



**Vyxeos**<sup>®</sup>  
(daunorubicin and cytarabine) 44 mg/100 mg  
per vial  
**liposome for injection**

# Dosing and Administration Information

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**Induction, consolidation, and outpatient considerations for treatment with VYXEOS**

## **INDICATION**

VYXEOS is indicated for the treatment of adults with newly-diagnosed therapy-related acute myeloid leukemia (t-AML) or AML with myelodysplasia-related changes (AML-MRC).

## **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 7 and 8 and full Prescribing Information, including BOXED Warning.**

# VYXEOS administration allows sAML patients time off therapy<sup>1</sup>

## First induction

<b>VYXEOS</b> Days 1, 3, 5: 44 mg/100 mg per m <sup>2</sup>	
<b>DAY 1</b>	90-min infusion
DAY 2	No VYXEOS administration
<b>DAY 3</b>	90-min infusion
DAY 4	No VYXEOS administration
<b>DAY 5</b>	90-min infusion

## Consolidation

<b>VYXEOS</b> Days 1 and 3: 29 mg/65 mg per m <sup>2</sup>	
<b>DAY 1</b>	90-min infusion
DAY 2	No VYXEOS administration
<b>DAY 3</b>	90-min infusion
51% of patients received consolidation with VYXEOS in an outpatient setting during the Phase 3 trial <sup>2</sup>	

## VYXEOS dosing and administration<sup>a,b</sup>

### First induction

Daunorubicin 44 mg/m<sup>2</sup> and cytarabine 100 mg/m<sup>2</sup> liposome on Days 1, 3, and 5

### Second induction (if needed)

Daunorubicin 44 mg/m<sup>2</sup> and cytarabine 100 mg/m<sup>2</sup> 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/m<sup>2</sup> and cytarabine 65 mg/m<sup>2</sup> liposome on Days 1 and 3

- 5 to 8 weeks after the start of last induction

### Second consolidation (if needed)

Daunorubicin 29 mg/m<sup>2</sup> and cytarabine 65 mg/m<sup>2</sup> 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

## Dosing considerations<sup>1</sup>

- 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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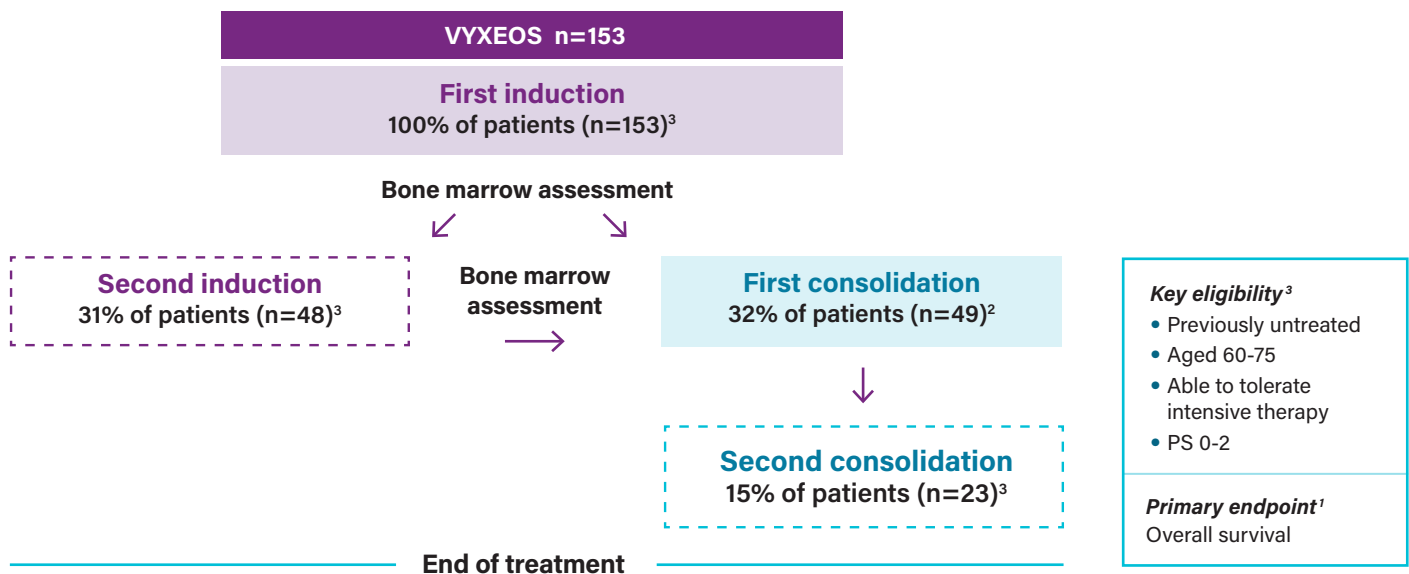
<sup>a</sup>Patients may receive up to 2 cycles of induction and up to 2 cycles of consolidation.

<sup>b</sup>All infusions administered intravenously.

# VYXEOS is a fixed course of therapy consisting of up to 2 cycles of induction and up to 2 cycles of consolidation<sup>1</sup>

## This fixed dosing schedule led to the clinical outcomes observed in the randomized Phase 3 trial (n=309)<sup>1</sup>

Phase 3 study design: randomized, multicenter, open-label, active-controlled trial of VYXEOS vs 7+3 (cytarabine and daunorubicin) in adults with newly-diagnosed t-AML or AML-MRC<sup>1</sup>



- Second induction was highly recommended for patients who did not achieve a response and was mandatory for patients achieving >50% reduction in percent blasts<sup>1</sup>
- Postremission therapy with HSCT was permitted either in place of or after consolidation chemotherapy<sup>1</sup>
- *In the Phase 3 trial, a bone marrow assessment following induction was done between Days 14 and 21<sup>4</sup>*

## 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<sup>2</sup> have been associated with an increased incidence of drug-induced congestive heart failure. The tolerable limit appears lower (400 mg/m<sup>2</sup>) 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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AML-MRC=AML with myelodysplasia-related changes; HSCT=hematopoietic stem cell transplant; PS=performance status; t-AML=therapy-related AML.

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# Chemotherapy and patient management in the outpatient setting

In recent years there has been a shift to delivering chemotherapy and managing some associated side effects in the outpatient setting<sup>5</sup>

The decision for outpatient chemotherapy depends on a comprehensive evaluation of patient characteristics that may include<sup>6</sup>:



It is important to prepare patients for the possibility of hospital admittance to manage complications that may occur<sup>6</sup>

The administration schedule for VYXEOS supports the opportunity for treatment in the outpatient setting for appropriate patients<sup>1,2</sup>

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<sup>2</sup>

Although few patients in the Phase 3 trial received induction with VYXEOS in an outpatient setting, **51% of patients received consolidation therapy as outpatients<sup>2</sup>**

Outpatient administration may decrease the number of days a patient needs to be hospitalized for treatment

## 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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## Two small, postapproval, single-institution studies assessed the feasibility of patients receiving VYXEOS induction in the inpatient/outpatient (IPOP) setting<sup>7,8,a</sup>

Treatment in the IPOP setting **enables appropriate patients to receive induction in an outpatient setting**<sup>7</sup>

- The institution must have the necessary infrastructure to support an IPOP approach (eg, blood product support<sup>6</sup>)
- The IPOP treatment plan includes an inpatient admission for continued monitoring and subsequent treatment



- 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 facility<sup>7</sup>
- 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 center<sup>8</sup>
- IPOP-eligible patients who received VYXEOS infusions in an outpatient setting were closely monitored.<sup>7,8</sup> In the Kubal et al study, patients were evaluated each day with CBC, CMP, and uric acid and phosphorus measures. Planned admission occurred on Day 6 for continued care<sup>7</sup>
- In the Deutsch et al study, patients were monitored at least every other day until count recovery and admitted for continued care if complications occurred<sup>8</sup>

### 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<sup>7</sup>

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<sup>8</sup>

## 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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<sup>a</sup>In the VYXEOS Phase 3 trial, most patients received induction in an inpatient setting.<sup>12</sup>

CBC=complete blood count; CMP=comprehensive metabolic panel; ECOG=Eastern Cooperative Oncology Group.

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# Summary

## 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<sup>1</sup>

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

## The administration schedule for VYXEOS supports the opportunity for treatment in an outpatient setting<sup>1,2</sup>



**51% of patients received consolidation with VYXEOS in an outpatient setting in the Phase 3 trial<sup>2</sup>**

## 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. 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.

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**Visit [vyxeospro.com](https://www.vyxeospro.com) to explore clinical data and learn how a full VYXEOS course can benefit your patients with newly-diagnosed sAML subtypes t-AML or AML-MRC<sup>1</sup>**

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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%).

Please see **full Prescribing Information, including BOXED Warning.**

**References:** 1. VYXEOS [package insert]. Palo Alto, CA: Jazz Pharmaceuticals. 2. 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. 3. Lancet JE, Uy GL, Cortes JE, et al. CPX-351 (cytarabine and daunorubicin) liposome for injection versus conventional cytarabine plus daunorubicin in older patients with newly diagnosed secondary acute myeloid leukemia. *J Clin Oncol.* 2018;36(26):2684-2692. 4. Data on file. VYX-2018-003. Palo Alto, CA: Jazz Pharmaceuticals. 5. 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. 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. 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. 8. Deutsch YE, Presutto JT, Brahim A, et al. 3559 Safety and feasibility of outpatient liposomal daunorubicin and cytarabine (Vyxeos) induction and management in patients with secondary AML. Paper presented at: American Society of Hematology Annual Meeting; December 1-4, 2018; San Diego, CA.