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 (daunorubicin and cytarabine) 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 10 and 11 and full Prescribing Information, including BOXED Warning.

[a]Category 1: Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.[1]

NCCN makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way.

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

VYXEOS provides a limited duration of therapy, which allows patients time off between doses and courses[2,a]

Dosing includes up to 2 cycles of induction and up to 2 cycles of consolidation[2]

FIRST INDUCTION — 1 2 3 4 5 6 7

Days 1, 3, and 5
Daunorubicin 44 mg/m^2
and cytarabine 100 mg/m^2

4.5 HOURS TOTAL INFUSION TIME

Second induction (if needed)[2]

Daunorubicin 44 mg/m^2 and cytarabine 100 mg/m^2 liposome on Days 1 and 3

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

The majority of patients received induction with VYXEOS in an inpatient setting during the Phase 3 trial[3]

Administer first consolidation cycle 5 to 8 weeks after the start of the last induction[2]

CONSOLIDATION — 1 2 3 4 5 6 7

Days 1 and 3
Daunorubicin 29 mg/m^2
and cytarabine 65 mg/m^2

3 HOURS TOTAL INFUSION TIME

Second consolidation (if needed)[2]

Daunorubicin 29 mg/m^2 and cytarabine 65 mg/m^2 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

Of the 49 patients who received consolidation with VYXEOS, 51% (n=25) received consolidation in an outpatient setting during the Phase 3 trial[4]

Administer VYXEOS by constant IV infusion over 90 minutes via an infusion pump through a central venous catheter or a peripherally inserted central catheter.[2]

[a]All infusions administered intravenously.[2]

IV=intravenous.

Dosing considerations

- Prior to initiating each cycle, calculate the prior cumulative anthracycline exposure for the patient[2]
- Assess cardiac function, complete blood counts, and liver and renal function before each consolidation cycle[2]
- 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[2]

The dosing schedule for VYXEOS allows for flexible administration through:

- ✓ **A fixed induction and consolidation dosing regimen over the course of therapy[2,4]**
- ✓ **Opportunity for outpatient treatment with appropriate patients[2,4]**
- ✓ **On-site infusion with VYXEOS that ensures patients are receiving treatment[2]**

- In the Phase 3 trial,[a] 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 institution[3,4]
  - Almost all patients in the Phase 3 trial received induction in an inpatient setting[3]
- Outpatient administration may decrease the number of days a patient needs to be hospitalized for treatment[4]

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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[a]Phase 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]

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One institution's strategies for outpatient administration of VYXEOS for appropriate patients[5,a-c]

Preparation[5]

- Designate a team of healthcare professionals, including registered nurses, pharmacists, APPs, and physicians
- Thoroughly train all personnel in managing outpatient care
- Ideally, allocate space for a dedicated patient center

Patient selection[5]

- Assess patient suitability for outpatient care:
  - Ensure patients are compliant and/or have a suitable caregiver
  - Limit a patient's commute to a treatment center to no more than 60 minutes
  - Evaluate patient's overall health/fitness (eg, ECOG performance status, risk for complications, comorbidities, etc)
  - Consider each patient's treatment goals and preferences

Patient education[5]

- Arrange calendar development and medication review
- Educate patients and caregivers on recognizing and reporting signs and symptoms of serious complications

Patient monitoring[5]

- Anticipate 2-3 monitoring visits per week, although frequency should be tailored to each patient
- Start infusions in the morning to allow time for monitoring
- Coordinate supportive care (eg, transfusions) to be administered following treatment/monitoring visits (same day)
- Carefully monitor for any signs and symptoms of toxicity

Adapted from Talati et al. *Future Oncol.* 2020;16(7):281-291.

[a]In the Phase 3 trial, 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 institution.[3,4]

[b]Most patients in the Phase 3 trial received induction in an inpatient setting.[3]

[c]Outpatient administration may decrease the number of days a patient needs to be hospitalized for treatment.[4]

APP=advanced practice provider; ECOG PS=Eastern Cooperative Oncology Group Performance Status.

Other strategies for outpatient treatment with VYXEOS

Timely access to supportive care is important in outpatient management. Supportive care may include:

***Blood and platelet transfusion support*[5-7]**

- Patients may require frequent transfusions during outpatient care

***Prophylactic antimicrobial implementation*[5,6]**

- Prophylaxis with antibacterials, antifungals, and antivirals may be recommended if a patient is considered at high risk for infection

***Supportive care*[5]**

- Supportive care such as hydration, antiemetic support, and correction of electrolyte imbalances are vital to patient care

Additional considerations for outpatient treatment

- Inpatient access allows for unplanned admission due to urgent adverse events or if a patient requires frequent monitoring and/or transfusion support[6]
- Some institutions may prefer preplanned admission to monitor patients more closely[8]
- A patient who does not experience any major complications may be able to complete all treatment in an outpatient setting[5]

IMPORTANT SAFETY INFORMATION

Cardiotoxicity

VYXEOS 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/m^2 have been associated with an increased incidence of drug-induced congestive heart failure. The tolerable limit appears lower (400 mg/m^2) 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 assessment and management for outpatient administration of VYXEOS based on one institution's experience[5]

Prior to treatment[5]

ASSESS PATIENT'S SUITABILITY FOR OUTPATIENT THERAPY

LABORATORY TESTS:

- CMP
- CBC with differential
- Magnesium
- Uric acid
- Phosphate
- LDH levels

During treatment[5]

PATIENT ASSESSMENTS (DAYS 2-5)

Conduct patient assessment daily to evaluate for signs of disease or treatment-related toxicities such as TLS and/or infection.

LABORATORY TESTS (DAYS 1-5):

- CMP
- CBC with differential
- Magnesium
- Uric acid
- Phosphate
- LDH levels

HOSPITAL ADMISSION:

- During Days 1-5, if any complications arise, such as infections or fever
- Planned for Day 6 to carefully monitor patient with laboratory testing until ANC[a] recovery is achieved[b]

Post-treatment[5]

Perform bone marrow biopsy to evaluate response to therapy (Day 14).

After patient is discharged, patient should be monitored at least 2x weekly[c] with laboratory testing.

Successful outpatient administration of acute myeloid leukemia therapy requires coordination of a multidisciplinary team, thorough patient evaluation, careful preparation, and rigorous patient monitoring[5]

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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[a]ANC > 0.5 x 10^9/L.

[b]The admission stay typically lasts an average of 30 days (ranging between 25 and 50 days).

[c]Frequency of assessment may be modified based on patient need.

CBC=complete blood count; CMP=comprehensive metabolic panel; LDH=lactate dehydrogenase; TLS=tumor lysis syndrome.

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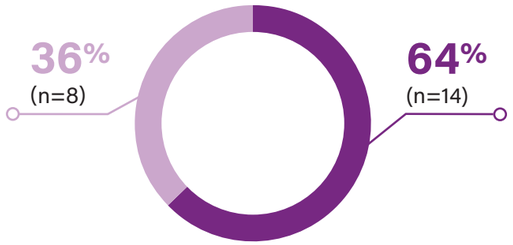
Institutions have evaluated administering VYXEOS in the outpatient setting[8,9]

In two small, postapproval, single-institution studies, over one-half of patients received VYXEOS induction in the outpatient setting[8,9]

***Kubal et al*[8]**



In a small, single-center pilot study by Kubal et al, 22 patients received a full induction course of VYXEOS[8]

- Patients were evaluated each day with CBC, CMP, and uric acid and phosphorus measures
- Planned admission occurred on Day 6 for continued care
- 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

***Deutsch et al*[9]**

In a small, single-center pilot study by Deutsch et al, 12 patients received a full induction course of VYXEOS[9]

- Patients were monitored at least every other day until count recovery and admitted for continued care if complications occurred
- 58% (n=7; median age 72) received induction in an IPOP setting
- Of these 7 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

IPOP=inpatient/outpatient.

These two studies assessed the feasibility of adult patients receiving VYXEOS induction in the inpatient/outpatient setting[8,9,a]

***Exclusion criteria for outpatient administration were similar across these 2 studies*[8,9]**

Kubal et al study (n=22)[8]	Deutsch et al study (n=12)[9]
Increased risk for tumor lysis including white count >50K	At risk for tumor lysis syndrome
Active cardiopulmonary symptoms	Signs or symptoms of active infection or cardiopulmonary disease
ECOG PS >2	ECOG PS >2
Lacked a caregiver or were unable to reside within 60 minutes of the treating facility	Lacked an appropriate caregiver or transportation to the cancer center
Increased creatinine or uric acid	

Treatment in an IPOP setting enables appropriate patients to receive induction in an outpatient setting, with inpatient admission scheduled as needed for continued monitoring and care or for treatment for adverse events[8,9]

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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[a]Most patients in the Phase 3 trial received induction in an inpatient setting.[3]

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INDICATION

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Contraindications

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

Warnings and Precautions

Hemorrhage
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Warnings and Precautions, continued

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.

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.

MOST COMMON ADVERSE REACTIONS

The most common adverse reactions (incidence ≥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%).

Please see full Prescribing Information, including BOXED Warning.

References: 1. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Acute Myeloid Leukemia V.1.2022. © National Comprehensive Cancer Network, Inc. 2021. All rights reserved. Accessed December 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. 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). Presented at: American Society of Clinical Oncology Annual Meeting; June 2-6, 2017; Chicago, IL. Poster 7036. **4.** 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. **5.** Talati C, Frantz D, Lubas A, et al. How I treat newly diagnosed acute myeloid leukemia in an outpatient setting: a multidisciplinary team perspective. *Future Oncol.* 2020;16(7):281-291. **6.** 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. **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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VYXEOS dosing includes up to 2 cycles of induction and up to 2 cycles of consolidation[2]

- First induction with VYXEOS consists of a **90-minute infusion** of daunorubicin 44 mg/m^2 and cytarabine 100 mg/m^2 liposome on **Days 1, 3, and 5**
- Consolidation with VYXEOS consists of a **90-minute infusion** of daunorubicin 29 mg/m^2 and cytarabine 65 mg/m^2 liposome on **Days 1 and 3**

VYXEOS allows patients time off between doses and cycles, a fixed treatment conclusion, and the possibility of outpatient administration[2,4]

Consider both patient and institutional factors when assessing a patient's suitability for outpatient treatment[7]

Institutions have published strategies and considerations for administering VYXEOS in outpatient settings[5,7-9]

- In two small, postapproval, single-institution studies, over one-half of patients received VYXEOS induction in the outpatient setting[8,9]

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