Dosing Guide

FOLOTYN®
(pralatrexate injection)

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Steps to optimise the use of *FOLOTYN*® injection in the treatment of PTCL

FOLOTYN® injection usage is associated with bone marrow suppression, mucosal inflammation and dermatologic reactions.[1] This guide provides steps to help prevent, monitor and manage serious side effects associated with use of *FOLOTYN*® injection.

- **Folic acid and vitamin B_{12} supplementation is recommended to potentially reduce haematologic toxicity and mucosal inflammation.**[1]

Pre-medication regimen[1]	
Timing before the first dose of *FOLOTYN*® injection	**Action**
No more than 10 weeks prior	Commence **vitamin B_{12}** therapy (1 mg IM)
At least 3 weeks prior	Dentist review and restorative dental procedures performed*
10 days prior	Commence **folic acid**: 1 – 1.25 mg/day orally
Immediately prior	Baseline assessment of oral mucosa, full blood count, serum chemistry and skin condition (see page 3). Patients with extensive skin disease or history of adverse skin reactions are at higher risk of severe skin reactions. The majority of skin reactions are mild and self-limiting. Most serious skin reactions occur early, often after the first dose.

*Pre-treatment dental assessment and restorative procedures performed at least 3 weeks prior to *FOLOTYN*® injection therapy combined with meticulous oral care during therapy can reduce the incidence and duration of oral mucositis.[2]

***FOLOTYN®* injection treatment**[1]							
Timing	**Monitoring prior to next dose of *FOLOTYN®* injection***				**Medication/dosing**		
	Oral cavity (mucositis)	**Full blood count***	**Serum chemistry (including hepatic & renal function)‡**	**Skin**	***FOLOTYN®* injection (IV infusion)**	**Folic acid (Oral)**	**Vitamin B_{12} (IM injection)**
Each cycle							
Week 1	✔	✔	✔	✔	30 mg/m²	1 – 1.25 mg/day	1 mg IM every 8 to 10 weeks, this can be administered on the same day as *FOLOTYN®* injection (IV infusion)
Week 2	✔	✔		✔	30 mg/m²†	1 – 1.25 mg/day	
Week 3	✔	✔		✔	30 mg/m²†	1 – 1.25 mg/day	
Week 4	✔	✔	✔	✔	30 mg/m²†	1 – 1.25 mg/day	
Week 5	✔	✔		✔	30 mg/m²†	1 – 1.25 mg/day	
Week 6	✔	✔		✔	30 mg/m²†	1 – 1.25 mg/day	
Week 7					**None – one week's rest**	1 – 1.25 mg/day	
Continue *FOLOTYN®* injection therapy until progressive disease or unacceptable toxicity							

Published literature suggests that Leucovorin® (folinic acid) may be added.[2-4]

Post-treatment – after the last dose of *FOLOTYN®* injection							
For 30 days after the last *FOLOTYN®* injection						1 – 1.25 mg/day	

* Prior to initiating any dose of *FOLOTYN®* injection, mucositis should be ≤ Grade 1, absolute neutrophil count (ANC) ≥ 1000/µL and platelet ≥ 100,000/µL for the first dose or ≥ 50,000/µL for all subsequent doses. If not, refer to the relevant dosage adjustment table to determine the next steps for *FOLOTYN®* injection dosing that week.

† The recommended *FOLOTYN®* injection dose is 30 mg/m² administered as an IV infusion over 3–5 minutes. Doses may be omitted or reduced based on patient tolerance. Omitted doses are not made up at the end of the cycle. Once the dosage is reduced due to toxicity, the dosing of *FOLOTYN®* injection should not be increased.

‡ Serum chemistry should be monitored before the first and fourth dose of *FOLOTYN®* injection in any given cycle, or more often if required.

Haematologic toxicities and *FOLOTYN*® injection dosage adjustments

Pretreatment:

- Commence folic acid and vitamin B_{12} supplementation[1]
- Full blood count monitoring:[1]
  - Absolute neutrophil count (ANC) should be ≥ 1,000/µL
  - Platelet count should be ≥ 100,000/µL before the first dose and ≥ 50,000/µL for subsequent doses

FOLOTYN® injection dosage adjustments for haematologic toxicities[1]

Blood count on treatment day	Duration of toxicity	Action	*FOLOTYN*® injection dose upon restart
Platelets < 50,000/µL	1 week	Omit dose	Continue prior dose
	2 weeks	Omit dose	20 mg/m^2
	3 weeks	Stop therapy	None
ANC 500 – 1,000/µL AND no fever	1 week	Omit dose	Continue prior dose
ANC 500 – 1,000/µL WITH fever or ANC < 500/µL	1 week	Omit dose Administer G-CSF or GM-CSF support	Continue prior dose with G-CSF or GM-CSF support
	2 weeks or first recurrence	Omit dose Administer G-CSF or GM-CSF support	20 mg/m^2 with G-CSF or GM-CSF support
	3 weeks or second recurrence	Stop therapy	None

G-CSF = Granulocyte colony-stimulating factor, GM-CSF = Granulocyte-macropharge colony-stimulating factor

Mucositis (mucosal inflammation) and *FOLOTYN*® injection dosage adjustments

Pretreatment:

- A baseline assessment should be conducted and documented to differentiate between pre-existing changes (e.g. lichen planus, leukoplakia) and changes to the oral mucosa following *FOLOTYN*® injection administration[5]
  - Use the same assessment tool or grading scale to assess grading of severity (e.g. NCI CTCAE grading criteria or eviQ oral mucositis assessment tool)[5]
- Commence folic acid and vitamin B_{12} supplementation[1]
- Provide advice on prophylactic oral care[6] including dentist review and restorative dental procedures performed at least 3 weeks prior to *FOLOTYN*® injection therapy[5]
- Instruct the patient to advise you immediately if they develop symptoms such as pain, difficulty swallowing or talking, bleeding, thrush or mouth ulcers[5]

Treatment:

- Provide patients with advice on oral care and diet, including the need to increase the frequency of brushing teeth and rinsing the mouth[5,7]
- Provide pain relief: topical and systemic analgesics used around-the-clock in preference to an as required (PRN) basis[5]
  - Avoid NSAIDs due to potential interaction that may decrease the renal clearance of *FOLOTYN*® injection[1]
- Adjust the dose of *FOLOTYN*® injection therapy if mucositis is ≥ grade 2[1]

Dosage adjustments:[1]

Mucositis grade* on treatment day	Action	*FOLOTYN*® injection dose upon recovery to ≤ Grade 1
Grade 2	Omit dose	Continue prior dose
Grade 2 recurrence	Omit dose	20 mg/m^2
Grade 3	Omit dose	20 mg/m^2
Grade 4	Stop therapy	None

* Per National Cancer Institute – Common Terminology Criteria for Adverse Events (NCI-CTCAE)

Other treatment-related toxicities and precautions

Other common grade 3 and 4 adverse reactions with *FOLOTYN*® injection include:[1]

Adverse reaction	Grade 3[8] (NCI-CTCAE)	Grade 4[8] (NCI-CTCAE)
Skin ulcers	Combined area of ulcers > 2 cm; full-thickness skin loss involving damage to or necrosis of subcutaneous tissue that may extend down to fascia	Any size ulcer with extensive destruction, tissue necrosis, or damage to muscle, bone, or supporting structures with or without full thickness skin loss
Infections	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention indicated	Life-threatening consequences; urgent intervention indicated
Anorexia	Associated with significant weight loss or malnutrition (e.g. inadequate oral caloric and/or fluid intake); tube feeding or TPN indicated	Life-threatening consequences; urgent intervention indicated
Dyspnoea	Shortness of breath at rest; limiting self-care or ADL	Life-threatening consequences; urgent intervention indicated
Vomiting	≥ 6 episodes (separated by 5 minutes) in 24 hours; tube feeding, TPN or hospitalisation indicated	Life-threatening consequences; urgent intervention indicated
Nausea	Inadequate oral caloric or fluid intake; tube feeding, TPN, or hospitalisation indicated	–
Pain	Severe pain; limiting self-care or ADL	–
Fatigue	Fatigue not relieved by rest, limiting self-care or ADL	–

ADL = activities of daily living, TPN = Total parenteral nutrition

FOLOTYN® injection dosage adjustments for all other treatment-related toxicities[1]

Toxicity grade† on treatment day	Action	*FOLOTYN*® injection dose upon recovery to ≤ Grade 2
Grade 3	Omit dose	20 mg/m^2
Grade 4	Stop therapy	None

†Per National Cancer Institute – Common Terminology Criteria for Adverse Events.

Patients with hepatic impairment

Liver function monitoring is recommended for patients with hepatic impairment. Liver function test abnormalities have been observed, but usually do not necessitate dosage modification. Persistent abnormalities may indicate liver toxicity and requires evaluation.[1]

Patients with moderate to severe renal impairment

Caution is recommended for patients with moderate to severe renal impairment, eGFR < 60 mL/min. Avoid *FOLOTYN*® injection in patients with end stage renal disease including those on dialysis, unless the potential benefits justify the risk. Renal function monitoring is recommended.[1]

All adverse events should be reported to Mundipharma Medical Information, call **1800 188 009.**

Please review the Product Information before prescribing. Approved Product Information can be accessed at www.mundipharma.com.au/products/prescription-medicines/

***FOLOTYN*® solution for infusion 20 mg in 1 mL, 40 mg in 2 mL. MINIMUM PRODUCT INFORMATION. Composition:** Pralatrexate. **Indications:** The treatment of adult patients with peripheral T-cell lymphoma (nodal, extranodal, and leukaemic/disseminated) who have progressed after at least one prior therapy. **Contraindications:** Hypersensitivity to the active substance or to any of the excipients. Breast-feeding. **Precautions:** Patients should be instructed to take folic acid and vitamin B12 to potentially reduce treatment-related haematological toxicity and mucosal inflammation. Mild to severe dermatological reactions have been observed: monitor patients with dermatological reactions closely, and if severe, discontinue FOLOTYN. Pneumonitis. Tumour lysis syndrome. Administration of pralatrexate to patients with hepatic or moderate to severe renal impairment should only be done with caution and close monitoring of liver and renal functions and adverse events. May impair ability to drive and operate machinery. FOLOTYN is not recommended during pregnancy or breastfeeding, or in women of childbearing potential, unless they are using reliable contraception (Pregnancy Category D). Sexually mature males are advised not to father a child during treatment or up to six months thereafter. Barrier contraceptive measures or abstinence are recommended. Safety and efficacy of FOLOTYN has not yet been established in children aged 0 to 18 years. **Interactions:** Probenecid, NSAIDs, penicillins, omeprazole, pantoprazole, etoposide, teniposide, methotrexate, trimethoprim/sulfamethoxazole. See full PI. **Adverse reactions:** The most frequently reported adverse reactions included mucosal inflammation, myelosuppression (thrombocytopenia, neutropenia and anaemia), gastrointestinal symptoms (nausea, vomiting and constipation), fatigue, and epistaxis. The most serious adverse reactions included bone marrow suppression (thrombocytopenia, neutropenia and anaemia), mucosal inflammation, dermatological reactions (including skin exfoliation, ulceration and toxic epidermal necrolysis) and tumour lysis syndrome. See full PI. **Dosage and administration:** Treatment should only be administered under the supervision of a physician experienced in the use of anticancer chemotherapy. FOLOTYN vials contain no antimicrobial preservative and are for use in one patient on one occasion only. *Premedication regimen:* patients should take low-dose (1.0-1.25 mg) oral folic acid on a daily basis. Folic acid should be initiated during the 10-day period preceding the first dose of FOLOTYN, and dosing should continue during the full course of therapy and for 30 days after the last dose of FOLOTYN. Patients should also receive a vitamin B12 (1 mg) intramuscular injection no more than 10 weeks prior to the first dose of FOLOTYN and every 8-10 weeks thereafter. Subsequent vitamin B12 injections may be given the same day as treatment with FOLOTYN. The premedication regimen should be strictly observed. *Adults:* 30 mg/m^2 administered as an intravenous infusion over 3-5 minutes, once weekly for six (6) weeks, followed by a one (1) week rest period (7-week treatment cycle), until progressive disease or unacceptable toxicity. *Dose adjustments during treatment:* see full PI. Please review Product Information before prescribing. Product Information is available from Mundipharma Pty Limited, 88 Phillip Street, Sydney, NSW 2000. Phone 1800 188 009. **Date of first inclusion in the Australian Register of Therapeutic Goods (the ARTG):** Folotyn® 20 mg in 1 mL; 40 mg in 2 mL solutions for infusion: 26 February 2015. **Date of most recent amendment:** 17 October 2018. Orbis RA-0251

References: 1. *FOLOTYN*® solution for infusion 20 mg in 1 mL and 40 mg in 2 mL Product Information, November 2016. **2.** Shustov AR, *et al.* Poster presented at: 60th American Society of Hematology (ASH) Annual Meeting. 2018 Dec 1-4; San Diego, CA. **3.** O'Connor OA, *et al.* Leuk Lymphoma. 2017 Nov;58(11):2548-2557. **4.** Haddad PA. Blood (ASH Annual Meeting Abstracts); 2011. Available from: http://www.bloodjournal.org/content/118/21/4745?sso-checked=true. **5.** eviQ cancer treatments online. Oral mucositis. ID 210 v3, Cancer Institute of NSW. **6.** Lalla RV, *et al.* Cancer 2014;120:1453-1461. **7.** eviQ cancer treatments online. Oral mucositis assessment tool. ID 10 v5. Cancer Institute of NSW.

PBS information: Authority required. Relapsed or chemotherapy refractory Peripheral T-cell Lymphoma. Refer to PBS Schedule for full authority information.

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