushed back gently to the seated position until it clicks into place.
12. Remove the syringe from the patient's mouth.
13. Ask the patient to swallow the medicine and then to drink some water, making sure no medicine is left in the mouth.
14. Put the cap back on the bottle with the adaptor left in place. Ensure that the cap is tightly closed.
15. Wash the syringe immediately after use with fresh warm, 'soapy' water and rinse well. The syringe should be held under water and the plunger drawn in and out several times until all traces of medicine are removed from inside the syringe including the tip. The plunger and barrel should then be separated and both washed thoroughly in the warm soapy water. They should then be rinsed thoroughly under COLD water and excess water shaken off before wiping dry with a clean paper towel. The plunger and barrel should be stored in a clean dry container with the medicine and reassembled before next use. All parts of the syringe should be completely dry before using it for the next dose.

Repeat the above instructions for each dose, as instructed by your doctor or pharmacist.

If you take more Jylamvo than you should
Follow your doctor's dose recommendations. Never change the dose on your own.

If you suspect that you (or someone else) have (has) taken too much Jylamvo, tell your doctor immediately or contact the nearest hospital casualty department. The doctor will decide whether any treatment is needed.

An overdose of methotrexate can cause serious reactions. The symptoms of an overdose can include bleeding, an unusual feeling of weakness, ulcers in the mouth, feeling sick, vomiting, black or bloody stools, coughing up blood or vomiting blood with a coffee grounds appearance and a reduced urine. See also section 4 "Possible side effects".

Take the medicine pack with you when you visit your doctor or the hospital.
The antidote in the event of an overdose is calcium folinate.

If you forget to take Jylamvo

Never take a double dose to make up for a forgotten dose but continue with the prescribed dose. Ask your doctor for advice.

If you stop taking Jylamvo
Do not interrupt or stop the treatment with Jylamvo without first discussing this with your doctor. If you suspect you have a severe side effect, talk to your doctor immediately.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Tell your doctor immediately if you suddenly get wheeziness, difficulty in breathing, swelling of the eyelids, face or lips, rash or itching (especially affecting your whole body).

Contact your doctor immediately if you develop any of the side effects listed below:

- breathing problems (these include a general feeling of illness, dry, irritating cough, shortness of breath, difficulty in breathing, chest pain or fever)
- spitting or coughing blood*
- serious peeling or blistering of the skin
- unusual bleeding (including vomiting blood), bruising or nose bleeds
- nausea, vomiting, abdominal discomfort or severe diarrhoea
- mouth ulcers
- black or tarry stools
- blood in the urine or stool
- small red spots on the skin
- fever, sore throat, flu-like symptoms
- yellow colouring of the skin (jaundice) or dark urine
- pain or difficulties in passing urine
- thirst and/or frequent urination
- seizures (convulsions)
- unconsciousness
- blurred or restricted vision
- severe fatigue.

*has been reported for methotrexate used in patients with underlying rheumatologic disease.

The following side effects have also been reported:

Very common (may affect more than 1 in 10 people):
- loss of appetite, feeling sick (nausea), vomiting, abdominal pain, indigestion, inflammation and ulcers of the mouth and throat
- blood test showing raised liver enzymes.

Common (may affect up to 1 in 10 people):
- infections
- reduced blood cell formation with a decrease in white and/or red blood cells and/or platelets (leucocytopenia, anaemia, thrombocytopenia)
- headache, tiredness, lightheadedness
- inflammation of the lungs (pneumonia) with dry cough, shortness of breath and fever
- diarrhoea
- skin rash, skin redness and itching.

Uncommon (may affect up to 1 in 100 people):
- lymphoma (lump in neck, groin or armpits with associated backache, weight loss or night sweats)
- severe allergic reactions
- diabetes
- depression
- dizziness, confusion, seizures
- lung damage
- ulcers and bleeding in the digestive tract
- liver diseases, reduced content of blood proteins
- nettle rash, skin reaction in strong light, brown discoloration of the skin, hair loss, increased number of rheumatic nodules, shingles, painful psoriasis, slow wound healing
- joint or muscle pain, osteoporosis (reduction in bone strength)
- kidney disease, inflammation or ulcers of the bladder (possibly also with blood in the urine), painful urination
- inflammation and ulcers of the vagina.

Rare (may affect up to 1 in 1,000 people):
- a blood disorder characterised by the appearance of very large red blood cells (megaloblastic anaemia)
- mood swings
- weakness in movements, also only limited to the left or right side of the body
- severe visual disorders
- inflammation of the heart sac, accumulation of fluid in the heart sac
- low blood pressure, blood clots
- tonsillitis, stopping breathing, asthma
- inflammation of the pancreas, inflammation of the digestive tract, bloody stools, inflamed gums, indigestion
- acute hepatitis (inflammation of the liver)
- discoloration of the nails,acne, red or purple spots due to bleeding from blood vessels
- worsening of psoriasis during treatment with UV therapy
- skin lesions resembling sunburn or dermatitis after radiotherapy
- bone fractures
- kidney failure, reduction or lack of urine production, abnormal levels of electrolytes in blood
- impaired sperm formation, menstrual disorders.

Very rare (may affect up to 1 in 10,000 people):
- viral, fungal or bacterial systemic infections,
- serious disorder of bone marrow (anaemia), swollen glands
- lymphoproliferative disorders (excessive growth of white blood cells)
- insomnia
- pain, muscle weakness, changes in the sense of taste (metallic taste), inflammation of the membrane lining the brain resulting in paralysis or vomiting, pins and needles in arm and legs
- impaired movement of the muscles used for speech production, difficulty in speaking, impairment of language, feeling sleepy or tired, feeling confused, having unusual sensations in the head, brain swelling, ringing in ears
- red eyes, damage to the retina of the eye
- accumulation of fluid in the lung, lung infections
- vomiting blood, severe complications in the digestive tract
- liver failure
- fingernail infections, detachment of the nail from the nail bed, boils, widening of small blood vessels, damage to the blood vessels of the skin, allergic inflammation of blood vessels
- protein in the urine
- loss of sex drive, erection problems, vaginal discharge, infertility, enlargement of the breasts in

men (gynaecomastia)
– fever.

Not known (frequency cannot be estimated from the available data)
– pathological change of the white matter of the brain (leukoencephalopathy)
– haemorrhages
– bleeding from the lungs*
– bone damage in the jaw (secondary to excessive growth of white blood cells).
*has been reported for methotrexate used in patients with underlying rheumatologic disease.

Methotrexate can reduce the number of white blood cells and therefore weaken your immune defences. If you notice any symptoms of an infection such as fever or a marked worsening in your general state of health or fever with local signs of an infection such as sore throat/inflammation of the throat or mouth or problems passing water, see your doctor immediately. A blood test will be done to check for reduction in the white blood cells (agranulocytosis). It is important to tell your doctor about all the medicines you take.

Methotrexate can cause serious (sometimes life-threatening) side effects. Your doctor will therefore do tests to check for any changes in your blood (such as a low white blood cell count, a low blood platelet count, lymphomas), kidneys or liver.

Reporting of side effects
If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V.

By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Jylamvo

Keep this medicine out of the sight and reach of children, preferably in a locked cupboard. Accidental ingestion can be lethal for children.

Do not use the medicine after the expiry date which is stated on the carton and label after ‘Exp’. The expiry date refers to the last day of that month.

Do not store above 25°C.

Keep the bottle tightly closed to prevent spoilage of the medicine and reduce the risk of accidental spillage.

After first opening, throw away any unused medicine after 3 months.

Any unused medicine or waste material should be disposed of in accordance with local requirements for cytotoxic products - check with your pharmacist.

6. Contents of the pack and other information

What Jylamvo contains
The active substance is methotrexate. One ml of solution contains 2 mg of methotrexate.

The other ingredients are: macrogol 400, glycerol, orange flavour, sucralose, ethyl parahydroxybenzoate (E214), sodium methyl parahydroxybenzoate (E219), citric acid, tri-sodium citrate, purified water. See section 2 “Jylamvo contains ethyl parahydroxybenzoate and sodium methyl parahydroxybenzoate”.

What Jylamvo looks like and contents of the pack

Jylamvo is a clear yellow solution. It is presented in a brown glass bottle containing 60 ml of solution and capped with a child-resistant closure. Each pack contains one bottle, a bottle adaptor and a white dosing syringe.

Marketing Authorisation Holder
Therakind (Europe) Limited
3 Inn's Quay
Dublin 7
D07 PW4F
Ireland

Manufacturer
Quay Pharmaceuticals Limited
Quay House
28 Parkway
Deeside Industrial Park
Flintshire
CH5 2NS
United Kingdom

This leaflet was last revised in

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu.

Annex IV

Scientific conclusions

Scientific conclusions

Methotrexate is authorised in the European Union since the 1960s. It is indicated in the treatment of cancers such as acute lymphoblastic leukaemia (ALL) and various inflammatory conditions, including rheumatoid arthritis, juvenile idiopathic arthritis, psoriasis, and psoriatic arthritis and as steroid sparing adjunctive therapy in Crohn's disease.

Each group of indications has a different administration schedule:

- For the treatment of cancer, various administration schedules including daily dosage may be used;
- For the treatment of autoimmune diseases, which require immunosuppressive therapy like rheumatoid arthritis, psoriasis, Crohn's disease and other autoimmune diseases, it is prescribed as a single low-dose, once a week.

Methotrexate-containing products are authorised in all EU Member States, and either oral or parenteral formulation or both pharmaceutical formulations are available.

Serious cases of overdose, sometimes fatal, have been reported in patients inadvertently receiving the product daily instead of weekly for indications that require weekly dosing. Despite additional risk minimisation measures having already been put in place, reports continued to be received.

On 22 March 2018 Spain therefore triggered a referral under Article 31 of Directive 2001/83/EC resulting from pharmacovigilance data, and requested the PRAC to assess the root causes and the impact of the risk of medication errors on the benefit-risk balance of oral formulation of methotrexate and to issue a recommendation on whether the relevant marketing authorisations should be maintained, varied, suspended or revoked.

The PRAC further agreed during its April 2018 plenary meeting to extend the scope to include also parenteral formulations of methotrexate, in view of a number of cases reported with these formulations as well, and due to the fact that for a high number of cases reported as "incorrect schedule of dose administration" with methotrexate, the route of administration and the pharmaceutical form had not been specified.

The PRAC adopted a recommendation on 11 July 2019 which was then considered by the CHMP, in accordance with Article 107k of Directive 2001/83/EC.

Overall summary of the scientific evaluation by the PRAC

The risks associated with inappropriate use of methotrexate daily instead of weekly make methotrexate one of the most known high-risk medications prone to medication errors. Systematic review by Saedder and colleagues (2014)[1] revealed that 47% of all serious medication errors were caused by only seven drug classes, with methotrexate topping the list in percentage of incidents. Furthermore, of the 74 articles that met the review's inclusion criteria, 73 contained information about a serious adverse reaction caused by methotrexate-related medication error (found in the FDA Adverse Event Reporting System). Since early 1996, harmful or fatal errors with low dose oral methotrexate have been reported to the Institute for Safe Medication Practices (ISMP) and published in more than 50 of its newsletters, but in spite of this and numerous risk minimization measures, methotrexate continues to be subject in documented serious medication errors (Grissinger, 2018[2]).

[1] Saedder EA1, Brock B, Nielsen LP, Bonnerup DK, Lisby M.:Identifying high-risk medication: a systematic literature review. Eur J Clin Pharmacol. 2014 Jun;70(6):637-45.
[2] Grissinger M. Severe Harm and Death Associated With Errors and Drug Interactions Involving Low-Dose Methotrexate. P T. 2018 Apr;43(4):191-248.

In EU/EEA, despite the risk minimisation measures in place, cases of medication errors are still occurring. In order to assess the root causes and the impact of the risk of medication errors due to inadvertent daily dosing instead of weekly dosing, the PRAC considered the analyses of cases report of inadvertent daily instead of weekly usage of methotrexate-containing products, including reports without adverse events, for the period 1 January 2013 until 31 March 2018 from the EudraVigilance database as well as from the data provided by the MAHs of methotrexate-containing products which included analyses of the medication error case reports from the companies' pharmacovigilance databases and in the literature. The data showed that severe, life-threatening and fatal cases of overdose due to medication errors with methotrexate-containing medicinal products continue to be reported despite the risk minimisation measures in place. While daily instead of once weekly use of methotrexate was mainly reported with oral dosage forms in non-oncologic indications, predominantly rheumatoid arthritis and psoriasis, there were also cases with the use of parenteral formulations, as well as many reports which did not specify the route of administration.

Extensive assessment of spontaneously reported post-marketing cases has been performed by the PRAC and although some relevant data might not have been provided in all spontaneously reported post-marketing cases, the root cause analysis was further substantiated by the assessment of literature data, which provided more detailed description of methotrexate medication error cases. The feedback received from healthcare professional organisations also provided further insight on the root causes for errors.

Based on the available data, the PRAC noted that the abovementioned risk of medication errors can occur at all stages of the medication process, from prescription to administration. Different reasons for the occurrence of medication error have been identified. The ambiguity due to the product being authorised in different indications with different dosing schedules and lacking clear and visible warnings alerting on the once weekly dosing schedule on the packaging and the use of bulk packaging were identified as root causes for medication errors. Lack of knowledge and clarity on the weekly dosing schedule in some indications was also recurring feature and not limited to patient level. Admission to hospital and transfer of care between institutions and physicians was also noted as a root cause due to poor or a lack of communication between patient/physician, physician/physician, physician/nurse. Dispensing errors have also been reported. The case report analyses showed that the elderly patient population was more predisposed for inadvertent daily use of methotrexate, with more than half of the cases reporting elderly population (65 or over). Other subgroups of patients were also identified at risk such as patients with impaired memory and cognitive functions, patients with visual impairment, patients who have difficulties to follow written instructions, patients who split their weekly oral methotrexate dose, patients with co-morbidities and co-medications.

In the context of this review, the PRAC discussed, in consultation with patients and healthcare professionals, how the risk minimisation measures already in place could be further strengthen and if further measures should be implemented.

To increase awareness and remind healthcare professionals and patients of the weekly dosing schedule required for the treatment of some conditions, the MAHs for oral methotrexate-containing products with at least an indication requiring dosing once a week had been requested, as outcome of the PSUSA (EMEA/H/C/PSUSA/00002014/201706), to implement a visual reminder on the outer and immediate packaging to warn patients to take the product once a week for those indications requiring dosing once a week. It was noted that many different wordings and styles of warnings have been implemented, from very small information on one side of the packaging in black to large red framed information on several sides of the outer packaging, inclusion of a calendar or place to mark the day of intake as well as different texts for the warning. In view of the differences, the PRAC recommended an increased consistency in the implementation of this measure by defining clear, concise and unambiguous warnings for the outer and inner packaging of these products. In addition, although the number of cases reporting medication errors with parenteral formulations was smaller than with oral

formulations, the risk of medication error by daily intake/use rather than once weekly is considered a general problem for all methotrexate-containing products with at least one indication that requires once a week dosing. For this reason, the PRAC was of the view that the visual reminder agreed for the outer packaging of the oral formulations of methotrexate should also be implemented on the outer packaging of the parenteral formulations of methotrexate with at least one indication requiring once weekly dosing, and that the shorter warning agreed for the immediate packaging of the oral formulations should be implemented on the intermediate (where applicable) and immediate packaging of the parenteral formulations. Similarly, the boxed warning in SmPC section 4.2 already agreed to be added to the product information of the oral formulations as outcome of the PSUSA should be also reflected in the product information of methotrexate parenteral formulations.

Medication errors were also associated with the use of bulk packaging. In particular, it was reported that bulk packaging such as bottles or tubes does not allow tracking, i.e. easy counting, of the remaining tablets, making it difficult both for patients and caregivers to notice the error. In addition, bulk packaging bear the risk of losing warning information at the time of repackaging which is e.g. common practice in medical centres/hospitals. To address this issue, the PRAC recommended that for all tablet formulations of methotrexate, bulk packaging such as bottles or tubes should be replaced by blisters. Taking into account that such replacement may require several technical changes and not to jeopardize the availability of methotrexate formulations in some Member States, the PRAC agreed to an implementation period of up to 4 years after finalisation of this procedure.

To minimise the risk of prescribing errors due to lack of knowledge by the prescriber of the weekly dosing schedule of methotrexate for the treatment of auto-immune diseases, the PRAC was of the view 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. An update of the product information of all methotrexate products with at least one indication requiring a once weekly dosing schedule was recommended accordingly. In addition, as understanding of the once weekly dosing schedule of methotrexate is essential to avoid dosing errors by the patients or their carer and for the adherence to this special treatment schedule, an update of the product information of methotrexate products with at least one indication requiring a once weekly dosing schedule was considered necessary to alert healthcare professionals to restrict the use of oral methotrexate to patients/carers who are able to comply with the once weekly dosing schedule.

Dividing the prescribed dose in multiple intakes was reported as a risk factor for medication error and no robust evidence could be provided to support the effectiveness of this regimen or identify patient groups for whom benefits of dividing the dose would outweigh the risk of medication errors. It was also noted that current European guidelines do not mention the possibility of dividing the dose. Overall, it was considered that such practice may generate more confusion and lead to more medication errors and should therefore not be recommended. Any reference to dividing the dose in the product information should therefore be deleted.

To increase awareness of HCPs on the risk of medication errors and their possible consequences, it was considered that for methotrexate oral formulations, educational materials for healthcare professionals should be developed or updated, if already in place, to inform them on the potential for fatal overdose due to medication errors (ME), including daily instead of once weekly use, highlight the need to inform patients and relatives/carers about the once weekly dosing, and provide information on the importance to fill in prescriptions with clear instructions about once weekly dosing, defined day of intake, and to not use abbreviations. The educational material should also include a reminder for the pharmacist to counsel the patient about the inadvertent daily instead of once-weekly dosing.

In addition, the PRAC requested the development of a patient card to be inserted inside or attached to the outer packaging. This card was considered a necessary tool to remind patients to take the product only once weekly, inform on serious adverse effects that may be fatal, on the symptoms of overdose and steps to be taken should symptoms arise, and recommend patients to show the card and alert any

healthcare professionals not familiar with their methotrexate treatment about their once weekly dosing schedule (e.g. on hospital admission, change of care). The day of the week methotrexate treatment should be taken should be written on the card by the patient.

The risk of medication errors due to inadvertent daily instead of once weekly dosing is an important identified risk and all methotrexate-containing products for which additional risk minimisation measures are required to address this risk (i.e. replacement of bottles/tubes by blisters, implementation of educational material and patient card), should have a risk management plan (RMP) in place listing all pharmacovigilance activities and risk minimisation measures agreed.

To gain further knowledge on the reasons leading to medication errors and prevent them adequately, as well as in support of the measurement of the effectiveness of the agreed risk minimisation measures, all MAHs are requested to implement and use a targeted follow-up questionnaire, as agreed by PRAC, for all medication errors reported with methotrexate and resulting in overdose.

A direct healthcare professional communication was also agreed, together with a communication plan, to inform relevant healthcare professionals of the new recommendations and risk minimisation measures agreed.

In view of the above, the Committee considers that the benefit-risk balance of methotrexate-containing medicinal products remains favourable subject to the agreed conditions to the marketing authorisations, and taking into account the agreed amendments to the product information and other risk minimisation measures.

Grounds for PRAC recommendation

Whereas,

- The Pharmacovigilance Risk Assessment Committee (PRAC) considered the procedure under Article 31 of Directive 2001/83/EC for medicinal products containing methotrexate;
- The PRAC considered the totality of the data submitted for methotrexate-containing products with regard to the important identified risk of medication errors when methotrexate intended for once weekly use is taken daily by mistake, the root causes for this risk and the effectiveness of the risk minimisation measures in place. This included the responses submitted by the marketing authorisation holders in writing as well as the views of patients and healthcare professionals;
- The PRAC investigated the root causes for the abovementioned risk of medication errors and noted that these can occur at all stages of the medication process;
- The PRAC noted that severe, life-threatening and fatal cases of overdose due to medication errors with methotrexate-containing medicinal products continue to be reported and that the risk minimisation measures in place have not been sufficiently effective to prevent medication errors, in particular with the oral formulations of methotrexate;
- The PRAC concluded that there is a need to further strengthen the current risk minimisation measures by adding warnings in the product information and visual reminders on the outer, intermediate and immediate packaging of methotrexate-containing medicinal products with at least one indication requiring a once weekly dosing, for both oral and parenteral use;
- In addition, the PRAC also recommended other changes to the product information of all methotrexate-containing products with at least one indication requiring once weekly dosing to include that only physicians with expertise in using methotrexate-containing medicines should prescribe them and that healthcare professionals should ensure that patients or their carers will

be able to follow the once weekly dosing schedule. In addition, splitting the dose in multiple intakes should no longer be recommended;

- Considering the number of reported inadvertent daily administration of methotrexate oral formulations, the PRAC concluded that for these products educational materials for healthcare professionals should be developed or updated, if already in place, in accordance with the key elements agreed, as well as a patient card to be provided with the medicinal product, to further increase awareness. It was also agreed that for all tablet formulations of methotrexate, bottles and tubes currently used as immediate packaging should be replaced by blisters. These risk minimisation measures should be reflected in a risk management plan.
- A direct healthcare professionals communication was also agreed, together with a communication plan;
- The PRAC finally agreed on targeted follow-up questionnaires should be used for all cases of medication errors reported with methotrexate and resulting in overdose.

In view of the above, the Committee considers that the benefit-risk balance of methotrexate-containing medicinal products remains favourable subject to the agreed conditions to the marketing authorisations, and taking into account the agreed amendments to the product information and other risk minimisation measures.

The Committee, as a consequence, recommends the variation to the terms of the marketing authorisations for methotrexate-containing medicinal products.

CHMP opinion

Having reviewed the PRAC recommendation, the CHMP agrees with the PRAC overall conclusions and grounds for recommendation.

The CHMP, as a consequence, considers that the benefit-risk balance of methotrexate-containing medicinal products remains favourable subject to the amendments to the product information and to the conditions described above.

Therefore the CHMP recommends the variation to the terms of the marketing authorisations for methotrexate-containing medicinal products.