FLAG Therapy

INDICATIONS FOR USE:

INDICATION	ICD10	Regimen Code	HSE approved reimbursement status*
Treatment of Acute Leukaemias in patients unsuitable for treatment with idarubicin or as consolidation post FLAG-Ida	C92	00363a	N/A
Treatment of patients with high blast count (>10%) Myelodysplastic Syndrome in patients unsuitable for treatment with idarubicin	D46	00363b	N/A
Salvage regimen for patients with relapsed/refractory acute leukaemia	C91 C92	00363c	N/A

* This is for post 2012 indications.

TREATMENT:

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

Treatment is administered as described in the treatment table below.
A second cycle may be administered when ANC > 1 x 10^9/L and platelets > 100 x 10^9/L at the discretion of the prescribing Consultant.

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

Day	Drug	Dose	Route	Diluent and rate
-1 to 6 (7 days) [a] Inclusive	G-CSF [b]	5microgram/kg	SC	Round to full syringe
1,2,3,4,5 Inclusive	[i]Fludarabine[c]	30mg/m^2	IV infusion	100mL 0.9% NaCl over 30 minutes
1,2,3,4,5 Inclusive	Cytarabine	[d] 2000mg/m^2	IV infusion	500mL 0.9% NaCl over 4 hours. **Commence 4 hours after start of Fludarabine infusion**
[a] G-CSF to be administered for 7 days starting the day before administration of fludarabine and cytarabine (Day -1,1,2,3,4,5,6) G-CSF priming can be omitted at the discretion of the prescribing Consultant particularly in the setting of consolidation.				
[b] G-CSF may be continued beyond day 6 or re-introduced later in the cycle to hasten neutrophil recovery at the discretion of the prescribing Consultant				
[c]All patients who have received fludarabine should receive irradiated blood products (lifetime recommendation)				
[d]Cytarabine dose may be reduced for older patients; consider 1000 mg/m^2 if the patient is older than 60 years of age				

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

ELIGIBILITY:

- Indications as above
- ECOG status 0-2
- Age <60 generally. May be used in older patients if deemed fit for intensive therapy by prescribing consultant

EXCLUSIONS:

- Hypersensitivity to fludarabine, cytarabine or any of the excipients
- Pregnancy
- Breast feeding

PRESCRIPTIVE AUTHORITY:

- The treatment plan must be initiated by a Haematology Consultant working in the area of haematological malignancies

TESTS:

Baseline tests:

- FBC, renal and liver profile
- Uric acid, LDH, blood glucose
- Coagulation profile (Activated Partial Thromboplastin time (APTT), Prothrombin time (PT), fibrinogen level) as per local policy
- Virology screen - Hepatitis B virus (HBV) serology [HBV sAg, HBV sAb, HBV cAb], hepatitis C virus (HCV) serology, human immunodeficiency virus (HIV) serology, cytomegalovirus (CMV) serology [IgG] and additional screening as clinically indicated
  *(Reference Regimen Specific Complications for information on Hepatitis B reactivation)

Regular tests:

- FBC, renal and liver profile daily or as clinically indicated
- Uric acid, blood glucose daily or as clinically indicated
- Coagulation profile: APTT, PT, fibrinogen level at least twice weekly or more frequently as clinically indicated

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.
- **Renal and Hepatic Impairment:** Dose reduce chemotherapy only after discussion with Consultant

Renal and Hepatic Impairment:

Table 1: Dose modification of Cytarabine and Fludarabine in renal and hepatic impairment

Drug	Renal Impairment		Hepatic Impairment
Fludarabine [a]	**Cr Cl (mL/min)**	**Dose**	No need for dose adjustment is expected
	>70	No dose adjustment is needed	
	30-70	Up to 50% of original dose. Close haematological monitoring should be used to assess toxicity.	
	<30	Contraindicated	
Cytarabine [b]	**CrCl (mL/min)**	**Dose**	Mild and moderate: no need for dose adjustment is expected Severe: consider 25-50% of the original dose and increase if tolerated
	≥60	No dose adjustment is needed	
	31-59	50% of the original dose	
	<30	Not recommended	
	Haemodialysis	80% of the original dose. Start dialysis 12h after administration.	

[a] Fludarabine (renal – SmPC and hepatic - Giraud et al 2023);
[b] Cytarabine (renal and hepatic – Giraud et al 2023);

SUPPORTIVE CARE:

EMETOGENIC POTENTIAL:

- As outlined in NCCP Classification Document for Systemic AntiCancer Therapy (SACT) Induced Nausea and Vomiting- Available on the NCCP website

Cytarabine: Moderate **(Refer to local policy)**

Fludarabine: Minimal **(Refer to local policy)**

For information:

Within NCIS regimens, antiemetics have been standardised by Medical Oncologists and Haemato-oncologists and information is available in the following documents:

- NCCP Supportive Care Antiemetic Medicines for **Inclusion in NCIS** (Medical Oncology) - Available on the NCCP website
- NCCP Supportive Care Antiemetic Medicines for **Inclusion in NCIS** (Haemato-oncology) - Available on the NCCP website

ANTIEMETICS

Table 2: Recommended antiemetics

Prevention of acute nausea and vomiting			When required for breakthrough emesis	
Admin Day	**Drug**	**Dose**	**Drug**	**Dose**
1,2,3,4,5	Ondansetron	8mg PO/IV three times daily	Cyclizine	50mg three times daily
			LORazepam	0.5-1mg PO/IV three times daily

PREMEDICATIONS:

To prevent a chemical induced conjunctivitis developing with cytarabine, prednisoLONE eye drops (e.g. Pred Mild®) 1-2 drops per eye 4 hourly during waking hours prior to cytarabine and continued 5 days post treatment should be considered.

OTHER SUPPORTIVE CARE:

- PJP Prophylaxis until CD4 counts have recovered to >200 cells/mm^3 in patients who have received fludarabine **(Refer to local policy)**
- All patients who have received fludarabine should receive irradiated blood products **(lifetime recommendation)**
- Tumour lysis syndrome prophylaxis **(Refer to local policy)**
- Proton pump Inhibitor **(Refer to local policy)**
- Anti-viral prophylaxis **(Refer to local policy)**
- Anti-fungal prophylaxis **(Refer to local policy)**
- Mouth/Oral care **(Refer to local policy**
- Severe PV Bleeding **(Refer to local policy)**

ADVERSE EFFECTS

Please refer to the relevant Summary of Product Characteristics (SmPC) for details.

REGIMEN SPECIFIC COMPLICATIONS:

- **Hepatitis B Reactivation:** Patients should be tested for both HBsAg and HBcoreAb as per local policy. If either test is positive, such patients should be treated with anti-viral therapy. **(Refer to local infectious disease policy).** These patients should be considered for assessment by hepatology.
- Patients treated with fludarabine should receive prophylaxis for Pneumocystis jirovecii pneumonia (PJP) – see supportive care section for more information.

DRUG INTERACTIONS:

- Current SmPC and drug interaction databases should be consulted for information.

REFERENCES:

1. Virchis A et al. Fludarabine, cytosine arabinosiode, granulocyte-colony stimulating factor with or without idarubicin in the treatmet of high risk acute leukaemia or myelodysplastic syndromes Br J Haem 2004;124, 26-32
2. 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/
3. 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
4. Fludarabine Phosphate 25mg/mL Concentrate for Solution for Injection or Infusion. Summary of product characteristics. Last updated 02/06/2023. Accessed 22/04/2025. Available at: https://assets.hpra.ie/products/Human/30862/Licence_PA2315-035-001_02062023143321.pdf
5. Cytarabine 100 mg/mL Solution for Injection. Summary of product characteristics. Last updated 18/08/2021. Accessed 22/04/2025. Available at: https://assets.hpra.ie/products/Human/27655/Licence_PA2315-082-001_26112020144445.pdf

Version	Date	Amendment	Approved By
1	17/9/2021		NCCP Myeloid Clinical Advisory Group
2	20/12/2021	Updated treatment table	NCCP Myeloid Clinical Advisory Group
3	22/04/2025	Reviewed. Updated renal and hepatic dose modifications to align with Giraud et al (2023) and SmPC. Added unlicensed indication footnote.	NCCP Myeloid Clinical Advisory 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.