Fludarabine/Melphalan/ATG Grafalon® - post-transplant Methotrexate – RIC – SIB

INDICATIONS FOR USE:

INDICATION	ICD-10	Regimen Code	HSE approved reimbursement status*
Reduced intensity conditioning for sibling donor allogeneic stem cell transplant in patients with myeloid disorders	C92-95	00922a	N/A

* This applies to post 2012 indications

TREATMENT:

- Conditioning chemotherapy is administered over 7 days
- Stem cells are infused on day 0
- Three doses of methotrexate are administered post stem cell transplant (days +1, +3 and +6)

Facilities to treat anaphylaxis MUST be present when systemic anti-cancer therapy (SACT) is administered.

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Day	Drug	Dose	Route	Diluent & Rate
-7, -6, -5, -4, -3	[i]Fludarabine[a]	30mg/m^2	IV infusion	100mL NaCl 0.9% over 30 minutes
-3	[b, c, d] ATG Grafalon®	10mg/kg	IV infusion	(see note[e]) mL NaCl 0.9% over 12 hours
-2 **(10:30)***	Melphalan[f]	140mg/m^2	IV push	Slow IV push into the side arm of a fast-flowing NaCl 0.9% infusion over 10-20 minutes
-2, -1	[b, c, d] ATG Grafalon®	10mg/kg	IV infusion	(see note[e]) mL NaCl 0.9% over 10 hours
0	Stem cell re-infusion			
+1, +3, +6 **(At least 24 hours post end of stem cell infusion)**	[i]Methotrexate[g]	10mg/m^2	IV infusion	50mL NaCl 0.9% over 10 minutes

Dose rounding:
Fludarabine doses ≤50mg to the nearest 2.5mg and doses >50mg to the nearest 5mg
ATG Grafalon® to the nearest 20mg
Melphalan to the nearest 5mg
Methotrexate to the nearest 2.5mg

[a]All patients who have received fludarabine should receive irradiated blood products (lifetime recommendation)

[b]Patient monitoring is required during the ATG Grafalon® infusion: BP, pulse, respiration and temperature at 15, 30 and then 60 minute intervals for the duration of the infusion.
[c]If an infusion reaction occurs during the administration of ATG Grafalon®, the infusion should be slowed. Chills and fever generally respond to antihistamines, antipyretics or corticosteroids. If the patient becomes hypotensive or experiences chest or back pain, indicating anaphylaxis, the infusion should be stopped and the medical team contacted immediately
[d]Platelets should be >50x10^9/L pre day 1 ATG Grafalon® treatment. If the patient has no reaction to ATG Grafalon®, platelets can be maintained at >30x10^9/L for the remaining days of ATG Grafalon® administration. Platelets should be maintained at >50x10^9/L in the setting of clinically symptomatic bleeding
[e]Each mL of ATG Grafalon® should be diluted with 6mL NaCl 0.9% in accordance with SPC. Pharmacy to complete volume.

[f] When reconstituted, melphalan has a very short expiry time. It must be administered once it reaches the ward due to instability. Melphalan is not compatible with glucose solutions. (Refer to local policy for guidance on stability and shelf life to co-ordinate administration with pharmacy compounding)

[g] Day +1 methotrexate should be administered at least 24 hours after the stem cells have infused. In the event where this timing results in methotrexate being infused during the night, it is reasonable to reschedule the administration time of the day +3 methotrexate to the next morning, to avoid administration during the night. The amended administration timing can then be maintained for subsequent methotrexate doses

*Recommended administration times

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

ELIGIBILITY:

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

EXCLUSIONS:

- Hypersensitivity to fludarabine, ATG Grafalon®, melphalan, methotrexate or any of the excipients

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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 work-up 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.

Renal and hepatic impairment:

- Dose modifications are generally not undertaken in conditioning regimens
- Discuss with the consultant if hepatic impairment or if creatinine clearance is <70mL/minute for advice on fludarabine dosing. Guidance to inform this discussion 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) available at: https://www.hpra.ie/
    - 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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SUPPORTIVE CARE:

Antiemetics:

Table 1: Recommended SJH Regimen Specific Antiemetics

Prevention of acute emesis			Prevention of delayed emesis			Comments
Drug	**Dose**	**Admin day**	**Drug**	**Dose**	**Admin day**	
Aprepitant	125mg PO	-2	Aprepitant	80mg PO	-1, 0	No additional dexAMETHasone is required due to steroid cover with ATG Grafalon® supportive medication
Ondansetron	8mg PO/IV TDS	-2, -1				

ATG Grafalon® supportive medication:

- methylPREDNISolone 2mg/kg OD IV administered 90 minutes before commencing ATG Grafalon® on day -3 to day -1
- Chlorphenamine 10mg IV administered 30 minutes before commencing ATG Grafalon® on day -3 to day -1
- prednisoLONE 1mg/kg OD PO (or IV equivalent) administered on day 0 and continuing for 5 days
    - Taper to zero over the next 5 days to prevent serum sickness

Melphalan hydration:

- NaCl 0.9% must be given at a rate of 125mL/m^2/hour for 2 hours pre-melphalan and for 6 hours post-melphalan

Other Supportive Care:

GvHD prophylaxis Refer to signed off BMT assessment form for confirmed ***choice and target level*** of immunosuppression	**Ciclosporin** • Ciclosporin 5mg/kg OD IV over 6 hours from day -1 • The equivalent oral dose is: (Total IV dose x 0.67) BD PO • Target levels: 100- 150 microgram/Litre	**Tacrolimus** • Tacrolimus 0.03mg/kg OD IV over 22 hours from day -1 • The equivalent oral dose is: Total IV dose, BD PO • Target level: 5-10 nanogram/mL
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/microL: • valACIclovir 500mg OD PO **or** • Aciclovir 250mg TDS IV (if oral 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 oral route not appropriate)	
CMV prophylaxis	**Prescribe CMV prophylaxis for all CMV seropositive recipients.**	

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Prescribe for all CMV seropositive recipients	• 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 oral dose should be prescribed only where the patient cannot tolerate oral or where there are concerns around absorption • CMV prophylaxis is usually continued until day +100 Patients should bring their oral letermovir supply with them on admission. High tech prescription will have been provided to patient at their counselling appointment preadmission. 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 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 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 Mon/Wed/Fri PO • 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 the phenoxymethylpenicillin until patients have been revaccinated and have adequate pneumococcal/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

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	Continue the 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% mouthwash QDS • Nystatin 1ml QDS PO (use 15 minutes after NaCl 0.9% mouthwash) Mucositis WHO grade ≥ 2: • 10mL chlorhexidine digluconate 0.12% mouthwash QDS • 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 oral route not appropriate)
Folate supplementation	• Methotrexate is included as GvHD prophylaxis • Folinic acid should not be administered on the same days as methotrexate • The first dose of folinic acid must be administered at a minimum of 24 hours post completion of methotrexate • Prescribe as outlined below: - Folinic acid 15mg OD IV on days +2, +4, +5, and +7 onwards - Switch to folic acid 5mg OD PO when oral route is 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. • Entecavir 500 micrograms 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

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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 unit or Ideos® 500mg/400 unit) one tablet BD

ADVERSE EFFECTS/REGIMEN SPECIFIC COMPLICATIONS:

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

DRUG INTERACTIONS:

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

REFERENCES:

1. Bryant, A., I. Nivison-Smith, E. S. Pillai, et al. 2014. "Fludarabine Melphalan reduced-intensity conditioning allotransplanation provides similar disease control in lymphoid and myeloid malignancies: analysis of 344 patients." Bone Marrow Transplant 49(1):17-23.
2. Kennedy G., J. Butler, S. Durrant et al. 2005. "Fludarabine/Melphalan Conditioning for Allogeneic Stem Cell Transplantation (SCT) in Elderly Patients with AML/MDS." Blood. 106:54101.
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/
4. NCCP Classification Document for Systemic Anti-Cancer Therapy (SACT) Induced Nausea and Vomiting. V6 2025. Available at: https://www.hse.ie/eng/services/list/5/cancer/profinfo/chemoprotocols/nccp-classification-document-for-systemic-anti-cancer-therapy-sact-induced-nausea-and-vomiting.pdf
5. Fludarabine phosphate (Accord) 25mg/mL Concentrate for Solution for Injection or Infusion. Summary of Product Characteristics (SmPC). Last updated 02/06/2023. Accessed 30/09/2025. Available at: https://www.hpra.ie/find-a-medicine/for-human-use/authorised-medicines/details/30862
6. ATG Grafalon® 20mg/mL Concentrate for Solution for Infusion. Summary of Product Characteristics (SmPC). Last updated 07/01/2025. Accessed 30/09/2025. Available at: https://www.hpra.ie/find-a-medicine/for-human-use/authorised-medicines/details/23846
7. Melphalan (Tillomed) 50mg Powder and Solvent for Solution for Injection and Infusion. Summary of Product Characteristics (SmPC). Last updated 06/06/2025. Accessed 30/09/2025. Available at: https://www.hpra.ie/find-a-medicine/for-human-use/authorised-medicines/details/30632
8. Methotrexate (Pfizer) 1g/10mL Injection. Summary of Product Characteristics (SmPC). Last updated 10/04/2025. Accessed 30/09/2025. Available at: https://www.hpra.ie/find-a-medicine/for-human-use/authorised-medicines/details/22091

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Version	Date	Amendment	Approved By
1	06/10/2025		SJH Stem Cell Transplant Group
1a	09/10/2025	Revision of order of administration of treatment table, addition of footnote regarding methotrexate administration timing.	NCCP

Comments and feedback welcome at oncologydrugs@cancercontrol.ie.

[i] This is an unlicensed indication for the use of fludarabine and methotrexate 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.

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