Promotional Review Committee (PRC) SUBMISSION FORM	
Product	JYLAMVO
MLR Review Date	12/19/2023
Submitted By	Mary Mehrabian (Medical)
Job Number (Material ID Code)	SH-JYL-102M
Job Name (Title of Reviewed Piece-must match PRC Tracker)	JYLAMVO (methotrexate) oral solution - HCP ISI
Intended Audience (HCP/Consumer)	HCP
OPDP Submission (Yes/No)	No
Planned Submission Date	12/14/2023
Application Number (NDA/ANDA/BLA)	N/A
Material Type (use FDA codes from list on page 2)	N/A
Proposed Use	12/21/2023
Forum	N/A
Leave Behind?	No
Representative User(s)	Commercial Rep ○ MAM ◉ Other ○ N/A ○
Does item include Prescribing Information (PI)?	Final Approved Label
PI version number and Date	Version: JYLPI002; Date: October 2023
Is there a prior piece? (provide job number of prior piece)? **Or Is this a resubmission?**	Yes (SH-JYL-102M) Resubmission
Initial Dissemination Date	12/21/2023
Approval required by	Robyn Addison

Comments:

Approved changes were made, material does not require OPDP Submission and is Approved for Distribution

APPROVAL		
Department	**Signature**	**Date**
Medical Affairs		
Legal		
Regulatory Affairs		

Approval comments: Click here to enter text.	
Executive PRC Approval:	
Name/Title/Signature	Date
Robyn Addison	12/19/2023
*Approved promotional material expires after: 1 year Resubmission to PRC for review/approval required after expiry period.	

MATERIAL TYPE

FDA CODE	DESCRIPTION
Audio	Audio Media (e.g. audio formats other than Internet Audio)
Book	Book
Carrier	Reprint Carrier (e.g. a folder or detail piece that houses a reprint)
Carton	Sample Carton (e.g. a box or container that houses a drug sample)
Catalog	Catalog (e.g. a pamphlet or book containing a systematically arranged list or record of items or products)
CD-ROM	CD ROMS/Programs/Discs (e.g. a CD ROM that is distributed to health care professionals or consumers that does not fall into one of the other material types)
Corrective Internet	Corrective Internet (e.g. corrective materials such as websites, Internet audio, or Internet video related to a Warning letter)
Corrective Letter	Corrective Letter (e.g. corrective letter to health care professionals or consumers or other printed correctives related to a Warning letter)
Corrective Print Ad	Corrective print advertisement related to a Warning letter
Corrective TV	Corrective TV (e.g. corrective television advertisement related to a Warning letter)
Direct Mail	Direct Mail (e.g. printed non-electronic materials mailed directly to individuals)
Drug Sample	Drug Sample (e.g. a small quantity of prescription drug not intended to be sold and given to prescribers for dissemination to patients)
Electronic Detail Aid	Electronic Detail Aid (e.g. electronic detail aids, sales aids, or applications used by sales representatives to detail the product)
Exhibit	Exhibit (e.g. electronic or non-electronic item(s) set out for public display such as vertical panels)
File Card Form	File Card Form (e.g. form for subsidy or patient support form)
Formulary Economic	Formulary Economic (e.g. material containing cost information about a product provided to a formulary committee)
Formulary Kit	Formulary Kit (e.g. packaged set of materials about a product provided to a formulary committee)
Giveaway	Giveaway House Organ House Organ (e.g. a periodical issued by a company dedicated to presenting news about the firm, its products, or its personnel)
Kit	Kit (e.g. a packaged set of related materials such as a sales kit)
Monograph Product	Monograph
Press Release	Press Release
Print Ad	Print Advertisement
Promotional Labeling	Promotional Labeling (e.g. generally any labeling other than FDA required labeling that is devised for promotion of the product such as brochures, booklets, or price lists. Use this category when materials do not fall into one of the other material types.)
Radio	Radio (e.g. audio broadcast over radio waves, can include the script)
Reply Card	Reply Card

Reprint	Reprint (e.g. a reproduction of printed material that has previously appeared in print)
Sales Aid	Sales Aid (e.g. print sales aid or detail aid)
Slides	Slides (e.g. professional or consumer slide presentations including official notes or mandatory talking points)
Telephone	Telephone (e.g. script for telephone calls)
Training Materials	Training Materials (e.g. learning modules, training video/brochure/other piece(s) provided to health care professionals or patients)
TV	Television Advertisement
Video	Video (e.g. video other than a Video News Release or Internet Video)
Video News Release	Video News Release (e.g. video provided to television newsrooms)
www-audio	Internet Audio (e.g. podcast or audio conference)
www-banner	Internet Banner (e.g. a banner that is intended to be embedded into a web page.)
www-ecomm	Internet Electronic Communication (e.g. email directed to health care professionals or consumers)
www-links	Internet Link (e.g. sponsored links)
www-mobile	Mobile Technology (e.g. smartphone or tablet app/widget, quick response (QR)codes, mobile websites)
www-soc-med	Internet Social Media (e.g. social networking, microblog/blog, online community, wiki)
www-video	Internet Video
www-website	Internet Website

JYLAMVO® (methotrexate) Oral Solution, 2 mg/mL

INDICATIONS

JYLAMVO is a folate analog metabolic inhibitor indicated for the:

- Treatment of adults with acute lymphoblastic leukemia (ALL) as part of a combination chemotherapy maintenance regimen.
- Treatment of adults with mycosis fungoides (cutaneous T-cell lymphoma) as a single agent or as part of a combination chemotherapy regimen.
- Treatment of adults with relapsed or refractory non-Hodgkin lymphoma as part of a metronomic combination chemotherapy regimen.
- Treatment of adults with rheumatoid arthritis.
- Treatment of adults with severe psoriasis.

IMPORTANT SAFETY INFORMATION

WARNING: EMBRYO-FETAL TOXICITY, HYPERSENSITIVITY REACTIONS, and SEVERE ADVERSE REACTIONS

- **Methotrexate can cause embryo-fetal toxicity, including fetal death. For non-neoplastic diseases, Jylamvo is contraindicated in pregnancy. For neoplastic diseases, advise females and males of reproductive potential to use effective contraception during and after treatment with Jylamvo.**
- **Jylamvo is contraindicated in patients with a history of severe hypersensitivity reactions to methotrexate, including anaphylaxis.**
- **Serious adverse reactions, including death, have been reported with methotrexate. Closely monitor for infections and adverse reactions of the bone marrow, gastrointestinal tract, liver, lungs, skin, and kidneys. Withhold or discontinue Jylamvo as appropriate.**

CONTRAINDICATIONS

- JYLAMVO is contraindicated in pregnant women with non-neoplastic disease and patients with a history of severe hypersensitivity reactions, including anaphylaxis, to methotrexate.

WARNINGS AND PRECAUTIONS

- **Embryo-Fetal Toxicity**: Based on published reports and its mechanism of action, methotrexate can cause fetal harm, including fetal death, when administered to a pregnant woman. JYLAMVO is contraindicated for use in pregnant women receiving JYLAMVO for the treatment of non-malignant diseases. Advise pregnant women with neoplastic diseases of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with JYLAMVO and for 6 months after the final dose. Advise males with female partners of reproductive potential to use effective contraception during JYLAMVO treatment and for at least 3 months after the final dose.
- **Hypersensitivity Reactions:** Hypersensitivity reactions, including anaphylaxis, can occur with methotrexate. If anaphylaxis or other serious hypersensitivity reaction occurs, immediately and permanently discontinue JYLAMVO. Advise patients and their caregivers of the potential risk of

hypersensitivity and that JYLAMVO is contraindicated in patients with a history of hypersensitivity reactions to methotrexate. Instruct patients to seek immediate medical attention for signs of a hypersensitivity reaction.

- **Myelosuppression:** Methotrexate suppresses hematopoiesis and can cause severe and life-threatening pancytopenia, anemia, leukopenia, neutropenia, and thrombocytopenia. Obtain blood counts at baseline and periodically during treatment, and as clinically indicated. Monitor patients for clinical complications of myelosuppression. Withhold, dose reduce, or discontinue JYLAMVO taking into account the importance of JYLAMVO treatment in the context of the severity of the disease being treated, the severity of the adverse drug reaction, and availability of alternative therapy. Inform patients and their caregivers that JYLAMVO can cause myelosuppression and the need for frequent monitoring of blood cell counts. Advise patients and their caregivers to immediately report new onset fever, symptoms of infection, easy bruising, or persistent bleeding to their healthcare provider.
- **Gastrointestinal Toxicity:** Diarrhea, vomiting, nausea, and stomatitis occurred in up to 10% of patients receiving methotrexate for treatment of non-neoplastic diseases. Hemorrhagic enteritis and fatal intestinal perforation have been reported. Patients with peptic ulcer disease or ulcerative colitis are at a greater risk of developing severe gastrointestinal adverse reactions. Withhold or discontinue JYLAMVO for severe gastrointestinal toxicity taking into account the importance of JYLAMVO treatment in the context of the severity of the disease being treated, the severity of the adverse drug reaction, and availability of alternative therapy. Advise patients and their caregivers to report new or worsening diarrhea, vomiting, or stomatitis to their healthcare provider. Advise patients to immediately contact their healthcare provider for high fever, rigors, persistent or severe abdominal pain, severe constipation, hematemesis, or melena.
- **Hepatotoxicity:** Methotrexate can cause severe and potentially irreversible hepatotoxicity, including fibrosis, cirrhosis, and fatal liver failure. The safety of JYLAMVO in patients with hepatic disease is unknown. The risk of hepatotoxicity is increased with heavy alcohol consumption. In patients with psoriasis, fibrosis or cirrhosis may occur in the absence of symptoms or abnormal liver tests; the risk of hepatotoxicity appears to increase with total cumulative dose and generally occurs after receipt of a total cumulative dose of 1.5 g or more. Monitor liver tests at baseline, periodically during treatment and as clinically indicated. Withhold or discontinue JYLAMVO taking into account the importance of JYLAMVO treatment in the context of the severity of the disease being treated, the severity of the adverse drug reaction, and availability of alternative therapy. Advise patients and their caregivers to report signs or symptoms of hepatic toxicity to their healthcare provider.
- **Pulmonary Toxicity:** Pulmonary toxicity, including acute or chronic interstitial pneumonitis and irreversible or fatal cases, can occur with methotrexate. Monitor patients for pulmonary toxicity and withhold or discontinue JYLAMVO taking into account the importance of JYLAMVO treatment in the context of the severity of the disease being treated, the severity of the adverse drug reaction, and availability of alternative therapy. Advise patients and their caregivers to report new or worsening cough, fever, or dyspnea to their healthcare provider.
- **Dermatologic Reactions:** Severe, including fatal, dermatologic reactions such as toxic epidermal necrolysis, Stevens-Johnson syndrome, exfoliative dermatitis, skin necrosis, erythema multiforme can occur with methotrexate. Exposure to ultraviolet radiation while taking methotrexate may aggravate psoriasis. Methotrexate can cause radiation recall dermatitis and photodermatitis (sunburn) reactivation. Monitor patients for dermatologic toxicity and withhold or permanently discontinue JYLAMVO for severe dermatologic reactions taking into account the importance of JYLAMVO treatment in the context of the severity of the disease being treated, the severity of the adverse drug reaction, and availability of alternative therapy. Advise patients and their caregivers that JYLAMVO

can cause serious skin rash and to immediately contact their healthcare provider for new or worsening skin rash. Advise patients and their caregivers to avoid excessive sun exposure and use sun protection measures.

- **Renal Toxicity:** Methotrexate can cause renal toxicity, including irreversible acute renal failure. Monitor renal function at baseline, periodically during treatment and as clinically indicated. Withhold or discontinue JYLAMVO for severe renal toxicity taking into account the importance of JYLAMVO treatment in the context of the severity of the disease being treated, the severity of the adverse drug reaction, and availability of alternative therapy. Administer glucarpidase in patients with toxic plasma methotrexate concentrations (> 1 micromole per liter) and delayed methotrexate clearance due to impaired renal function. Refer to the glucarpidase prescribing information for additional information. Advise patients and their caregivers to immediately contact their healthcare provider for signs or symptoms of renal toxicity, such as marked increases or decreases in urinary output.
- **Risk of Serious Adverse Reactions with Medication Error:** Deaths occurred in patients as a result of medication errors. Most commonly, these errors occurred in patients who were taking methotrexate daily when a weekly dosing regimen was prescribed. For patients prescribed a once weekly dosing regimen, instruct patients and caregivers to take the recommended dosage as directed, because medication errors have led to death. Before use, instruct patients and caregivers on how to measure, dose, and administer the recommended dosage, utilizing the co-packaged syringe and that a teaspoon is not an appropriate measuring device. Advise patients and caregivers to only use the co-packaged syringe and that a household spoon is not an accurate measuring device.
- **Folic Acid Supplementation:**

  Neoplastic Diseases - Products containing folic acid or its derivatives may decrease the clinical effectiveness of methotrexate. Therefore, instruct patients not to take products containing folic acid or folinic acid unless directed to do so by their healthcare provider.

  Non-neoplastic Diseases - Folate deficiency may increase methotrexate adverse reactions. Administer folic acid or folinic acid for patients with rheumatoid arthritis and psoriasis.
- **Serious Infections:** Patients treated with methotrexate are at increased risk for developing life-threatening or fatal bacterial, fungal, or viral infections, including opportunistic infections such as *Pneumocystis jirovecii* pneumonia, invasive fungal infections, hepatitis B reactivation, tuberculosis primary infection or reactivation, and disseminated *Herpes zoster* and cytomegalovirus infections. Monitor patients for infection during and after treatment with JYLAMVO. Withhold or discontinue JYLAMVO for serious infections taking into account the importance of JYLAMVO treatment in the context of the severity of the disease being treated, the severity of the adverse drug reaction, and availability of alternative therapy. Inform patients and their caregivers that JYLAMVO can cause myelosuppression and the need for frequent monitoring of blood cell counts. Advise patients and their caregivers to immediately report new onset fever, symptoms of infection, easy bruising or persistent bleeding to their healthcare provider.
- **Neurotoxicity:** Methotrexate can cause severe acute and chronic neurotoxicity, which can be progressive, irreversible, and fatal. The risk of leukoencephalopathy is increased in patients who received prior cranial radiation. Monitor patients for neurotoxicity and withhold or discontinue JYLAMVO taking into account the importance of JYLAMVO treatment in the context of the severity of the disease being treated, the severity of the adverse drug reaction, and availability of alternative therapy. Advise patients and their caregivers to report new neurological signs or symptoms to their healthcare provider.

- **Secondary Malignancies:** Secondary malignancies can occur with methotrexate. The risk of cutaneous malignancies is further increased when cyclosporine is administered to patients with psoriasis who received prior methotrexate. In some cases, lymphoproliferative disease occurring during therapy with low-dose methotrexate regressed completely following withdrawal of methotrexate. If lymphoproliferative disease occurs, discontinue JYLAMVO. Advise patients on the risk of second primary malignancies during treatment with JYLAMVO.
- **Tumor Lysis Syndrome:** Methotrexate can induce tumor lysis syndrome in patients with rapidly growing tumors. Institute appropriate prophylactic measures in patients at risk for tumor lysis syndrome prior to initiation of JYLAMVO.
- **Immunization and Risks Associated with Live Vaccines:** Disseminated infections following administration of live vaccines have been reported. Immunization with live vaccines is not recommended during treatment. Follow current vaccination practice guidelines for administration of immunizations in patients receiving JYLAMVO. Update immunizations according to immunization guidelines prior to initiating JYLAMVO. The interval between live vaccinations and initiation of methotrexate should be in accordance with current vaccination guidelines for patients on immunosuppressive agents.
- **Infertility:** Based on published reports, methotrexate can cause impairment of fertility, oligospermia, and menstrual dysfunction. It is not known if the infertility may be reversible. Discuss the risk of infertility with females and males of reproductive potential.
- **Increased Risk of Adverse Reactions Due to Third-Space Accumulation:** Methotrexate accumulates in third-spaces (e.g., pleural effusions or ascites), which results in prolonged elimination and increases the risk of adverse reactions. Evacuate significant third-space accumulations prior to JYLAMVO administration taking into account the importance of JYLAMVO treatment in the context of the severity of the disease being treated, the severity of the adverse drug reaction, and availability of alternative therapy.

ADVERSE REACTIONS

In clinical trials, common adverse reactions were: ulcerative stomatitis, leukopenia, nausea, and abdominal distress. Other clinically relevant adverse reactions were infection, malaise, fatigue, chills, fever, and dizziness.

DRUG INTERACTIONS

Drugs that Increase Methotrexate Exposure: Coadministration of methotrexate with the following products may increase methotrexate plasma concentrations, which may increase the risk of methotrexate severe adverse reactions. In some cases, the coadministration of methotrexate with these products may also subsequently reduce active metabolite formation, which may decrease the clinical effectiveness of methotrexate. Increased organ specific adverse reactions may also occur when methotrexate is coadministered with hepatotoxic or nephrotoxic products.

If coadministration cannot be avoided, monitor closely for methotrexate adverse reactions when coadministered with:

- Oral antibiotics (including neomycin)
- Oral or intravenous penicillin or sulfonamide antibiotics
- Antifolate drugs (e.g., dapsone, pemetrexed, pyrimethamine, and sulfonamides)
- Aspirin and other nonsteroidal anti-inflammatory drugs
- Hepatotoxic products

- Highly protein-bound drugs (e.g., oral anticoagulants, phenytoin, salicylates, sulfonamides, sulfonylureas, and tetracyclines)
- Probenecid
- Proton pump inhibitors
- Weak acids (e.g., salicylates)
- Nephrotoxic products

Nitrous Oxide: Coadministration of methotrexate with nitrous oxide anesthesia potentiates the effect of methotrexate on folate-dependent metabolic pathways, which may increase the risk of severe methotrexate adverse reactions. Avoid nitrous oxide anesthesia in patients receiving methotrexate. Consider alternative therapies in patients who have received prior nitrous oxide anesthesia.

Folic Acid: Coadministration of methotrexate with folic acid or its derivatives decreases the clinical effectiveness of methotrexate in patients with neoplastic diseases. Methotrexate competes with reduced folates for active transport across cell membranes. Instruct patients to take folic or folinic acid only as directed by their healthcare provider.

Advise patients and caregivers to inform their healthcare provider of all concomitant medications, including prescription medicines, over-the-counter drugs, vitamins, and herbal products.

USE IN SPECIFIC POPULATIONS

Pregnancy: Based on published reports and methotrexate's mechanism of action, methotrexate can cause embryo-fetal toxicity and fetal death when administered to a pregnant woman. There are no animal data that meet current standards for nonclinical developmental toxicity studies. In pregnant women with non-malignant disease, JYLAMVO is contraindicated. Consider the benefits and risks of JYLAMVO and risks to the fetus when prescribing JYLAMVO to a pregnant patient with a neoplastic disease. Advise patients to inform their healthcare provider of a known or suspected pregnancy.

Lactation: Limited published literature report the presence of methotrexate in human milk in low amounts, with the highest breast milk to plasma concentration ratio reported to be 0.08:1. There are no data on the effects of methotrexate or its metabolites on the breastfed child or their effects on milk production. Because of the potential for serious adverse reactions in a breastfed child, including myelosuppression, advise women not to breastfeed during treatment with JYLAMVO and for 1 week after the final dose.

Females and Males of Reproductive Potential: Methotrexate can cause malformations and fetal death at doses less than or equal to the recommended clinical doses.

Pregnancy Testing - Verify the pregnancy status of females of reproductive potential prior to initiating JYLAMVO.

Contraception for Females - JYLAMVO can cause fetal harm when administered to a pregnant woman. Advise females of reproductive potential to use effective contraception during treatment with JYLAMVO and for 6 months after the final dose of JYLAMVO.

Contraception for Males - Methotrexate can cause chromosomal damage to sperm cells. Advise males with female partners of reproductive potential to use effective contraception during treatment with JYLAMVO and for at least 3 months after the final dose of JYLAMVO.

Female Infertility - Based on published reports of female infertility after treatment with methotrexate, advise females of reproductive potential that methotrexate can cause impairment of fertility and menstrual dysfunction during treatment with JYLAMVO and after the final dose. It is not known if the infertility may be reversed in all affected females.

Male Infertility - Based on published reports of male infertility after treatment with methotrexate, advise males of reproductive potential that methotrexate can cause oligospermia or infertility during treatment with JYLAMVO and after the final dose. It is not known if the infertility may be reversed in all affected males.

Pediatric Use: JYLAMVO is not approved for use in pediatric patients.

Renal Impairment: Methotrexate elimination is reduced in patients with renal impairment. Patients with renal impairment are at increased risk for methotrexate adverse reactions. Closely monitor patients with renal impairment [creatinine clearance (CLcr) less than 90 mL/min, Cockcroft-Gault] for adverse reactions. Reduce the dosage or discontinue JYLAMVO as appropriate.

Hepatic Impairment: The pharmacokinetics and safety of methotrexate in patients with hepatic impairment is unknown. Patients with hepatic impairment may be at increased risk for methotrexate adverse reactions based on the elimination characteristics of methotrexate. Closely monitor patients with hepatic impairment for adverse reactions. Reduce the dosage or discontinue JYLAMVO as appropriate.

To report suspected adverse reactions, contact Shorla Oncology at 844-9-SHORLA (844-974-6752) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

For Print: Please see the accompanying full Prescribing Information, including Boxed Warning.

For Digital: Please click here for full Prescribing Information, including Boxed Warning.