Fludarabine and Total Body Irradiation (Flu/TBI) with post-transplant cycloPHOSphamide Therapy (PTCy)

INDICATIONS FOR USE:

INDICATION	ICD10	Regimen Code	HSE approved reimbursement status*
Acute lymphoblastic leukaemia (ALL), myeloablative conditioning (MAC) with peripheral blood stem cell (PBSC) or mismatched donor	C91	00913a	N/A

* This applies to post 2012 indications

TREATMENT:

- Conditioning chemotherapy is administered over 3 days
- Total body irradiation (TBI) is performed over 3 days
- Stem cells are infused on day 0
- Facilities to treat anaphylaxis must be present when conditioning therapy and stem cells are administered

Day	Drug	Dose	Route	Diluent & Rate
-6, -5, -4	[i]Fludarabine[a]	30mg/m^2	IV infusion	100mL NaCl 0.9% over 30 minutes
-3, -2, -1	Fractionated TBI	Twice daily		
0	Stem Cell Re-infusion			
+3, +4 (Start at 09.30)*	Mesna	20mg/kg	Slow IV push	Into side arm of a fast-flowing NaCl 0.9% infusion
+3, +4 (Start at 10:00)* (first dose between 60 and 72 hours after the start of the PBSC infusion)	cycloPHOSphamide	50mg/kg (See Dose Modifications section for dosing in obesity)	IV infusion	1000mL NaCl 0.9% over 3 hours
+3, +4 (Start at 13:00)*	Mesna	20mg/kg	Slow IV push	Into side arm of a fast-flowing NaCl 0.9% infusion
+3, +4 (Start at 16:00)*	Mesna	20mg/kg	Slow IV push	Into side arm of a fast-flowing NaCl 0.9% infusion
+3, +4 (Start at 19:00)*	Mesna	20mg/kg	Slow IV push	Into side arm of a fast-flowing NaCl 0.9% infusion
+3, +4 (Start at 22:00)*	Mesna	20mg/kg	Slow IV push	Into side arm of a fast-flowing NaCl 0.9% infusion
+4, +5 (Start at 02:00)*	Mesna	20mg/kg	Slow IV push	Into side arm of a fast-flowing NaCl 0.9% infusion
+4, +5 (Start at 06:00)*	Mesna	20mg/kg	Slow IV push	Into side arm of a fast-flowing NaCl 0.9% infusion
+5 (Start at 10:00)*	Mesna	20mg/kg	Slow IV push	Into side arm of a fast-flowing NaCl 0.9% infusion

Dose rounding:
Fludarabine doses ≤50mg to the nearest 2.5mg and doses >50mg to the nearest 5mg
Mesna to the nearest 100mg
cycloPHOSphamide to the nearest 20mg

[a]All patients who have received fludarabine should receive irradiated blood products (lifetime recommendation)
*denotes recommended administration time

Note: Administration volumes and fluids have been standardised to facilitate electronic prescribing system builds.

ELIGIBILITY:

- Indications as above
- Medical assessment as per SJH BMT assessment

EXCLUSIONS:

- Hypersensitivity to fludarabine, cyclophosphamide or any of the excipients

PRESCRIPTIVE AUTHORITY:

- The treatment plan must be initiated by a Haematology Consultant working in the area of stem cell transplantation in a unit suitable for carrying out this treatment.

TESTS:

- Baseline and regular tests in accordance with SJH Haematopoietic Stem Cell Transplant workup protocols

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 Haematology Consultant.

Chemotherapy dosing in obese adult patients:

- For patients with a BMI > 30kg/m^2 please refer to 'Chemotherapy Dosing in Obese Adult Stem Cell Transplant Recipients – Guidelines' for guidance on individual drug dosing as per SJH policy available on the SJH intranet
- The cycloPHOSphamide dose should be calculated using Ideal Body Weight. However, if Actual Body Weight < Ideal Body Weight, use Actual Body Weight

Table 1: Calculation of different dosing methods in obesity

IBW	Male	IBW = 50kg + 2.3kg for every 2.54 cm above 152.4 cm
	Female	IBW = 45.5kg + 2.3kg for every 2.54 cm above 152.4 cm
ABW 25	IBW + 0.25 x (TBW – IBW)	

Renal and Hepatic Impairment:

- Dose modifications are generally not undertaken in conditioning regimens
- Discuss with the Haematology Consultant if hepatic impairment or if creatinine clearance is <70mL/minute for advice on fludarabine dosing. Guidance to inform this discussion is available at: U:\PHARMCOMP\Clinical\haematology\Haematology Drugs\Fludarabine
- Consult the following resources to inform any renal or hepatic dose modification discussions:
    - Summary of product characteristics (SmPC)
    - Giraud E L, Lijster B D, et al. Dose recommendations for anticancer drugs in patients with renal or hepatic impairment: an update. Available at: https://pubmed.ncbi.nlm.nih.gov/37269847/

SUPPORTIVE CARE:

No systemic immunosuppressive agents, such as corticosteroids, should be given from day 0 until 24 hours after the completion of the post-transplant cycloPHOSphamide (i.e. Day +5).

Antiemetics:

Avoid dexAMETHasone as an antiemetic from day -1 to day +5.

Table 2: Recommended SJH Regimen Specific Antiemetics

Prevention of acute emesis			Prevention of delayed emesis		
Drug	**Dose**	**Admin Day**	**Drug**	**Dose**	**Admin Day**
Ondansetron	8mg PO/IV TDS	TBI = -3, -2, -1 then review	Aprepitant	80mg PO OD	+4, +5, +6
dexAMETHasone	8 mg PO OD	TBI = -3, -2 only	Cyclizine	50mg PO TDS	PRN
Ondansetron	8mg PO/IV TDS	+3 to +7			
Aprepitant	125mg PO	+3			

cycloPHOSphamide hydration and diuresis:

Post stem cell infusion:

- Start pre–hydration 4 hours before cycloPHOSphamide begins (usually on day +3). The recommended hydration regimen is 2-3L/m^2 NaCl 0.9% over 24 hours
- Continue hydration for at least 24 hours after completion of cycloPHOSphamide
- Diuretics may be indicated for positive fluid balance, weight gain or declining urine production (<100mL/m^2/hour). Furosemide 20-40mg IV PRN should be prescribed

PREMEDICATIONS:

None usually required.

OTHER SUPPORTIVE CARE:

Table 3: Recommended SJH regimen specific supportive care

GvHD prophylaxis Refer to signed off BMT assessment form for confirmed **choice and target level** of immunosuppression	**Tacrolimus** • Tacrolimus 0.03mg/kg OD IV over 22 hours from day +5 • The equivalent PO dose: ○ Total IV dose, BD PO • Target levels: 5-10 nanogram/mL	**Mycophenolate mofetil** • Mycophenolate mofetil 15mg/kg BD PO/IV from day +5 • IV dose is the same as PO given over 2 hours in glucose 5% at a concentration of 6mg/mL • Maximum total daily dose not to exceed 3g • If renal failure, do not exceed dose of 1g BD • No dose adjustment for liver disease • Mycophenolate mofetil dosing should be monitored and altered as clinically appropriate. Stop mycophenolate mofetil at day +35 unless active GvHD present (discuss with Haematology Consultant)
GvHD and VOD prophylaxis	• Ursodeoxycholic acid 250mg TDS PO • Continue until day +90	
HSV prophylaxis	All patients should receive the following until CD4 count >200/µL: • valACIclovir 500mg OD PO **or** • Aciclovir 250mg TDS IV (if PO route not appropriate or ANC < $0.5X10^9$/L) Patients with an active herpes infection should receive the following: • valACIclovir 1g TDS PO **or** • Aciclovir 10mg/kg TDS IV (if PO route not appropriate)	
CMV prophylaxis	**Prescribe CMV prophylaxis for all CMV seropositive recipients.** Patients receiving CMV prophylaxis with letermovir also require HSV prophylaxis above. • Letermovir 240mg OD PO/IV, as appropriate, starting day +1 if patient is receiving ciclosporin immunosuppression • Letermovir 480mg OD PO/IV, as appropriate, starting day +1 if patient is receiving tacrolimus immunosuppression • Letermovir PO is first line • Letermovir IV at the same PO dose should be prescribed only where the patient cannot tolerate PO or where there are concerns around absorption • CMV prophylaxis is usually continued until day +100 Patients should bring their PO letermovir supply with them on admission. High tech prescription will have been provided to patient at their counselling appointment pre-admission. Liaise with transplant pharmacist if any supply issues arise When ANC >1.0 x 10^9/L, pre-emptive monitoring (9mL in EDTA [purple tube] (Tuesday and Fridays) should be carried out for CMV reactivation/infection in all patients	
Antifungal prophylaxis Refer to signed off BMT assessment form for confirmed choice of antifungal prophylaxis	When ANC <$0.5x10^9$/L or if patients on high dose steroids: • Liposomal amphotericin (Ambisome®) 1mg/kg OD IV Mon/Wed/Fri **or** • Caspofungin 70mg OD IV Mon/Wed/Fri **or**	

	• Isavuconazole 200mg OD IV If at higher risk due to prior possible/probable fungal infection: • Liposomal amphotericin (Ambisome®) 1mg/kg OD IV **or** • Caspofungin 70mg OD IV if >80kg **or** • Caspofungin 70mg OD IV on day 1 of treatment followed by 50mg OD IV thereafter if <80kg **or** • Isavuconazole 200mg OD IV
PJP prophylaxis	<u>1st line therapy</u> • Co-trimoxazole 960mg BD PO Mon/Wed/Fri Commence only on engraftment when ANC >1.0x10^9/L if appropriate <u>2nd line therapy (if allergic to co-trimoxazole or contraindicated):</u> *PJP Prophylaxis and T. gondii IgG NEGATIVE:* • Pentamidine 300mg nebule and salbutamol 2.5mg nebule pre-pentamidine, every 4 weeks **plus** • Phenoxymethylpenicillin 333mg BD PO Continue phenoxymethylpenicillin until patients have been revaccinated and have adequate pneuococcal/haemophilus titres *PJP Prophylaxis and T gondii IgG POSITIVE:* • Atovaquone 750mg BD PO **plus** • Pyrimethamine 25mg OD PO **plus** • Folinic acid 15mg OD PO **plus** • Phenoxymethylpenicillin 333mg BD PO Continue phenoxymethylpenicillin until patients have been revaccinated and have adequate pneumococcal/haemophilus titres Please note: If a patient is to be discharged on atovaquone, pyrimethamine or folinic acid, please contact pharmacy in advance to arrange supply and funding through a community drugs scheme
Mouthcare	Mucositis WHO grade <2: • 10mL NaCl 0.9% QDS mouthwash • Nystatin 1mL QDS PO (use 15 minutes after NaCl 0.9% mouthwash) Mucositis WHO grade ≥2: • Chlorhexidine digluconate 0.12% 10mL QDS PO • Nystatin 1mL QDS PO (use 15 minutes after chlorhexidine digluconate 0.12% mouthwash)
Gastroprotection	• Lansoprazole 30mg OD PO **or** • Omeprazole 40mg OD PO **or**

	• Esomeprazole 40mg OD IV (if PO not appropriate)
Folate supplementation	• Folinic acid 15mg OD IV commenced from day + 2 onwards • Switch to folic acid 5mg OD PO when appropriate
Vitamin K supplementation	Beginning on day +2 post stem cell transplant: • Vitamin K (phytomenadione) 10mg once weekly IV
Prevention of vaginal bleeding	If required for menstruating female patients until platelets > 50 x10^9/L: • Norethisterone 5mg TDS PO if >55Kg • Norethisterone 5mg BD PO if <55kg
Tumour Lysis Syndrome	Consider allopurinol in active disease pre transplant: • Allopurinol 300mg OD PO for 5-7 days then review
Hepatitis B prophylaxis/treatment	A virology screen is completed as part of transplant workup. Hepatitis B prophylaxis or treatment may be initiated in consultation with a Virology Consultant or Hepatology Consultant if required. Options may include: • Entecavir 500 microgram OD PO
Prevention of constipation	Consider laxatives if appropriate e.g. • Senna 15mg nocte PO while on ondansetron
Antibiotic standing order	Antibiotic standing order should be prescribed for neutropenic sepsis/neutropenic fever based on previous microbiology and renal function: • Piptazobactam 4.5g QDS IV **plus** • Amikacin* 15mg/kg OD IV *Ciprofloxacin 400mg BD IV may be considered instead of amikacin in cases of renal impairment Refer to Antimicrobial Guidelines for antibiotic choice where a patient is allergic to any of the above.
Magnesium and potassium standing order	Magnesium and potassium standing orders should be prescribed for all transplant patients in accordance with stem cell unit practice as indicated on EPMAR
VTE prophylaxis	Consider VTE prophylaxis in accordance with SJH policy
Bone Health	Consider calcium and vitamin D supplementation prior to discharge for patients who are on high dose steroids. Other medications for maintenance of bone health may need to be considered as appropriate. • Calcium carbonate and colecalciferol (Caltrate® 600mg/400 units) one tablet BD

Hepatic veno-occlusive disease (VOD):

- Defibrotide may be prescribed for the treatment of VOD in consultation with the haematology consultant
- Dosing of IV defibrotide:
    - The recommended dose is 6.25mg/kg IV every 6 hours (25mg/kg/day)
        - Calculate the total daily dose. Divide by 200 to calculate the total number of vials needed and split the dose such that the minimum amount of wastage can be achieved.
    - Defibrotide should be administered for a minimum of 21 days and continued until the signs and symptoms VOD resolve.

- IV infusion is given over 2 hours (maximum concentration is 400mg/100mL NaCl 0.9%)

ADVERSE EFFECTS:

- Please refer to the relevant Summary of Product Characteristics (SmPC) and SJH Stem Cell Transplant Programme PPPGs for full details

REGIMEN SPECIFIC COMPLICATIONS:

- Please refer to the relevant Summary of Product Characteristics (SmPC) and SJH Stem Cell Transplant Programme PPPGs for details

DRUG INTERACTIONS:

- Current Summary of Product Characteristics (SmPC) and drug interaction databases should be consulted for information

REFERENCES:

1. A Multi-Center, Phase II Trial of Transplantation of HLA Mismatched Unrelated Donor Bone Marrow Transplantation with Post-Transplantation Cyclophosphamide for Patients with Hematologic Malignancies. Bronwen E. Shaw, MD, PhD. et al. Available at: JCO.20.03502 1971..1985
2. A Randomized, Multicenter, Phase III Trial of Tacrolimus/Methotrexate versus Post-Transplant Cyclophosphamide/Tacrolimus/Mycophenolate Mofetil in Non-Myeloablative/Reduced Intensity Conditioning Allogeneic Peripheral Blood Stem Cell Transplantation. Javier Bolaños-Meade, MD and Shernan Holtan, MD. Available at: https://cdn.clinicaltrials.gov/large-docs/41/NCT03959241/Prot_SAP_ICF_000.pdf
3. Giraud E L, Lijster B D, et al. Dose recommendations for anticancer drugs in patients with renal or hepatic impairment: an update. Available at: https://pubmed.ncbi.nlm.nih.gov/37269847/
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5. Fludarabine 25mg/mL Accord Summary of Product Characteristics. Accessed 11/08/2025. Available at: https://assets.hpra.ie/products/Human/30862/Licence_PA2315-035-001_02062023143321.pdf
6. cycloPHOSphamide 500mg Seacross Powder for Solution for Injection/Infusion. Summary of Product Characteristics. Accessed: 11/08/2025. Available at: https://assets.hpra.ie/products/Human/40371/Licence_PA22766-013-002_06122024142806.pdf

Version	Date	Amendment	Approved By
1	26/08/2025		SJH Stem Cell Transplant Group

Comments and feedback welcome at oncologydrugs@cancercontrol.ie.

[i] This is an unlicensed indication for the use of fludarabine in Ireland. Patients should be informed of this and consented to treatment in line with the hospital's policy on the use of unlicensed medication and unlicensed or "off label" indications. Prescribers should be fully aware of their responsibility in communicating any relevant information to the patient and also ensuring that the unlicensed or "off label" indication has been acknowledged by the hospital's Drugs and Therapeutics Committee, or equivalent, in line with hospital policy