Vyxeos liposomal® (DAUNOrubicin and Cytarabine) Induction Therapy

INDICATIONS FOR USE:

INDICATION	ICD10	Regimen Code	Reimbursement Status
For the treatment of adults with newly diagnosed, therapy-related acute myeloid leukaemia (t-AML) or AML with myelodysplasia-related changes (AML-MRC)	C92	00613a	ODMS 04/02/2021

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.

- Induction cycle 1 is administered on days 1, 3 and 5 as detailed in the treatment table below.
- A subsequent course of induction may be administered in patients who do not show disease progression or unacceptable toxicity (Induction cycle 2 as detailed below)
    - The attainment of a normal-appearing bone marrow may require more than one induction course. Evaluation of the bone marrow following recovery from the previous course of induction therapy determines whether a further course of induction is required.
- Treatment should be continued as long as the patient continues to benefit or until disease progression, up to maximum of 2 induction courses.

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

	Day	Drug	Dose	Route	Diluent & Rate
Induction cycle 1	1, 3 and 5	[a]Vyxeos liposomal®	DAUNOrubicin[b] 44 mg/m^2 and cytarabine 100 mg/m^2	IV infusion	500ml NaCl 0.9% over 90 minutes
Induction cycle 2	1 and 3	[a]Vyxeos liposomal®	DAUNOrubicin[b] 44 mg/m^2 and cytarabine 100 mg/m^2	IV infusion	500ml NaCl 0.9% over 90 minutes
[a]When reconstituted, Vyxeos liposomal® has a very short expiry time **(Refer to local policy for guidance on stability and shelf life to co-ordinate administration with pharmacy compounding).**					
[b]Lifetime cumulative dose of DAUNOrubicin is 550mg/m^2**.** In establishing the maximal cumulative dose of an anthracycline, consideration should be given to the risk factors outlined below[i] and to the age of the patient**.**					

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ELIGIBILITY:

- Indications as above
- Pathological diagnosis of therapy-related acute myeloid leukaemia (t-AML) or AML with myelodysplasia-related changes (AML-MRC) as confirmed by a validated test method
- ECOG 0-2
- Cardiac ejection fraction ≥ 45% by echocardiography or MUGA

EXCLUSIONS:

- Acute promyelocytic leukemia [t(15;17)] or favourable cytogenetics, including t(8;21) or inv16
- Clinical evidence of active CNS leukaemia
- Patients with prior cumulative anthracycline exposure of greater than 368 mg/m^2 DAUNOrubicin (or equivalent)
- Patients with myocardial impairment of any cause (e.g. cardiomyopathy, ischaemic heart disease, significant valvular dysfunction, hypertensive heart disease, and congestive heart failure) resulting in heart failure by New York Heart Association Criteria (Class III or IV staging)
- LVEF <45% (The treatment of patients with baseline LVEF <45% should only be initiated at the discretion of the treating consultant)
- Active or uncontrolled infection
- Hypersensitivity to cytarabine, DAUNOrubicin or liposomal products
- History of Wilson's disease or other copper-metabolism disorder
- Breastfeeding

PRESCRIPTIVE AUTHORITY:

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

TESTS:

Baseline tests:

- FBC, renal and hepatic profile
- Coagulation profile (PT, APTT, fibrinogen)
- ECG, MUGA or ECHO
- Chest X-Ray
- Pregnancy test

Regular tests:

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

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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:

Table 1: Dose modification of Vyxeos liposomal® in renal and hepatic impairment

Renal Impairment		Hepatic Impairment
Stage	**Dose**	Dose adjustment is not required for patients with a bilirubin level less than or equal to 50 micromol/L. There is no experience in patients with hepatic impairment resulting in a bilirubin level greater than 50 micromol/L. Clinical decision in patients with severe hepatic impairment.
Mild/moderate/severe	100%	
End stage renal failure	Has not been studied. Clinical decision.	

SUPPORTIVE CARE:

EMETOGENIC POTENTIAL

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

Vyxeos liposomal®: Moderate (**Refer to local policy).**

For information:
Within NCIS regimens, antiemetics have been standardised by the Medical Oncologists and Haemato-oncologists. 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

PREMEDICATIONS: Not usually required

OTHER SUPPORTIVE CARE:

- Tumour lysis syndrome prophylaxis. If at high risk consider rasburicase **(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)**

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ADVERSE EFFECTS / REGIMEN SPECIFIC COMPLICATIONS:

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

- **Other DAUNOrubicin and/or cytarabine-containing products:** Vyxeos liposomal® must not be substituted or interchanged with other DAUNOrubicin and/or cytarabine containing products. Due to substantial differences in the pharmacokinetic parameters, the dose and schedule recommendations for Vyxeos liposomal® are different from those for DAUNOrubicin hydrochloride injection, cytarabine injection, DAUNOrubicin citrate liposome injection, and cytarabine liposome injection. The medicinal product name and dose should be verified prior to administration to avoid dosing errors.
- **Severe myelosuppression:** Severe myelosuppression (including fatal infections and haemorrhagic events) has been reported in patients after administration of a therapeutic dose of Vyxeos liposomal®. Serious or fatal haemorrhagic events, including fatal central nervous system (CNS) haemorrhages, associated with severe thrombocytopenia, have occurred in patients treated with Vyxeos liposomal®. Baseline assessment of blood counts should be obtained, and patients should be carefully monitored during treatment with Vyxeos liposomal® for possible clinical complications due to myelosuppression. Due to the long plasma half-life of Vyxeos liposomal®, time to recovery of ANC and platelets may be prolonged and require additional monitoring.
  Prophylactic anti-infectives (including anti-bacterial, anti-virals, anti-fungals) may be administered during the period of profound neutropenia until ANC returns to 500/microlitre or greater. If myelosuppressive complications occur, appropriate supportive measures should be used, e.g., anti-infectives, colony-stimulating factors, transfusions. Blood counts should be regularly monitored until recovery.
- **Cardiotoxicity:** Cardiotoxicity is a known risk of anthracycline treatment. Prior therapy with anthracyclines (including patients who have previously received the recommended maximum cumulative doses of doxorubicin or DAUNOrubicin hydrochloride), pre-existing cardiac disease (including impaired cardiac function), previous radiotherapy of the mediastinum, or concomitant use of cardiotoxic products may increase the risk of DAUNOrubicin-induced cardiac toxicity. Total cumulative doses of non-liposomal DAUNOrubicin greater than 550 mg/m^2 have been associated with an increased incidence of treatment-induced congestive heart failure. This limit appears lower (400 mg/m^2) in patients who received radiation therapy to the mediastinum. The relationship between cumulative Vyxeos liposomal® dose and the risk of cardiac toxicity has not been determined.
- **Pregnancy warning/women of childbearing potential:** Patients should be advised to avoid becoming pregnant while receiving Vyxeos liposomal®. Male patients and women of childbearing potential must use an effective method of contraception during treatment and for 6 months following the last dose of Vyxeos liposomal®.
- **Hypersensitivity reactions:** Serious hypersensitivity reactions, including anaphylactic reactions, have been reported with DAUNOrubicin and cytarabine.
- **Tissue necrosis:** DAUNOrubicin has been associated with local tissue necrosis at the site of medicinal product extravasation. In clinical studies with Vyxeos liposomal®, one event of extravasation occurred, but no necrosis was observed. Vyxeos liposomal® should be

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administered intravenously only. Do not administer via an intramuscular, intrathecal, or subcutaneous route.

- **History of Wilson's disease or other copper-related disorder:** Each vial contains 100 mg of copper gluconate, which corresponds to 14 mg of elemental copper. Vyxeos liposomal® should only be used in patients with a history of Wilson's disease or other copper-related disorder if the benefits outweigh the risks. Discontinue Vyxeos liposomal® in patients with signs or symptoms of acute copper toxicity.

DRUG INTERACTIONS:

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

REFERENCES:

1. Lancet et al. CPX-351 (cytarabine and DAUNOrubicin) Liposome for Injection Versus Conventional Cytarabine Plus DAUNOrubicin in Older Patients With Newly Diagnosed Secondary Acute Myeloid Leukaemia. J Clin Oncol 2018: 36:2684-2692
2. NCCP Classification Document for Systemic Anti-Cancer Therapy (SACT) Induced Nausea and Vomiting. V5 2023. 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
3. Vyxeos liposomal® 44 mg/100 mg powder for concentrate for solution for infusion. Summary of Product Characteristics. Last updated 27/07/2022. Accessed June 2023. Available at: https://www.ema.europa.eu/en/documents/product-information/vyxeos-liposomal-epar-product-information_en.pdf

Version	Date	Amendment	Approved By
1	04/02/2021		NCCP Myeloid Clinical Advisory Group
2	19/01/2024	Reviewed. Updated dose modifications for renal impairment.	Dr. Janusz Krawczyk
2a	26/06/2025	Updated emetogenic potential section with added links.	NCCP

Comments and feedback welcome at oncologydrugs@cancercontrol.ie.

[i] Cardiotoxicity is a risk associated with anthracycline therapy that may be manifested by early (acute) or late (delayed) effects.
Risk factors for developing anthracycline-induced cardiotoxicity include:
• high cumulative dose, previous therapy with other anthracyclines or anthracenediones
• prior or concomitant radiotherapy to the mediastinal/pericardial area
• pre-existing heart disease
• concomitant use of other potentially cardiotoxic drugs
In establishing the maximal cumulative dose of an anthracycline, consideration should be given to the risk factors above and to the age of the patient

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