

Vyxeos[®]
(daunorubicin and cytarabine) 44 mg/100 mg
per vial
liposome for injection

Dosing and Administration Information

Learn more about patient and institutional factors to consider when assessing a patient for outpatient treatment with VYXEOS

Liposomal daunorubicin and cytarabine (VYXEOS) is the ONLY treatment recommended in the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines[®]) for induction in patients ≥60 years of age with therapy-related AML or antecedent MDS/CMML or AML-MRC (Category 1)^{1,a}

INDICATION

VYXEOS is indicated for the treatment of newly-diagnosed therapy-related acute myeloid leukemia (t-AML) or AML with myelodysplasia-related changes (AML-MRC) in adults and pediatric patients 1 year and older.

IMPORTANT SAFETY INFORMATION

WARNING: DO NOT INTERCHANGE WITH OTHER DAUNORUBICIN AND/OR CYTARABINE-CONTAINING PRODUCTS

VYXEOS has different dosage recommendations than daunorubicin hydrochloride injection, cytarabine injection, daunorubicin citrate liposome injection, and cytarabine liposome injection. Verify drug name and dose prior to preparation and administration to avoid dosing errors.

Contraindications

VYXEOS is contraindicated in patients with a history of serious hypersensitivity reactions to cytarabine, daunorubicin, or any component of the formulation.






Please see additional Important Safety Information on pages 8 and 9 and full Prescribing Information, including BOXED Warning.

^aCategory 1: Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.¹

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AML=acute myeloid leukemia; AML-MRC=AML with myelodysplasia-related changes; CMML=chronic myelomonocytic leukemia; MDS=myelodysplastic syndromes; NCCN=National Comprehensive Cancer Network.

VYXEOS administration allows sAML patients time off therapy²

<i>First induction</i>	1	2	3	4	5	6	7
Days 1, 3, and 5 44 mg/100 mg per m ² 90-min infusions							
<i>Consolidation</i>	1	2	3	4	5	6	7
Days 1 and 3 29 mg/65 mg per m ² 90-min infusions							
	<i>51% of patients received consolidation with VYXEOS in an outpatient setting during the Phase 3 trial³</i>						

Dosing considerations²

- Prior to initiating each cycle, calculate the prior cumulative anthracycline exposure for the patient
- Assess cardiac function, complete blood counts, and liver and renal function before each consolidation cycle
- Do not start consolidation until the absolute neutrophil count (ANC) recovers to greater than 0.5 Gi/L and the platelet count recovers to greater than 50 Gi/L in the absence of unacceptable toxicity

IMPORTANT SAFETY INFORMATION

Hemorrhage

Serious or fatal hemorrhage events, including fatal CNS hemorrhages, associated with prolonged thrombocytopenia, have occurred with VYXEOS. The overall incidence (grade 1-5) of hemorrhagic events was 74% in the VYXEOS arm and 56% in the control arm. The most frequently reported hemorrhagic event was epistaxis (36% in VYXEOS arm and 18% in control arm). Grade 3 or greater events occurred in 12% of VYXEOS-treated patients and in 8% of patients in the control arm. Fatal treatment-emergent CNS hemorrhage not in the setting of progressive disease occurred in 2% of patients in the VYXEOS arm and in 0.7% of patients in the control arm. Monitor blood counts regularly and administer platelet transfusion support as required.

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sAML=secondary AML.

VYXEOS dosing and administration schedule^{2,a,b}

First induction

Daunorubicin 44 mg/m² and cytarabine 100 mg/m² liposome on Days 1, 3, and 5

Second induction (if needed)

Daunorubicin 44 mg/m² and cytarabine 100 mg/m² liposome on Days 1 and 3

- In patients not achieving a response, start 2 to 5 weeks after first induction

First consolidation

Daunorubicin 29 mg/m² and cytarabine 65 mg/m² liposome on Days 1 and 3

- 5 to 8 weeks after the start of last induction

Second consolidation (if needed)

Daunorubicin 29 mg/m² and cytarabine 65 mg/m² liposome on Days 1 and 3

- 5 to 8 weeks after the start of first consolidation in patients who do not show disease progression or unacceptable toxicity

^aPatients may receive up to 2 cycles of induction and up to 2 cycles of consolidation.

^bAll infusions administered intravenously.

The dosing schedule for VYXEOS allows for flexibility in administration setting^{2,3}

- ✓ **Fixed induction and consolidation dosing regimen throughout course of therapy**
- ✓ **Allows for a treatment-free interval**
- ✓ **Administration schedule allows for outpatient administration for appropriate patients**
- ✓ **Treatment monitoring: on-site infusion with VYXEOS allows healthcare professionals to confirm their patients are receiving treatment**

- In the Phase 3 trial,^c site of induction and consolidation administration—inpatient vs outpatient—was not defined. The decision was left to the discretion of the investigators according to the standard practices of their institution³
 - Almost all patients in the Phase 3 trial received induction in an inpatient setting⁴
- Outpatient administration may decrease the number of days a patient needs to be hospitalized for treatment⁴

^cPhase 3 study design (N=309): randomized, multicenter, open-label, active-controlled trial of VYXEOS vs 7+3 (cytarabine and daunorubicin) in adults 60 to 75 years of age with newly-diagnosed t-AML or AML-MRC.²

IMPORTANT SAFETY INFORMATION

Cardiotoxicity

VYXEOS® (daunorubicin and cytarabine) liposome for injection 44 mg/100 mg contains daunorubicin, which has a known risk of cardiotoxicity. This risk may be increased in patients with prior anthracycline therapy, preexisting cardiac disease, previous radiotherapy to the mediastinum, or concomitant use of cardiotoxic drugs. Assess cardiac function prior to VYXEOS treatment and repeat prior to consolidation and as clinically required. Discontinue VYXEOS in patients with impaired cardiac function unless the benefit of initiating or continuing treatment outweighs the risk. VYXEOS is not recommended in patients with cardiac function that is less than normal.

Total cumulative doses of non-liposomal daunorubicin greater than 550 mg/m² have been associated with an increased incidence of drug-induced congestive heart failure. The tolerable limit appears lower (400 mg/m²) in patients who received radiation therapy to the mediastinum. Calculate the lifetime cumulative anthracycline exposure prior to each cycle of VYXEOS. VYXEOS is not recommended in patients whose lifetime anthracycline exposure has reached the maximum cumulative limit.

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PATIENT FACTORS

to consider for outpatient administration with VYXEOS

1 Deemed stable by medical team^{5,7}



ECOG performance status 0-1 and no significant comorbidities such as kidney or pulmonary diseases or active uncontrolled infections

2 Capable of self-care activities^{5,7}



Ability to consistently attend all scheduled visits and participate in self-care activities such as taking temperature

3 In close proximity to their infusion center^{5,7}



Ability to consistently attend all scheduled visits for treatment and monitoring

IMPORTANT SAFETY INFORMATION

Hypersensitivity Reactions

Serious or fatal hypersensitivity reactions, including anaphylactic reactions, have been reported with daunorubicin and cytarabine. Monitor patients for hypersensitivity reactions. If a mild or moderate hypersensitivity reaction occurs, interrupt or slow the rate of infusion with VYXEOS and manage symptoms. If a severe or life-threatening hypersensitivity reaction occurs, discontinue VYXEOS permanently, treat the symptoms, and monitor until symptoms resolve.

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INSTITUTIONAL FACTORS

to consider for outpatient administration with VYXEOS^a

1 Timely access to supportive care that may include^{5,7}:



Blood and platelet transfusion support



Prophylactic antimicrobial implementation

2 A multidisciplinary team that can^{5,7}:



Coordinate and manage expectations for outpatient care with the patient



Assess and evaluate lab results



Monitor symptoms, side effects, and/or signs of toxicity

3 Inpatient access that allows for⁵:



Unplanned admission due to urgent adverse events

^aAlmost all patients in the Phase 3 trial received induction in an inpatient setting.⁴

IMPORTANT SAFETY INFORMATION

Copper Overload

VYXEOS contains copper. Consult with a hepatologist and nephrologist with expertise in managing acute copper toxicity in patients with Wilson's disease treated with VYXEOS. Monitor total serum copper, serum non-ceruloplasmin-bound copper, 24-hour urine copper levels, and serial neuropsychological examinations during VYXEOS treatment in patients with Wilson's disease or other copper-related metabolic disorders. Use only if the benefits outweigh the risks. Discontinue in patients with signs or symptoms of acute copper toxicity.

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Institutions have evaluated administering VYXEOS in the outpatient setting

Two small, postapproval, single-institution studies assessed the feasibility of adult patients receiving VYXEOS induction in the inpatient/outpatient (IPOP) setting^{8,9,a}

Treatment in the IPOP setting enables appropriate patients to receive induction in an outpatient setting with inpatient admission scheduled or as needed for continued monitoring and subsequent treatment^{8,9}



IPOP-eligible patients who received VYXEOS infusions in an outpatient setting were closely monitored^{8,9}

- In a study by Kubal et al, patients were excluded for IPOP if they had increased risk for tumor lysis including white count >50K, increased creatinine/uric acid, active cardiopulmonary symptoms, ECOG >2, or lacked a caregiver or were unable to reside within 60 minutes of the treating facility⁸
 - Patients were evaluated each day with CMP and uric acid and phosphorus measures. Planned admission occurred on Day 6 for continued care⁹
- In another study, by Deutsch et al, patients were excluded if they had signs or symptoms of active infection or cardiopulmonary disease, were at risk for tumor lysis syndrome, had ECOG >2, or did not have an appropriate caregiver or transportation to the cancer center⁹
 - Patients were monitored at least every other day until count recovery and admitted for continued care if complications occurred⁹

Study information

In a small, single-center pilot study by Kubal et al, 22 patients received a full induction course of VYXEOS. Of these, 64% (n=14; median age 69) received induction in an IPOP setting, and 93% of those patients (n=13) were admitted for continued care on Day 6, as planned. One patient was admitted on Day 2 of induction.⁹

In a small, single-center pilot study by Deutsch et al, 12 patients received a full induction course of VYXEOS, with 58% (n=7; median age 72) receiving induction in an IPOP setting. Of these patients, 86% (n=6) were eventually admitted for continued care; all admissions were due to infection complications. One patient was admitted prior to completing the third induction dose.⁹

^aAlmost all patients in the Phase 3 trial received induction in an inpatient setting.⁴

IMPORTANT SAFETY INFORMATION

Tissue Necrosis

Daunorubicin has been associated with severe local tissue necrosis at the site of drug extravasation. Administer VYXEOS by the intravenous route only. Confirm patency of intravenous access before administration. Do not administer by intramuscular or subcutaneous route.

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CMP=comprehensive metabolic panel.

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One institution's experience with VYXEOS administration in the outpatient setting

Real-world experience from another institution's implementation of VYXEOS administration in the outpatient setting⁷

Patient factors for outpatient treatment⁷:

- No active, uncontrolled infections
- Ability to travel to
 - Infusion center during the first week of therapy for infusions and supportive care
 - Infusion center twice per week after initial induction for continued monitoring
 - A cancer center close to home to help with transfusion support if infusion center is too distant

Institutional factors to conduct outpatient treatment⁷:

- Access to advanced practice providers (APPs)
- Multidisciplinary team trained in transfusion support, symptom management, and transfer of patients to the inpatient setting

There is no planned day of admission; however, when treating patients with VYXEOS, it is not uncommon for a patient to experience fevers. When fever persists, inpatient admission allows further observation and intervention⁷



Successful implementation of an outpatient approach requires that patients have quick, easy access to providers.⁷

- Treating hematologist



IMPORTANT SAFETY INFORMATION

Embryo-Fetal Toxicity

VYXEOS can cause embryo-fetal harm when administered to a pregnant woman. Patients should avoid becoming pregnant while taking VYXEOS. If VYXEOS is used during pregnancy or if the patient becomes pregnant while taking VYXEOS, apprise the patient of the potential risk to a fetus. Advise females and males of reproductive potential to use effective contraception during treatment and for 6 months following the last dose of VYXEOS.

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Warnings and Precautions

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Warnings and Precautions, continued

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MOST COMMON ADVERSE REACTIONS

The most common adverse reactions (incidence $\geq 25\%$) were hemorrhagic events (74%), febrile neutropenia (70%), rash (56%), edema (55%), nausea (49%), mucositis (48%), diarrhea (48%), constipation (42%), musculoskeletal pain (43%), fatigue (39%), abdominal pain (36%), dyspnea (36%), headache (35%), cough (35%), decreased appetite (33%), arrhythmia (31%), pneumonia (31%), bacteremia (29%), chills (27%), sleep disorders (26%), and vomiting (25%).

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References: **1.** Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Acute Myeloid Leukemia V.3.2021. © National Comprehensive Cancer Network, Inc. 2021. All rights reserved. Accessed March 2, 2021. To view the most recent and complete version of the guideline, go online to NCCN.org. **2.** VYXEOS [package insert]. Palo Alto, CA: Jazz Pharmaceuticals. **3.** Kolitz JE, Strickland SA, Cortes JE, et al. Consolidation outcomes in CPX-351 versus cytarabine/daunorubicin-treated older patients with high-risk/secondary acute myeloid leukemia. *Leuk Lymphoma*. 2020;61(3):631-640. **4.** Kolitz JE, Strickland SA, Cortes JE, et al. Efficacy by consolidation administration site: subgroup analysis of a phase 3 study of CPX-351 versus 7+3 in older adults with newly diagnosed, high-risk acute myeloid leukemia (AML). Poster presented at: American Society of Clinical Oncology Annual Meeting; June 2-6, 2017; Chicago, IL. **5.** Aw A, Sabloff M, Sheppard D, et al. Evaluation of an outpatient model for treatment of acute myeloid leukemia. *J Hematol*. 2016;5(1):1-7. **6.** Vaughn JE, Othus M, Powell MA, et al. Resource utilization and safety of outpatient management following intensive induction or salvage chemotherapy for acute myeloid leukemia or myelodysplastic syndrome: a nonrandomized clinical comparative analysis. *JAMA Oncol*. 2015;1(8):1120-1127. **7.** Kasner MT. Outpatient administration of liposomal daunorubicin and cytarabine (Vyxeos) in patients with secondary acute myeloid leukemia. *Clin Adv Hematol Oncol*. 2019;17(11):604-606. **8.** Kubal TE, Salamanca C, Komrokji RS, et al. Safety and feasibility of outpatient induction chemotherapy with CPX-351 in selected older patients with newly diagnosed AML. *J Clin Oncol*. 2018;36(15)(suppl):e19013. **9.** Deutsch YE, Presutto JT, Brahim A, et al. Safety and feasibility of outpatient liposomal daunorubicin and cytarabine (Vyxeos) induction and management in patients with secondary AML. *Blood*. 2018;132(suppl 1):3559.

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The VYXEOS administration schedule consists of 90-minute infusions on Days 1, 3, and 5 for first induction and on Days 1 and 3 for consolidation^{2,b}

- First induction with VYXEOS consists of a 90-minute infusion of daunorubicin 44 mg/m² and cytarabine 100 mg/m² liposome on Days 1, 3, and 5
- Consolidation with VYXEOS consists of a 90-minute infusion of daunorubicin 29 mg/m² and cytarabine 65 mg/m² liposome on Days 1 and 3

The administration schedule for VYXEOS supports the opportunity for treatment in an outpatient setting^{2,3}

- 51% of patients received consolidation with VYXEOS in an outpatient setting in the Phase 3 trial³

Consider both patient and institutional factors when assessing a patient's suitability for outpatient treatment⁷

Small, single-center studies have assessed the feasibility of induction with VYXEOS in the IPOP setting for eligible patients^{8,9}

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