Guide for Healthcare Professionals
Jylamvo (methotrexate) 2 mg/ml oral solution

Jylamvo (methotrexate) 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.

This Guide is not a substitute for the Jylamvo Summary of Product Characteristics (SmPC). Please consult the SmPC for full prescribing information.

NOTE: Special warnings and precautions for use

The oral solution contains 2 milligram (mg) of methotrexate in each 1 millilitre (ml) of solution; the scaling of the dosing syringe is in milliliter (ml); care should be taken that the correct dosing volume is prescribed.

Patients with <u>rheumatological or dermatological diseases</u> must be informed unequivocally that treatment is to be taken just <u>once a week</u> and not any other frequency. Incorrect use of methotrexate can result in severe and even fatal adverse reactions. Medical staff and patients must be clearly instructed.

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1. Purpose of this guide

This Guide has been prepared for doctors, nurses and other healthcare professionals or care-givers who prescribe, dispense or work with patients who use Jylamvo (Methotrexate) and is intended to ensure that the medicine is used correctly. This Guide is not a substitute for the Jylamvo Summary of Product Characteristics (SmPC); please consult the SmPC for full prescribing information.

The main objective of this guide is to help mitigate the potential risk of medication errors in patients being treated for arthritis and psoriasis in a weekly regimen. It also provides some guidance for preparing the correct and generally more frequent dosage for children over 3 years of age, adolescents and adults being treated for acute lymphoblastic leukaemia. It is recognized that medication errors can sometimes happen despite appropriate prescribing and patient/carer instruction and so this guide also describes the risks and what to do in the event of a medication error.

2. Dosing and measuring

Each 1 ml of the solution contains 2 mg methotrexate (2mg/ml). A 10ml syringe is provided with the solution including major graduations at every 1ml and minor graduations at every 0.25 ml for accurate withdrawal of the required volume. Note that the syringe is graduated in milliliter (ml); however, the dose is expressed in milligram (mg).

When prescribing Jylamvo, doctors should always prescribe the dose in mg with the ml equivalence based on the correct age or body surface area of the patient. Further details on measuring and administering the correct dose with the syringe are provided in section 6.6 of the SmPC and in section 3 of the Package Leaflet.

Adult RA and psoriasis patients:

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 (see section 4.2 of the SmPC for more details).

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.

In children, dosing is prescribed by body surface area. 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 (see section 4.2 of the SmPC for more details).

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.

The tables overleaf are provided to assist in working out dosage in mg based on body surface area (BSA) and the dose equivalent in ml for children/adolescents being treated for JIA and ALL, respectively.

Dosing guidance for paediatric and adolescent patients with juvenile idiopathic arthritis (JIA)

Body Surface Area (BSA) (m^2)	Examples of PRESCRIBED DOSES					
	10mg/m^2		15mg/m^2		20mg/m^2	
	mg of methotrexate	**Volume of Jylamvo (mL)**	mg of methotrexate	**Volume of Jylamvo (mL)**	mg of methotrexate	**Volume of Jylamvo (mL)**
0.2	2	**1**	3	**1.5**	4	**2**
0.25	2.5	**1.25**	3.75	**1.75***	5	**2.5**
0.3	3	**1.5**	4.5	**2.25**	6	**3**
0.35	3.5	**1.75**	5.25	**2.5***	7	**3.5**
0.4	4	**2**	6	**3**	8	**4**
0.45	4.5	**2.25**	6.75	**3.25***	9	**4.5**
0.5	5	**2.5**	7.5	**3.75**	10	**5**
0.55	5.5	**2.75**	8.25	**4***	11	**5.5**
0.6	6	**3**	9	**4.5**	12	**6**
0.65	6.5	**3.25**	9.75	**4.75***	13	**6.5**
0.7	7	**3.5**	10.5	**5.25**	14	**7**
0.75	7.5	**3.75**	11.25	**5.5***	15	**7.5**
0.8	8	**4**	12	**6**	16	**8**
0.85	8.5	**4.25**	12.75	**6.25***	17	**8.5**
0.9	9	**4.5**	13.5	**6.75**	18	**9**
0.95	9.5	**4.75**	14.25	**7***	19	**9.5**
1	10	**5**	15	**7.5**	20	**10**
1.05	10.5	**5.25**	15.75	**7.75***	21	**10.5**
1.1	11	**5.5**	16.5	**8.25**	22	**11**
1.15	11.5	**5.75**	17.25	**8.5***	23	**11.5**
1.2	12	**6**	18	**9**	24	**12**
1.25	12.5	**6.25**	18.75	**9.25***	25	**12.5**
1.3	13	**6.5**	19.5	**9.75**	26	**13**
1.35	13.5	**6.75**	20.25	**10***	27	**13.5**
1.4	14	**7**	21	**10.5**	28	**14**
1.45	14.5	**7.25**	21.75	**10.75***	29	**14.5**
1.5	15	**7.5**	22.5	**11.25**	30	**15**
1.55	15.5	**7.75**	23.25	**11.5***	31	**15.5**
1.6	16	**8**	24	**12**	32	**16**
1.65	16.5	**8.25**	24.75	**12.25***	33	**16.5**
1.7	17	**8.5**	25.5	**12.75**	34	**17**
1.75	17.5	**8.75**	26.25	**13***	35	**17.5**
1.8	18	**9**	27	**13.5**	36	**18**
1.85	18.5	**9.25**	27.75	**13.75***	37	**18.5**
1.9	19	**9.5**	28.5	**14.25**	38	**19**
1.95	19.5	**9.75**	29.25	**14.5***	39	**19.5**
2	20	**10**	30	**15**	40	**20**
2.05	20.5	**10.25**	30.75	**15.25***	41	**20.5**
2.1	21	**10.5**	31.5	**15.75**	42	**21**
2.15	21.5	**10.75**	32.25	**16***	43	**21.5**
2.2	22	**11**	33	**16.5**	44	**22**

* dose rounded down

Dosing guidance for paediatric and adolescent patients with acute lymphoblastic leukemia (ALL)

Body Surface Area (BSA) (m^2)	Examples of PRESCRIBED DOSES					
	20mg/m^2		30mg/m^2		40mg/m^2	
	mg of methotrexate	**Volume of Jylamvo (mL)**	mg of methotrexate	**Volume of Jylamvo (mL)**	mg of methotrexate	**Volume of Jylamvo (mL)**
0.2	4	**2**	6	**3**	8	**4**
0.25	5	**2.5**	7.5	**3.75**	10	**5**
0.3	6	**3**	9	**4.5**	12	**6**
0.35	7	**3.5**	10.5	**5.25**	14	**7**
0.4	8	**4**	12	**6**	16	**8**
0.45	9	**4.5**	13.5	**6.75**	18	**9**
0.5	10	**5**	15	**7.5**	20	**10**
0.55	11	**5.5**	16.5	**8.25**	22	**11**
0.6	12	**6**	18	**9**	24	**12**
0.65	13	**6.5**	19.5	**9.75**	26	**13**
0.7	14	**7**	21	**10.5**	28	**14**
0.75	15	**7.5**	22.5	**11.25**	30	**15**
0.8	16	**8**	24	**12**	32	**16**
0.85	17	**8.5**	25.5	**12.75**	34	**17**
0.9	18	**9**	27	**13.5**	36	**18**
0.95	19	**9.5**	28.5	**14.25**	38	**19**
1	20	**10**	30	**15**	40	**20**
1.05	21	**10.5**	31.5	**15.75**	42	**21**
1.1	22	**11**	33	**16.5**	44	**22**
1.15	23	**11.5**	34.5	**17.25**	46	**23**
1.2	24	**12**	36	**18**	48	**24**
1.25	25	**12.5**	37.5	**18.75**	50	**25**
1.3	26	**13**	39	**19.5**	52	**26**
1.35	27	**13.5**	40.5	**20.25**	54	**27**
1.4	28	**14**	42	**21**	56	**28**
1.45	29	**14.5**	43.5	**21.75**	58	**29**
1.5	30	**15**	45	**22.5**	60	**30**
1.55	31	**15.5**	46.5	**23.25**	62	**31**
1.6	32	**16**	48	**24**	64	**32**
1.65	33	**16.5**	49.5	**24.75**	66	**33**
1.7	34	**17**	51	**25.5**	68	**34**
1.75	35	**17.5**	52.5	**26.25**	70	**35**
1.8	36	**18**	54	**27**	72	**36**
1.85	37	**18.5**	55.5	**27.75**	74	**37**
1.9	38	**19**	57	**28.5**	76	**38**
1.95	39	**19.5**	58.5	**29.25**	78	**39**
2	40	**20**	60	**30**	80	**40**
2.05	41	**20.5**	61.5	**30.75**	82	**41**
2.1	42	**21**	63	**31.5**	84	**42**
2.15	43	**21.5**	64.5	**32.25**	86	**43**
2.2	44	**22**	66	**33**	88	**44**

3. What are the risks associated with overdose?

In post marketing experience for methotrexate, reports of oral overdose that indicate accidental daily administration instead of weekly (single or divided doses) is associated with a risk of serious harm. Symptoms commonly reported following oral overdose include leukopenia, thrombocytopenia, anaemia, pancytopenia, bone marrow suppression, mucositis, stomatitis, oral ulceration, nausea, vomiting, gastrointestinal ulceration, gastrointestinal bleeding; these signs and symptoms are largely reported at pharmacological doses. However, there have been reports of death following overdose due to such medication error. In these cases, events such as sepsis or septic shock, renal failure, and aplastic anaemia were also reported.

4. Considering home or self-administration

It is the responsibility of the prescribing physician to determine which patients are suitable for home or self-administration of Jylamvo.

If home or self-administration is offered to a patient, the healthcare professional should advise the patient and/ or care giver on how to accurately measure the prescribed dose using the syringe provided (please see also SmPC section 6.6 or Package Leaflet section 3). This should be discussed with every prescription.

Patients who are taking Jylamvo for arthritis or psoriasis should be made aware of the importance of this medicine being taken weekly and the risk of serious adverse reactions including death if taken more frequently.

5. What should I discuss with my patients?

It is important to discuss signs and symptoms of adverse reactions of interest with the patient which will enable them to recognise possible events of overdose. The importance of reporting any adverse reactions as soon as possible should be highlighted. Known adverse reactions for Jylamvo include those listed in the SmPC section 4.8 and in the Package Leaflet Section 4.

If a patient is being considered suitable for home or self-administration by his/ her physician, it is important to discuss with the patient/carer how the medication should be taken (see section 3 of the Package Leaflet).

Furthermore, for the rheumatological/dermatological indications, it is very important to remind the patient/parent/guardian/carer(s) and to be sure that they have understood:

- Only to take/administer Jylamvo once a week;
- Which same day of the week the dose should be taken (this will be written on the prescription);
- How to withdraw the required dose using the syringe provided (refer to section 3 of the Package Leaflet);
- that greater doses or higher frequencies are associated with an increased risk of serious adverse events/reactions including death;
- If they do make an error to record and report to their physician what they have taken and when;
- To report any medication errors and adverse events.

6. Jylamvo prescribing & dispensing requirements

Please do not use medical abbreviations /shorthand on the prescription.

The dose should be prescribed in mg with the ml equivalence based on the correct age or body surface area of the patient.

For once weekly dosing regimens:

- On the prescription include the defined day of intake as well as clear instructions on once weekly dosing.

- On dispensing Jylamvo, the pharmacist should transcribe the defined day of the week for Jylamvo intake onto the patient card provided within the Jylamvo pack and the Jylamvo outer packaging. The pharmacist should show the patient card to the patient, reiterate the weekly dosing schedule and the other elements described on the patient card.

7. Follow-up visits and medication errors

Patients should be monitored for signs and symptoms of overdose (these predominantly affect the haematopoietic and gastrointestinal systems), such as bleeding, unusual feeling of weakness, ulcers in the mouth, feeling sick, vomiting, black or bloody stools, coughing up blood or vomiting blood and reduced urine output.

8. Therapeutic management of overdose

If the patient is not already in the clinical setting then the patient will need to immediately go to their local Emergency Department with their medication, including the packaging which includes prescriber and product information. On arrival they should ensure that they present their medication and tell the reception/registration desk that they have been instructed by the prescriber that immediate treatment is required in the event of an overdose.

Calcium folinate is the specific antidote for neutralising the adverse toxic effects of methotrexate. In the event of 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.

9. Adverse Event (AE)

An **Adverse Event (Adverse Experience, AE, Adverse Drug Experience, ADE)** is any untoward medical occurrence in a patient or clinical trial subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment.

An adverse event can be any unfavourable and unintended sign (e.g. an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

An **Adverse Drug Reaction (Adverse Reaction, ADR)** is a response to a medicinal product which is noxious and unintended. Response in this context means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility.

Adverse reactions may arise from use of the product within or outside the terms of the marketing authorisation or from occupational exposure. Conditions of use outside the marketing authorisation include off-label use, overdose, misuse, abuse and medication errors.

The following **Other Safety Related Information,** reported either with or without an AE/ADR, from any source should be reported as an Adverse Reaction in the same way:

- Exposure during pregnancy,
- Exposure via lactation,
- Foetal exposure via the mother or father,
- Lack of efficacy,
- Overdose,
- Misuse or abuse by any individual [see definitions*],
- Medication Errors,
- Unintended beneficial effect,
- Transmission of an infectious agent via the Product(s),
- Occupational exposure [see definitions*],
- Off-label use [see definitions*].

**** Definitions:***
Misuse *refers to situations where the medicinal product is intentionally and inappropriately used not in accordance with the authorised product information.*
Abuse *corresponds to the persistent or sporadic, intentional excessive use of a medicinal product, which is accompanied by harmful physical or psychological effects.*
Occupational exposure *refers to the exposure to a medicinal product as a result of one's professional or non-professional occupation.*
Off-label use *relates to situations where the medicinal product is intentionally used for a medical purpose not in accordance with the authorised product information.*

10. Adverse Reaction reporting

Jylamvo (methotrexate) even at the correct dose can cause Adverse Drug Reactions and it is important to report any suspected adverse drug reaction that are serious or result in harm (even if the causal relationship is in doubt. If it is in doubt, then please state this in the report).

Suspected adverse reactions should be reported to the Malta medicines Authority using

Suspected Adverse Drug Reactions (side effects) or medication errors may be reported using the Malta Medicines Authority ADR reporting form, which is available online at http://www.medicinesauthority.gov.mt/adrportal, and sent by post or email to;

P: Pharmacovigilance Section at Post-Licensing Directorate, Malta Medicines Authority,

Sir Temi Żammit Buildings, Malta Life Sciences Park, San Ġwann SĠN 3000

E: postlicensing.medicinesauthority@gov.mt
or
to Oresund Pharma (pv@oresundpharma.com).
If reporting to more than one party/Regulatory Authority, please state this in the report.

11. Where can I obtain more information?

For all Medical Information enquiries, please use the following contact details:
Distributor Medical Information email address: info@integris.gr and contact number +30 2108778240

Additional copies of this Guide can be obtained using the above contact details.

Notes