SMILE Therapy (NK or T-cell lymphoma)

INDICATIONS FOR USE:

INDICATION	ICD10	Regimen Code	*Reimbursement Status
Newly diagnosed stage II- IV or relapsed/refractory extranodal natural killer/T-cell lymphoma	C86	00407a	Hospital

**If reimbursement status is not defined[i], the indication has yet to be assessed through the formal HSE reimbursement process.*

TREATMENT:

Treatment is administered as described in the treatment table below.
A cycle may be repeated every 28 days for up to 4 cycles.
Patients may be considered for autologous/allogeneic Hematopoietic Stem Cell Transplantation (HSCT) following remission induction with SMILE.

Note:

- **Hydration, alkalinisation and folinic acid therapy required with high dose methotrexate (See Table Below)**
- **Hydration therapy required for safe administration of ifosfamide (See Table below)**

Facilities to treat anaphylaxis MUST be present when therapy is administered.

Day	Drug	Dose	Route and Method of Administration	Diluent & Rate
1	[a]Methotrexate	2000mg/m^2	IV infusion	1000ml 0.9% NaCl over 6 hours
2	Folinic acid	15mg/m^2	IV infusion	100ml 0.9% NaCl over 10 minutes. Commence 36 hours after the start of methotrexate infusion and repeat every 6 hours until methotrexate level is less than 0. 1 micromol/L (See Table 1 below for calculation of dose of Folinic acid based on Methotrexate levels)
2,3,4	Mesna	600mg/m^2	IV bolus	10-15 min prior to ifosfamide infusion
2,3,4	[b]Ifosfamide	1500mg/m^2	IV infusion	1000ml 0.9% NaCl over 2 hours
2,3,4	Mesna	600mg/m^2	IV bolus	3 hours after start of ifosfamide infusion
2,3,4	Mesna	600mg/m^2	IV bolus	6 hours after start of ifosfamide infusion
2,3,4	Mesna	600mg/m^2	IV bolus	9 hours after start of ifosfamide infusion
2,3,4	Dexamethasone	40mg	PO	
2,3,4	Etoposide	100mg/m^2	IV infusion	1000mls 0.9% NaCl over 2 hours
6 onwards	G-CSF	5mcg/kg	SC (Round to nearest whole syringe)	Daily injection until white blood cells > 5 x 10^{9}L
8	[c]L-asparaginase (E.Coli)	1000 IU (test dose)	IV infusion	50ml 0.9% NaCl over 30mins[d]
8	[c]L-asparaginase (E.Coli)	6000 IU/m^2 minus test dose	IV infusion	250ml 0.9% NaCl over 2 hours
10, 12, 14, 16, 18, 20	[c]L-asparaginase (E.Coli)	6000 IU/m^2	IV infusion	250ml 0.9% NaCl over 2 hours

[a]**Methotrexate :** See below for suggested hydration, alkalinisation regimen to be followed with methotrexate **or** Refer to local policy

GFR to be calculated prior to administration of methotrexate infusion**.**

Hydration and urinary alkalinisation should be commenced 12 hours before the infusion of methotrexate.

A suggested regimen is as follows

- Hydration: Administer at 3L/m^2/24 hours of **IV fluids** during the methotrexate infusion, continued until the methotrexate level is <0. 1 micromol/L
- Urine pH should be ≥ 7.0 prior to commencement and during the methotrexate and folinic acid rescue.
- **Alkalinisation** can be achieved with 80mmol of sodium bicarbonate over 8 hours in 1000ml sodium chloride 0.9%. (This volume administered for alkalinisation is included in the total volume of hydration.)

  If the target pH is not reached:
  - the rate of infusion can be increased to 1L over 6 hours
- **Potassium** should be supplemented according to the local policy.
- Check **fluid balance** at regular intervals (4 hourly) through each day. (Furosemide may be administered if fluid output falls below 400mls/m^2 in a 4 hour period).
- **Methotrexate levels** must be taken 48 hours, 72 hours, 96 hours and 120 hours as appropriate after commencement of the initial methotrexate infusion
- Continue alkalinisation, hydration and folinic acid rescue (Table 1) until methotrexate level is <0. 1 micromol/L

[b]**Ifosfamide: Suggested Hydration therapy. (Refer to local policy or see suggested hydration below).** Ensure IV hydration (1L NaCL 0.9% IV every 6 hours) is given, commencing prior to first dose of ifosfamide and continuing for 24 hours after the ifosfamide has stopped. **Note: Where there is crossover between hydration therapy for methotrexate and treatment with ifosfamide, prioritise the hydration therapy for methotrexate**. Furosemide should also be administered if required to ensure a urinary output of at least 100ml/hour
Maintain strict fluid balance during therapy, by (1) monitoring fluid balance and (2) daily weights. If fluid balance becomes positive by >1000mls or weight increases by >1 Kg, the patient should be reviewed and consideration given to diuresing with furosemide.
[c]Different formulations of asparaginase are available which may be used in this regimen **(Refer to local policy for guidance on dosing and toxicity)**
Observe patient for 1 hour after administration of the intravenous test dose. If no adverse reaction occurs, the remainder of the dose on day 8 may be given as an IV infusion over 2 hours. Ensure facilities to treat anaphylaxis are present. A test dose is also recommended prior to restarting therapy or when there has been an interval of several days since the last dose. Therefore, a test dose must be given on Day 8 of every cycle (5).

The starting dose of the drugs detailed may be adjusted downward by the prescribing clinician, using their independent medical judgement, to consider each patients individual clinical circumstances.

Table1: Table for the Calculation of Folinic Acid Rescue on the basis of Methotrexate Levels

Time after starting Methotrexate infusion	**Methotrexate Plasma Concentration micromol/L**				
	<0.1	**0.1-2**	**2-20**	**20-100**	**>100**
48 hours	No folinic Acid	15mg/m^2 every 6 hours	15mg/m^2 every 6 hours	10mg/m^2 every 3 hours	100mg/m^2 every 3 hours
72 hours	No folinic Acid	15mg/m^2 every 6 hours	10mg/m^2 every 3 hours	100mg/m^2 every 3 hours	1000mg/m^2 every 3 hours
96 hours	No folinic Acid	15mg/m^2 every 6 hours	10mg/m^2 every 3 hours	100mg/m^2 every 3 hours	1000mg/m^2 every 3 hours
120 hours	No folinic Acid	15mg/m^2 every 6 hours	10mg/m^2 every 3 hours	100mg/m^2 every 3 hours	1000mg/m^2 every 3 hours
If serum creatinine increases by more than 50% above baseline at 24 hours increase folinic acid rescue.					
At time points over 120 hours continue folinic acid as recommended for 120 hours					

ELIGIBILTY:

- Indications as above

EXCLUSIONS:

- Hypersensitivity to etoposide, ifosfamide, methotrexate, L-asparaginase or any of the excipients
- L-asparaginase should not be administered to patients with severe hepatic impairment

PRESCRIPTIVE AUTHORITY:

The treatment plan must be initiated by a Consultant Medical Oncologist or Consultant Haematologist working in the area of haematological malignancies.

TESTS:

Baseline tests:

- FBC, renal and liver profile
- LDH, Uric acid

- Blood glucose
- Coagulation Screen including fibrinogen
- Virology screen -Hepatitis B (HBsAg, HBcoreAb) & C, HIV.
  *Hepatitis B reactivation: See Adverse events / Regimen specific complications

Regular tests:

- FBC, renal and liver profile, LDH and uric acid daily while on chemotherapy and prior to each asparaginase dose
- Regular glucose monitoring while receiving steroid therapy-urinalysis daily
  If glucose detected in urinalysis, monitor blood glucose daily
- Coagulation screen including fibrinogen. Fibrinogen levels should be monitored prior to each asparaginase dose (Refer to Adverse Reactions/Regimen Specific Complications)
- Assess neurological function daily while on ifosfamide
- Check urinalysis for haematuria prior to ifosfamide and daily during treatment with ifosfamide

Disease monitoring:
Disease monitoring should be in line with the patient's treatment plan and any other test/s as directed by the supervising Consultant.

DOSE MODIFICATIONS:

- Any dose modification should be discussed with a Consultant.
- Ensure that ANC ≥ 1.0 x 10^9/L and platelets ≥ 75 x 10^9/L prior to another cycle of treatment

Renal and Hepatic Impairment:

Table 2: Dose modifications based on renal and hepatic impairment

Drug	Renal impairment		Hepatic impairment			
Ifosfamide	**GFR (ml/min)**	**Dose**	Dose reductions are probably not necessary for patients with altered liver function. However ifosfamide is extensively hepatically metabolised and some clinicians recommend a 25% dose reduction for patients with significant hepatic dysfunction (serum AST > 300IU/L or bilirubin > 51.3 micromol/L (7) The SPC states that it is not recommended in patients with a bilirubin >17 micromol/L or transaminases >2-3xULN			
	>60	100%				
	40-59	70%				
	<40	Clinical Decision				
Etoposide	**Cr Cl (ml/min)**	**Dose**	**Total Bilirubin (micromol/L)**		**AST**	**Dose**
	>50	100%	26-51	or	60-180	50%
	15-50	75%	>51	or	>180	Clinical decision
	<15	50%				
	Subsequent doses should be based on clinical response					
Methotrexate	**Cr Cl (ml/min)**	**Dose**	**Bilirubin (micromol/L)**		**AST**	**Dose**
	>80	100%	<50	and	<180	100%
	60	65%	51-85	or	>180	75%
	45	50%	>85	Contraindicated		
	<30	contraindicated				
L-asparaginase	No dose adjustment necessary		No dose adjustment is necessary in patients with mild to moderate hepatic impairment. L-asparaginase should **not** be used in patients with **severe** hepatic impairment(i.e. bilirubin >3 xULN, transaminases > 10 x ULN) See adverse events/ regimen specific complications for more detail			

Other Toxicity:

Methotrexate:

Table 4: Dose modification based on plasma concentration of Methotrexate post infusion

	Dose Modification of Methotrexate
Concentration of methotrexate exceeded 0.1 **micromol/L** 72 hours **post** MTX administration in cycle 1	Reduce the dose by 33% for second course

Table 5: Dose modification of L-Asparaginase based on adverse events

Adverse Event	Dose Modification of L-asparaginase
Grade ≥ 3 Allergic reactions/hypersensitivity	Discontinue
Pancreatitis	Discontinue
Hypotension	Discontinue
Grade 3 Non haematological toxicity	Discontinue If the patient recovers in cycle 2, L-asparaginase may be re-administered

SUPPORTIVE CARE:

EMETOGENIC POTENTIAL:

Day 1-4: Moderate
Day 8 onwards: Minimal (**Refer to local policy).**

PREMEDICATIONS: None

OTHER SUPPORTIVE CARE:

- Tumour lysis syndrome prophylaxis **(Refer to local policy)**
- Proton pump Inhibitor**(Refer to local policy)**
- PJP prophylaxis **(Refer to local policy) Avoid co-trimoxazole due to an interaction with methotrexate.**
- Mouth care **(Refer to local policy)**
- Anti-viral prophylaxis **(Refer to local policy)**
- Anti-fungal prophylaxis **(Refer to local policy)**

ADVERSE EFFECTS / REGIMEN SPECIFIC COMPLICATIONS

The adverse effects listed are not exhaustive. Please refer to the relevant Summary of Product Characteristics for full details.

- **Coagulation disorders**: Due to the inhibition of protein synthesis (decreased synthesis of factors II, V, VII, VIII, and IX, proteins C and S, antithrombin III [AT III]) caused by asparaginase, coagulation disorders can occur which can manifest either as thrombosis, disseminated intravascular coagulation (DIC), or bleeding. The risk of thrombosis seems to be higher than the risk of bleeding. Frequent evaluation of coagulation and fibrinogen is important before and during asparaginase treatment. Fibrinogen levels are used as a surrogate for other coagulation factors and if the level of fibrinogen is below 1g/L replacement therapy with Octaplas™ should be initiated and a haematologist should be consulted regarding management
- **Hepatotoxicity:** In rare cases severe liver impairment has been described, including cholestasis, icterus, hepatic necrosis and hepatic failure with fatal outcome. Liver parameters should be monitored closely before and during treatment with asparaginase. Treatment with asparaginase should be interrupted if patients develop severe hepatic impairment (bilirubin > 3 times the upper limit of normal [ULN]; transaminases > 10 times ULN), severe hypertriglyceridaemia, hyperglycaemia or coagulation disorder (e.g. sinus vein thrombosis, severe bleeding).
- **Ifosfamide-induced encephalopathy**: This may occur in patients treated with high doses of ifosfamide.
    - Consider risk factors for ifosfamide induced encephalopathy (renal insufficiency, low serum albumin, large pelvic mass).
    - Methylene blue may be a treatment option for the prevention and management of ifosfamide-associated encephalopathy **(Refer to local policy)**
- **Renal and urothelial toxicity:** Ifosfamide is both nephrotoxic and urotoxic. Urinalysis should be performed daily to exclude haematuria. For prophylaxis of hemorrhagic cystitis, ifosfamide should be used in combination with mesna. Ifosfamide should be used with caution, in patients with active urinary tract infections.
- **Hepatitis B Reactivation:** All lymphoma patients should be tested for both HBsAg and HBcoreAb as

per local policy. If either test is positive, such patients should be treated with lamivudine 100 mg/day orally, for the entire duration of chemotherapy and for six months afterwards. Such patients should also be monitored with frequent liver function tests and hepatitis B virus DNA at least every two months. If the hepatitis B virus DNA level rises during this monitoring, management should be reviewed with an appropriate specialist with experience managing hepatitis and consideration given to stopping chemotherapy.

- **Hypersensitivity** reactions have been reported with l-asparaginase. If allergic symptoms occur, administration of asparaginase must be discontinued immediately and appropriate treatment given.
- **Acute pancreatitis:** Treatment with asparaginase should be discontinued in patients developing acute pancreatitis. Acute pancreatitis has developed in less than 10 % of patients.
- **Hyperglycaemic conditions:** Asparaginase may induce hyperglycaemia as a consequence of decreased insulin production. Concomitant treatment with corticosteroids contributes to this effect. Serum and urine glucose levels should be regularly monitored and managed as clinically indicated.

DRUG INTERACTIONS:

- Current drug interaction databases should be consulted for more information.

ATC CODE:

Ifosfamide	L01AA06
Etoposide	L01CB01
L-Asparaginase	L01XX02
Methotrexate	L01BA01

REFERENCES:

1. SMILE for natural killer/T-cell lymphoma: analysis of safety and efficacy from the Asia Lymphoma Study Group Blood 2012; 120(15) 2973-2980.
2. Yamaguchi, M., et al. Phase II study of SMILE chemotherapy for newly diagnosed stage IV, relapsed, or refractory extranodal natural killer (NK)/Tcell lymphoma, nasal type: the NK-Cell Tumor Study Group study. J Clin Oncol, 2011;29(33): 4410-6.
3. Yamaguchi, M., et al. Phase I study of dexamethasone, methotrexate,ifosfamide, L-asparaginase, and etoposide (SMILE) chemotherapy for advanced-stage, relapsed or refractory extranodal natural killer (NK)/T-cell lymphoma and leukemia. Cancer Sci 2008;99(5): 1016-20.
4. BCCA Drug Monograph Asparaginase Revised 1 June 2013. http://www.bccancer.bc.ca/drug-database-site/Drug%20Index/Asparaginase_monograph_1June2013_formatted.pdf
5. Dosage Adjustment for Cytotoxics in Renal Impairment January 2009; North London Cancer Network. Available at http://londoncancer.org/media/65600/renal-impairment-dosage-adjustment-for-cytotoxics.pdf
6. Dosage Adjustment for Cytotoxics in Hepatic Impairment January 2009;North London Cancer Network. Available at http://londoncancer.org/media/65594/hepatic-impairment-dosage-adjustment-for-cytotoxics.pdf
7. Floyd J and Kerr TA. Chemotherapy hepatotoxicity and dose modification in patients with liver disease UptoDate https://www.uptodate.com/contents/chemotherapy-hepatotoxicity-and-dose-modification-in-patients-with-liver-disease#H14
8. Etoposide Summary of Product Characteristics Accessed Feb 2018. Available at http://www.hpra.ie/img/uploaded/swedocuments/LicenseSPC_PA1380-168-001_18072014171144.pdf

9. Mitoxana Summary of Product Characteristics. Accessed Feb 2018. Available at http://www.hpra.ie/img/uploaded/swedocuments/LicenseSPC_PA0167-135-001_29092016170101.pdf
10. Methotrexate Summary of Product Characteristics Accessed Feb 2018. Available at http://www.hpra.ie/img/uploaded/swedocuments/LicenseSPC_PA0437-005-003_22042013144145.pdf3.
11. Spectrila Summary of Product Characteristics. Accessed Feb 2018. Available at http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/002661/WC500200538.pdf

Version	Date	Amendment	Approved By
1	09/03/2018		Prof Elisabeth Vandeberghe
2	04/06/2019	Clarification of methotrexate monitoring levels	Prof Elisabeth Vandeberghe

Comments and feedback welcome at oncologydrugs@cancercontrol.ie.

[i] ODMS – Oncology Drug Management System
CDS – Community Drug Schemes (CDS) including the High Tech arrangements of the PCRS community drug schemes
Further details on the Cancer Drug Management Programme is available at;
http://www.hse.ie/eng/services/list/5/cancer/profinfo/medonc/cdmp/