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

# A GUIDE FOR NURSES AND PHARMACISTS

A guide to dosing and administering VYXEOS, including ordering and reimbursement information

Visit **vyxeospro.com** for helpful tools and videos, including additional outpatient support

90-minute infusions that may allow for **OUTPATIENT ADMINISTRATION FOR APPROPRIATE PATIENTS**[1,2]

NCCN

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)**[3,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.**

**Please see additional Important Safety Information on page 13 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.[3]



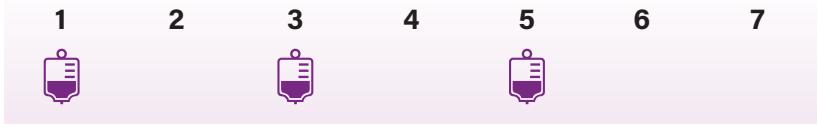
AML=acute myeloid leukemia; AML-MRC=AML with myelodysplasia-related changes; CMML=chronic myelomonocytic leukemia; MDS=myelodysplastic syndromes; NCCN=National Comprehensive Cancer Network.

# VYXEOS is a fixed course of therapy that allows patients time off sAML treatment[1,a,b]

**FIRST INDUCTION**

**90-min infusions**

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




*Administer first consolidation cycle 5 to 8 weeks after the start of the last induction*[1]

**CONSOLIDATION**

**90-min infusions**

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


***The majority of patients received induction with VYXEOS in an inpatient setting during the Phase 3 trial*[4]**

**Second induction** (if needed)[1]

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

***51% of patients received consolidation with VYXEOS in an outpatient setting during the Phase 3 trial*[2]**

**Second consolidation** (if needed)[1]

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

## Dosing considerations

- Prior to initiating each cycle, calculate the prior cumulative anthracycline exposure for the patient[1]
- Assess cardiac function, complete blood counts, and liver and renal function before each consolidation cycle[1]
- 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[1]

[a]Patients may receive up to 2 cycles of induction and up to 2 cycles of consolidation.[1]

[b]All infusions administered intravenously.[1]



# Dosing designed with patients in mind[1,2]

- **Fixed dosing regimen**
- **Allows patients time off sAML treatment**
- **Outpatient opportunity for appropriate patients, based on assessment of patient and institutional factors**
- **90-minute infusions**

- 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[2,4]
  - Most patients in the Phase 3 trial received induction in an inpatient setting[4]
  - Outpatient administration may decrease the number of days a patient needs to be hospitalized for treatment[2]

**Study Design**[1,5]
The Phase 3 study was a randomized, multicenter, open-label, active-controlled superiority study of VYXEOS (N=153) versus cytarabine and daunorubicin (7+3) (N=156) in patients 60 to 75 years of age with newly-diagnosed t-AML or AML-MRC (N=309). Efficacy was established on the basis of overall survival from the date of randomization to death from any cause.[1]

VYXEOS 44 mg/100 mg per m$^2$ (daunorubicin/cytarabine) was given intravenously on Days 1, 3, and 5 for first induction and on Days 1 and 3 for those needing a second induction. For consolidation, the VYXEOS dose was 29 mg/65 mg per m$^2$ (daunorubicin/cytarabine) on Days 1 and 3. In the 7+3 arm, first induction was cytarabine 100 mg/m$^2$/day on Days 1-7 by continuous infusion + daunorubicin 60 mg/m$^2$/day on Days 1-3. For second induction and consolidation, cytarabine was dosed on Days 1-5 and daunorubicin on Days 1 and 2. Patients could receive up to 2 cycles of induction and 2 cycles of consolidation in each arm. Subsequent induction was highly recommended for patients who did not achieve a response and was mandatory for patients achieving >50% reduction in percent blasts.[1]

A preplanned overall survival analysis was conducted based on the final 5-year follow-up results from the Phase 3 trial.[5]

## IMPORTANT SAFETY INFORMATION

### Contraindications

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

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t-AML=therapy-related AML.

# Factors to consider for outpatient administration with VYXEOS[a]

## PATIENT FACTORS

### 1 Deemed stable by medical team[6-9]

- ECOG PS 0-1 and no significant comorbidities such as kidney or cardiopulmonary diseases or active uncontrolled infections

### 2 Capable of self-care activities[6,8]

- 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[6,8]

- Ability to consistently attend all scheduled visits for treatment and monitoring

## INSTITUTIONAL FACTORS

### 1 Timely access to supportive care that may include[6,8]

- Blood and platelet transfusion support
- Prophylactic antimicrobial implementation

### 2 A multidisciplinary team that can[6,8]

- 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 for[6]

- Unplanned admission due to urgent adverse events

## IMPORTANT SAFETY INFORMATION

### Warnings and Precautions

**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]Most patients in the Phase 3 trial received induction in an inpatient setting.[4]

ECOG=Eastern Cooperative Oncology Group; PS=performance status.



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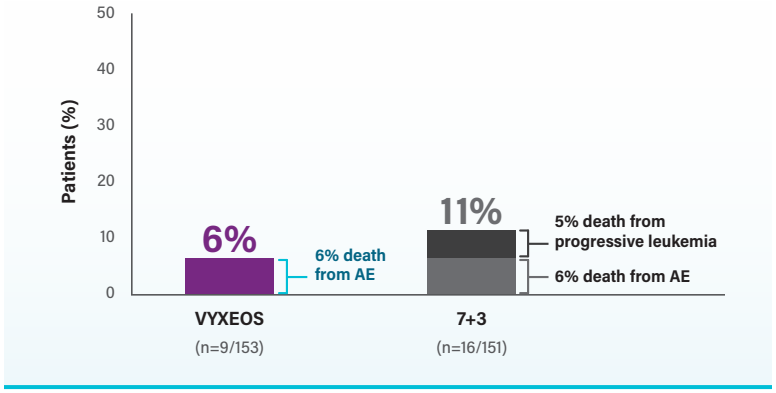
# VYXEOS was associated with lower 30- and 60-day mortality rates compared to 7+3[1,a]

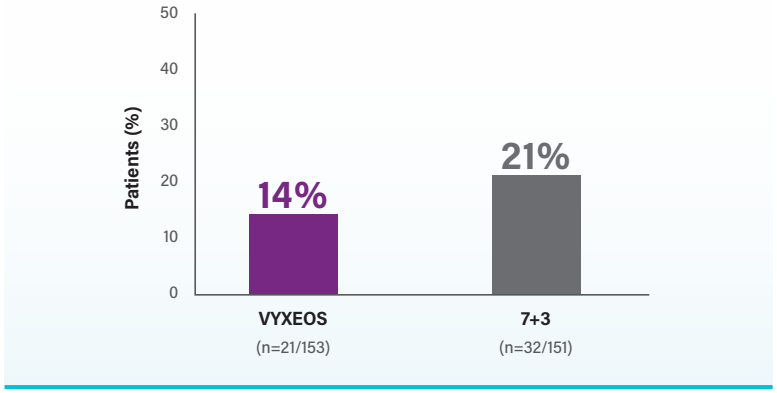
**30-DAY**

***overall all-cause mortality in sAML patients aged 60-75 (safety population[b])[1]***




**60-DAY**

***overall all-cause mortality in sAML patients aged 60-75 (safety population[b])[1]***




- 9 patients each in the VYXEOS arm (6%) and control arm (6%) had a fatal adverse reaction on treatment or within 30 days of treatment that was not in the setting of progressive disease[1]
- 8 patients in the control arm (5%) died within 30 days of treatment due to progressive leukemia[1]
- Fatal adverse reactions in the VYXEOS arm included infection, CNS hemorrhage, and respiratory failure[1]

## 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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[a]Cytarabine 100 mg/m$^2$ and daunorubicin 60 mg/m$^2$.[1]

[b]The safety population included all patients in the VYXEOS cohort and 151 patients from the 7+3 cohort (5 patients withdrew consent before the receipt of treatment).[10]

AE=adverse event; CNS=central nervous system.

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# Safety profile consistent with 7+3 in the Phase 3 trial[1]

Fatal treatment-emergent CNS hemorrhage not in the setting of progressive disease occurred in 2% of patients in the VYXEOS arm and 0.7% in the control arm[1]

***Common adverse reactions (≥20% incidence in all grades in the VYXEOS arm) during the induction phase[1]***

| ADVERSE REACTION | ALL GRADES[a] | |
|---|---|---|
| | VYXEOS (N=153) n (%) | 7+3 (N=151) n (%) |
| **Hemorrhage** | 107 (70) | 74 (49) |
| **Febrile neutropenia** | 104 (68) | 103 (68) |
| **Rash** | 82 (54) | 55 (36) |
| **Edema** | 78 (51) | 90 (60) |
| **Nausea** | 72 (47) | 79 (52) |
| **Diarrhea/colitis** | 69 (45) | 100 (66) |
| **Mucositis** | 67 (44) | 69 (46) |
| **Constipation** | 61 (40) | 57 (38) |
| **Musculoskeletal pain** | 58 (38) | 52 (34) |
| **Abdominal pain** | 51 (33) | 45 (30) |
| **Cough** | 51 (33) | 34 (23) |
| **Headache** | 51 (33) | 36 (24) |
| **Dyspnea** | 49 (32) | 51 (34) |
| **Fatigue** | 49 (32) | 58 (38) |
| **Arrhythmia** | 46 (30) | 41 (27) |
| **Decreased appetite** | 44 (29) | 57 (38) |
| **Pneumonia** (excluding fungal) | 39 (26) | 35 (23) |
| **Sleep disorders** | 38 (25) | 42 (28) |
| **Bacteremia** (excluding sepsis) | 37 (24) | 37 (25) |
| **Vomiting** | 37 (24) | 33 (22) |
| **Chills** | 35 (23) | 38 (25) |
| **Hypotension** | 30 (20) | 32 (21) |
| **Non-conduction cardiotoxicity** | 31 (20) | 27 (18) |

Other adverse reactions that occurred in ≥10% of patients in the VYXEOS arm included: dizziness, fungal infection, hypertension, hypoxia, upper respiratory infections (excluding fungal), chest pain, pyrexia, catheter/device/injection site reaction, delirium, pleural effusion, anxiety, pruritus, sepsis (excluding fungal), hemorrhoids, petechiae, renal insufficiency, transfusion reactions, and visual impairment (except bleeding)[1]

Table below is a subset of common adverse reactions incidence table at left.

***Corresponding grade 3-5 common adverse reactions (≥20%) during the induction phase[1]***

| ADVERSE REACTION | GRADES 3 TO 5[a] | |
|---|---|---|
| | VYXEOS (N=153) n (%) | 7+3 (N=151) n (%) |
| **Hemorrhage** | 15 (10) | 9 (6) |
| **Febrile neutropenia** | 101 (66) | 102 (68) |
| **Rash** | 8 (5) | 2 (1) |
| **Edema** | 2 (2) | 5 (3) |
| **Nausea** | 1 (1) | 1 (1) |
| **Diarrhea/colitis** | 4 (3) | 10 (7) |
| **Mucositis** | 2 (1) | 7 (5) |
| **Constipation** | 0 | 0 |
| **Musculoskeletal pain** | 5 (3) | 4 (3) |
| **Abdominal pain** | 3 (2) | 3 (2) |
| **Cough** | 0 | 1 (1) |
| **Headache** | 2 (1) | 1 (1) |
| **Dyspnea** | 17 (11) | 15 (10) |
| **Fatigue** | 8 (5) | 8 (5) |
| **Arrhythmia** | 10 (7) | 7 (5) |
| **Decreased appetite** | 2 (1) | 5 (3) |
| **Pneumonia** (excluding fungal) | 30 (20) | 26 (17) |
| **Sleep disorders** | 2 (1) | 1 (1) |
| **Bacteremia** (excluding sepsis) | 35 (23) | 31 (21) |
| **Vomiting** | 0 | 0 |
| **Chills** | 0 | 0 |
| **Hypotension** | 7 (5) | 1 (1) |
| **Non-conduction cardiotoxicity** | 13 (9) | 15 (10) |

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[a]Adverse reactions were graded using National Cancer Institute Common Terminology Criteria for Adverse Events version 3.0.

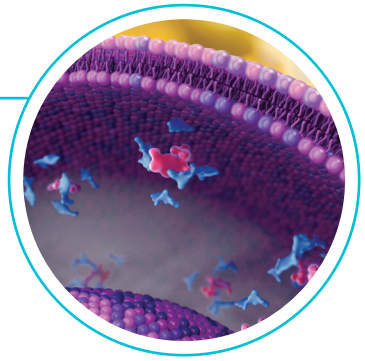
# Synergistic combination for potent delivery[1,11]

## VYXEOS (CPX-351) is a unique combination liposome, engineered to deliver 2 established therapies at a synergistic ratio[1,11]

***Based on animal studies[a]...***

### Increased activity vs free drug

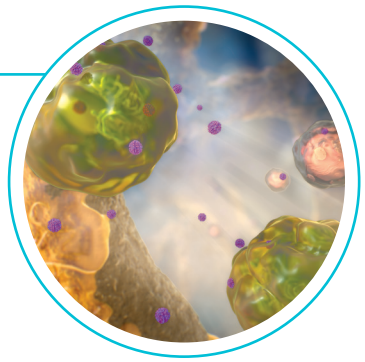
The synergistic 1:5 molar ratio of daunorubicin and cytarabine has been shown to enhance the killing of leukemia cells in vitro and in murine models[1]



### Greater leukemia cell uptake

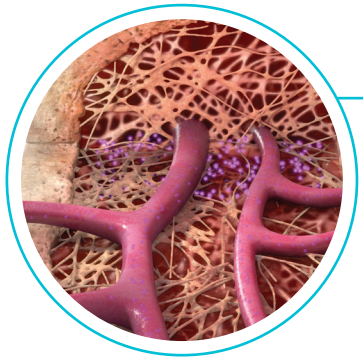
VYXEOS liposomes enter the bone marrow and are preferentially taken up by leukemia cells to a greater extent than by normal bone marrow cells in a murine model[1,12]

Their unique composition allows the negatively charged VYXEOS liposomes to interact with receptors that are overexpressed by leukemic cells compared to the expression by normal bone marrow cells[12,13]



[a]The clinical relevance of this is unknown.

***Based on pharmacokinetic Phase 1 trial data...***



### Prolonged delivery

The longer half-life of VYXEOS resulted in greater drug exposure within the plasma and bone marrow than traditional chemotherapy[1,14]

Estimated median half-life of daunorubicin was 32 hours with VYXEOS vs 19 hours as free drug[1,15]

Estimated median half-life of cytarabine was 40 hours with VYXEOS vs approximately 1 to 3 hours as free drug[1,16]

## 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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# Time to count recovery may be prolonged with VYXEOS and require monitoring[1]

***Neutrophil/platelet recovery in patients who achieved CR+CRi with induction[17]***

| | 1 INDUCTION | |
|---|---|---|
| | **VYXEOS (n=58)** | **7+3 (n=34)** |
| Median time to neutrophil recovery (≥500 neutrophils/µL), days | 35 | 29 |
| Median time to platelet recovery (≥50,000 platelets/µL), days | 36.5 | 29 |
| | **2 INDUCTIONS** | |
| | **VYXEOS (n=15)** | **7+3 (n=18)** |
| Median time to neutrophil recovery (≥500 neutrophils/µL), days | 35 | 28 |
| Median time to platelet recovery (≥50,000 platelets/µL), days | 35 | 24 |

***Neutrophil/platelet recovery in patients who achieved CR+CRi with consolidation[2]***

| | 1 CONSOLIDATION | |
|---|---|---|
| | **VYXEOS (n=25)** | **5+2 (n=20)** |
| Median (Q1-Q3) time to ANC recovery ≥500 neutrophils/µL, days | 35 (34-44) | 32.5 (29-43) |
| Median (Q1-Q3) time to platelet recovery ≥50,000 platelets/µL, days | 40 (35-43) | 30 (28-41) |
| | **2 CONSOLIDATIONS[a]** | |
| | **VYXEOS (n=23)** | **5+2 (n=12)** |
| Median (Q1-Q3) time to ANC recovery ≥500 neutrophils/µL, days | 36 (28-48) | 33.5 (27-39) |
| Median (Q1-Q3) time to platelet recovery ≥50,000 platelets/µL, days | 36 (28-47) | 31.5 (27-37) |

[a]Measured from the treatment start date.

CR=complete remission; CRi=complete remission with incomplete recovery; Q=quartile.

# Common practices to help manage myelosuppression and associated complications

## Frequent monitoring of ANC and platelets

**During profound neutropenia or until ANC returns to a clinically desired level, consider**

- A broad-spectrum antibiotic[18]

**If myelosuppressive complications occur, consider using these appropriate supportive measures**

- Colony-stimulating factors[3,19,20]
- Red blood cell and platelet transfusions[3,19]

## 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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# Hypersensitivity reactions

Serious or fatal hypersensitivity reactions, including anaphylactic reactions, have been reported with daunorubicin and cytarabine. Monitor patients for hypersensitivity reactions[1]

For hypersensitivity reactions of any grade/severity, interrupt VYXEOS infusion immediately and manage symptoms. Reduce the rate of infusion or discontinue treatment as outlined below[1]

**Mild symptoms[1]**

- Once symptoms resolve, reinitiate infusion slowly (halving the rate of infusion)
- Consider premedication with antihistamines and/or corticosteroids for subsequent doses

**Moderate symptoms[1]**

- Do not reinitiate infusion
- For subsequent doses, premedicate with antihistamines and/or corticosteroids prior to initiating infusion at same rate

**Severe or life-threatening hypersensitivity reactions[1]**

- Permanently discontinue VYXEOS
- Treat symptoms according to the standard of care
- Monitor until symptoms resolve

## 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.

**Please see additional Important Safety Information on page 13 and full Prescribing Information, including BOXED Warning.**

# Treatment considerations

***Considerations for patients with hepatic impairment[1]***

| BILIRUBIN ≤3 mg/dL | BILIRUBIN >3 mg/dL |
|---|---|
| The pharmacokinetics of total cytarabine and daunorubicin were ***NOT altered*** | The pharmacokinetics are ***UNKNOWN*** |

***Considerations for patients with renal impairment[1]***

| MILD OR MODERATE ($CL_{CR}$ 30 mL/min to 89 mL/min, as estimated by C-G) |
|---|
| Pharmacokinetics of total daunorubicin and cytarabine were ***NOT clinically significantly altered*** |

| SEVERE ($CL_{CR}$ 15 mL/min to 29 mL/min, as estimated by C-G) |
|---|
| The potential effects on the pharmacokinetics of daunorubicin and cytarabine administered as VYXEOS are ***UNKNOWN*** |

# Dosing calculation[1]

## Calculate the number of vials of VYXEOS needed based on the daunorubicin dose and the patient's BSA

***Calculate the required volume using the equation below:***

$$\frac{\text{Dose of daunorubicin (mg/m}^2\text{)} \times \text{patient's BSA (m}^2\text{)}}{\text{2.2 mg/mL}} = \textbf{mL volume required}$$

Each vial contains 20 mL of solution after reconstitution

BSA=body surface area; C-G=Cockcroft-Gault equation; $CL_{CR}$=creatinine clearance.

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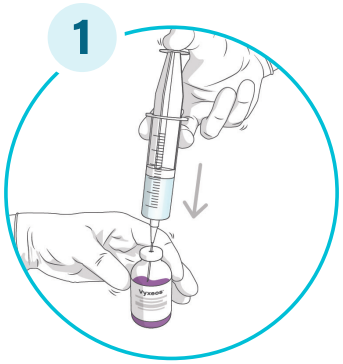
# Preparation and handling[1]

## VYXEOS is a cytotoxic drug. Follow applicable special handling and disposal procedures[1]

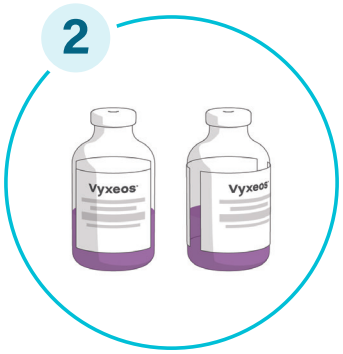
**Equilibrate the appropriate number of vials of VYXEOS to room temperature for 30 minutes[1]**

Reconstitute and further dilute VYXEOS prior to intravenous infusion[1]




**Reconstitute each vial with 19 mL of Sterile Water for Injection using a sterile syringe**

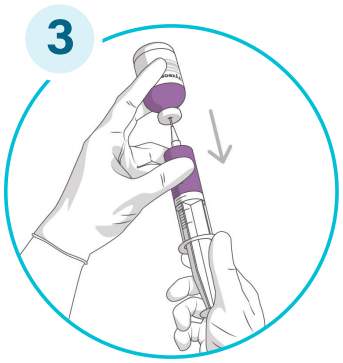
- **Carefully swirl the contents of the vial for 5 minutes** while gently inverting the vial every 30 seconds
- Do not heat, vortex, or shake vigorously



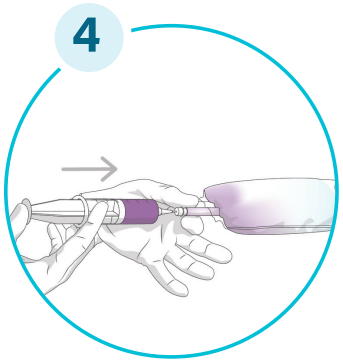

**After reconstitution, let rest for 15 minutes**

- The reconstituted product should be an opaque, purple, homogeneous dispersion, essentially free from visible particulates
- After reconstitution but before final dilution, each mL of VYXEOS will contain 2.2 mg of daunorubicin and 5 mg of cytarabine

***Use the reconstituted solution immediately. If needed, store the reconstituted solution in the vial refrigerated at 2°C to 8°C (36°F to 46°F) for up to 4 hours. Note that the reconstituted product in the vial and the reconstituted product which has been diluted into an infusion solution are stable for a total of 4 hours (not 4 hours each) when stored at 2°C to 8°C***




**Gently invert each vial 5 times and aseptically withdraw the calculated volume of reconstituted product from the vial(s) using a sterile syringe**




**Transfer the calculated volume to an infusion bag containing 500 mL of 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP**

- Discard any unused portion or residual product remaining in the vial and do not save any unused portions for later administration

**Gently invert the bag to mix the solution**

- The dilution of the reconstituted product results in a deep purple, translucent, homogeneous dispersion, free from visible particulates
- Only solutions without visible particulates should be used

***If the diluted infusion solution is not used immediately, store in a refrigerator at 2°C to 8°C (36°F to 46°F) for up to 4 hours. If the reconstituted solution in the vial was stored for 4 hours, the diluted infusion solution must be used immediately and cannot be stored for an additional 4 hours***

**Please see the VYXEOS full Prescribing Information for full preparation and handling instructions.**

## 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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USP=United States Pharmacopeia.

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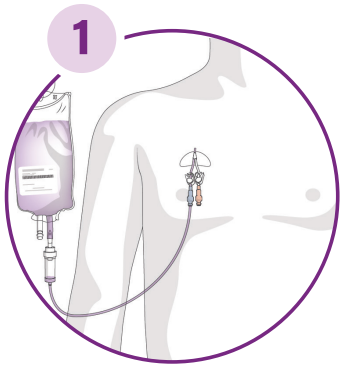
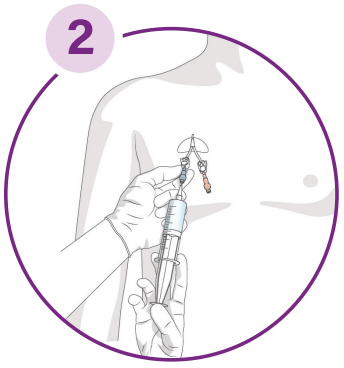
# Administration instructions[1]




**Administer VYXEOS by constant intravenous infusion over 90 minutes via an infusion pump through a central venous catheter or a peripherally inserted central catheter**

***An in-line membrane filter may be used for the intravenous infusion of VYXEOS, provided the minimum pore diameter of the filter is ≥15 µm***




**Flush the line after administration with 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP**

***Do not mix VYXEOS with, or administer as an infusion with, other drugs. VYXEOS is for IV use only***

## 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 additional Important Safety Information on page 13 and full Prescribing Information, including BOXED Warning.**

# Important patient counseling information[1]

## Hemorrhage

- Inform patients of the risk of fatal bleeding
- Advise patients of the need for periodic monitoring of blood counts and keeping scheduled appointments for blood work and necessary transfusions
- Advise patients to contact a healthcare provider for new onset fever or symptoms of infections or if they notice signs of bruising or bleeding

## Cardiotoxicity

- Advise patients to contact their healthcare provider if they develop symptoms of heart failure

## Hypersensitivity reactions

- Inform patients of the risk of hypersensitivity reactions, including anaphylaxis
- Describe the symptoms of hypersensitivity reactions, including anaphylaxis
- Instruct the patient to seek medical attention immediately if they experience such symptoms

## Embryo-fetal toxicity

- VYXEOS can cause fetal harm when administered during pregnancy
- Advise females of reproductive potential to use effective contraception during treatment and for 6 months following the last dose of VYXEOS
- Advise patients to inform their healthcare provider of a known or suspected pregnancy before and during treatment with VYXEOS

## Lactation

- Advise patients not to breastfeed during treatment with VYXEOS and for at least 2 weeks after the last dose

## Infertility

- Advise males of reproductive potential that VYXEOS may cause temporary or permanent infertility

## Concomitant medications

- Advise patients to speak with their physicians about any other medication they are currently taking

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



IV=intravenous.

# VYXEOS reimbursement

## J code issued for VYXEOS

***Permanent, product-specific HCPCS J code for VYXEOS***

| | DOSAGE |
|---|---|
| **J9153** | Injection, liposomal, 1 mg daunorubicin and 2.27 mg cytarabine |
| | **BILLING** |
| | Units per dose: 1 |
| | Units per vial: 44 |

# Ordering and storage information

## Ordering

VYXEOS can be ordered in cartons containing 2 or 5 vials through your supplier

***Carton containing 5 vials[1]:***
NDC 68727-745-05

***Carton containing 2 vials[1]:***
NDC 68727-745-02

## VYXEOS is now partnering with certain group purchasing organizations (GPOs)

- ION Solutions (AmerisourceBergen)
- Onmark GPO (McKesson Specialty Health)
- Unity GPO (The US Oncology Network/McKesson Specialty Health
- VitalSource (Cardinal Health)

## Storing and handling[1]

- Store unreconstituted VYXEOS vials in a refrigerator at 2°C to 8°C (36°F to 46°F) in an upright position
- The vial should be stored in its original carton to protect from light
- VYXEOS is a cytotoxic drug. Follow applicable special handling and disposal procedures

HCPCS=Healthcare Common Procedure Coding System.

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Jazz Cares™
Making a difference in Patients' lives, one Patient at a time

The JazzCares Program is sponsored by Jazz Pharmaceuticals to help improve access to Jazz products for appropriate patients. Dedicated JazzCares specialists are available to assist patients and practices with coverage and reimbursement support for Jazz products

## Ask our JazzCares specialists about...

**Understanding insurance coverage**

Resources to help patients understand their insurance coverage and find information on sources of financial support

**Paying for medication**
(commercially insured patients only)[a]

Only available for certain Jazz products

Provides eligible patients with assistance for out-of-pocket costs, subject to annual maximum

**Free-drug program for eligible patients**

Designed to provide Jazz products at no cost to patients who are uninsured or deemed uninsured due to lack of coverage for a Jazz product. Subject to financial and residency eligibility criteria

***Call the support hotline 1-833-533-JAZZ (5299), Monday through Friday between 8 AM and 8 PM ET to speak with a representative***

[a]Insurance coverage and plans may vary. The JazzCares Program provides general information only and is not a guarantee of any coverage or reimbursement outcome. All treatment decisions rest solely with the treating physician or qualified healthcare professional.

You can also request to be contacted by an Access and Reimbursement Manager (ARM) to assist you with additional reimbursement-related questions.

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# VYXEOS distribution partners

## Specialty Distributors

VYXEOS (daunorubicin and cytarabine) is available for purchase from the authorized Specialty Distributors listed here. Verify that your facility has an account with their Specialty Distributor before ordering. If not, they should contact their Specialty Distributor. The facility should also contact their Specialty Distributor with questions regarding product returns.

### AmerisourceBergen

#### ASD Healthcare

***Online***
https://www.asdhealthcare.com

***Phone***
1-800-746-6273

***Fax***
1-800-547-9413

***Email***
asd.customerservice@asdhealthcare.com

#### Oncology Supply

***Online***
https://www.oncologysupply.com

***Phone***
1-800-633-7555

***Fax***
1-800-248-8205

***Email***
custserv@oncologysupply.com

### Cardinal Health

#### Cardinal Specialty Pharmaceutical Distribution

***Online***
Order Express (hospitals): https://orderexpress.cardinalhealth.com
Specialty Online (clinics): https://specialtyonline.cardinalhealth.com

***Phone***
1-877-453-3972

***Fax***
1-877-274-9897

***Email***
SPDOncologyTeam@cardinalhealth.com

### McKesson

#### McKesson Plasma and Biologics

***Online***
http://connect.mckesson.com

***Phone***
1-877-625-2566

***Fax***
1-888-752-7626

***Email***
MPBOrders@mckesson.com

#### McKesson Specialty Health

***Online***
http://mscs.mckesson.com

***Phone***
1-800-482-6700

***Fax***
1-800-289-9285

***Email***
MSH-CustomerCare@mckesson.com

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# Important Safety Information

## 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.

## Warnings and Precautions

**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.

**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.

## Warnings and Precautions, continued

**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.

**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.

**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%).

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**References: 1.** VYXEOS [package insert]. Palo Alto, CA: Jazz Pharmaceuticals. **2.** 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. **3.** 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. **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). Presented at: American Society of Clinical Oncology Annual Meeting; June 2-6, 2017; Chicago, IL. Poster 7036. **5.** Lancet JE, Uy GL, Newell LF, et al. Five-year final results of a phase 3 study of CPX-351 versus 7+3 in older adults with newly diagnosed high-risk/secondary AML. Presented at: American Society of Clinical Oncology ASCO20 Virtual Scientific Program; May 29-31, 2020. Poster 283. **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.** 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. **8.** 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. **9.** 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. **10.** 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. **11.** Mayer LD, Tardi P, Louie AC. CPX-351: a nanoscale liposomal co-formulation of daunorubicin and cytarabine with unique biodistribution and tumor cell uptake properties. *Int J Nanomedicine.* 2019;14:3819-3830. **12.** Lim WS, Tardi PG, Dos Santos N, et al. Leukemia-selective uptake and cytotoxicity of CPX-351, a synergistic fixed-ratio cytarabine:daunorubicin formulation, in bone marrow xenografts. *Leuk Res.* 2010;34(9):1214-1223. **13.** Dicko A, Kwak S, Frazier AA, et al. Biophysical characterization of a liposomal formulation of cytarabine and daunorubicin. *Int J Pharm.* 2010;391(1-2):248-259. **14.** Feldman EJ, Lancet JE, Kolitz JE, et al. First-in-man study of CPX-351: a liposomal carrier containing cytarabine and daunorubicin in a fixed 5:1 molar ratio for the treatment of relapsed and refractory acute myeloid leukemia. *J Clin Oncol.* 2011;29(8):979-985. **15.** Daunorubicin hydrochloride injection [package insert]. Eatontown, NJ: Hikma Pharmaceuticals USA, Inc; 2015. **16.** Cytarabine injection [package insert]. Lake Forest, IL: Hospira, Inc; 2019. **17.** Supplement to: 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. **18.** Roe H, Lennan E. Role of nurses in the assessment and management of chemotherapy-related side effects in cancer patients. *Nurs: Res Rev*. 2014;4:103-115. **19.** Data on File (VYX-2018-014). Jazz Pharmaceuticals, Inc. **20.** Smith TJ, Khatcheressian J, Lyman GH, et al. 2006 update of recommendations for the use of white blood cell growth factors: an evidence-based clinical practice guideline. *J Clin Oncol*. 2006;24(19):3187-3205.

Jazz Pharmaceuticals