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.

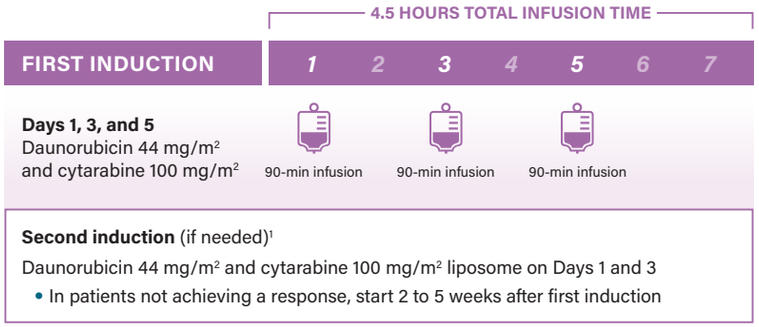
[a]Category 1: Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.[3]

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 from sAML treatment[1,a]

Dosing includes up to 2 cycles of induction and up to 2 cycles of consolidation[1]



Second induction (if needed)[1]

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

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

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

Second consolidation (if needed)[1]

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

Of the 49 patients who received first consolidation with VYXEOS, 51% (n=25) received consolidation in an outpatient setting during the Phase 3 trial[2]

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]

The dosing schedule for VYXEOS allows for flexible administration through:

- ✓ **A fixed induction and consolidation dosing regimen over the course of therapy[1,2]**
- ✓ **Opportunity for outpatient treatment with appropriate patients[1,2]**
- ✓ **On-site infusion with VYXEOS that ensures patients are receiving treatment[1]**
  - 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]
    - Almost all 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 m² (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 m² (daunorubicin/cytarabine) on Days 1 and 3. In the 7+3 arm, first induction was cytarabine 100 mg/m²/day on Days 1-7 by continuous infusion + daunorubicin 60 mg/m²/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 prospectively planned overall survival analysis of the ITT population was conducted based on the final 5-year follow-up results from the Phase 3 trial.[5] Exploratory post hoc subgroup analyses were also conducted.

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.

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

[a]VYXEOS is administered by constant intravenous infusion over 90 minutes via an infusion pump through a central venous catheter or peripherally inserted central catheter.[1]

sAML=secondary AML.

ITT=intent to treat; t-AML=therapy-related AML.

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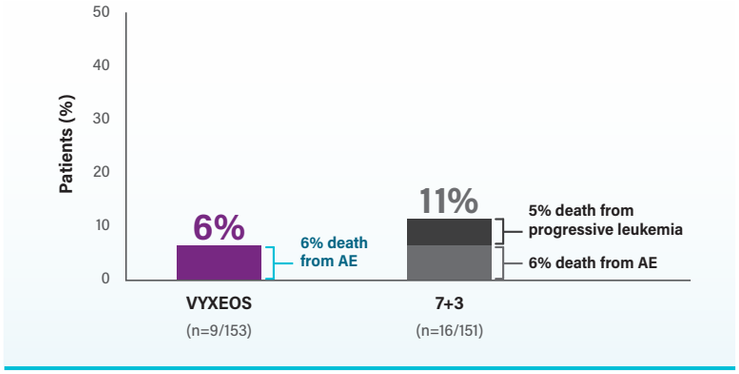
VYXEOS was associated with lower 30- and 60-day mortality rates compared to 7+3[1,a]

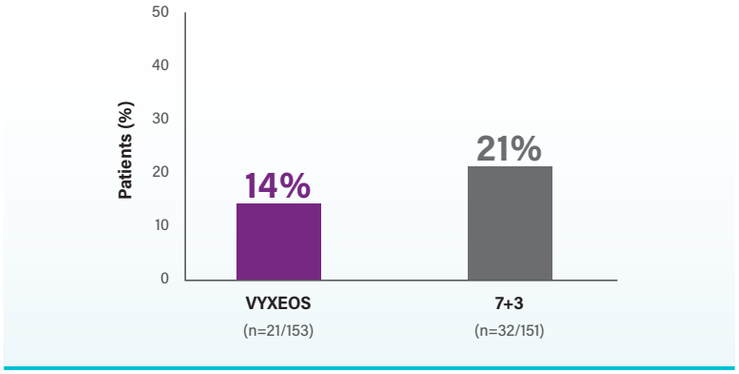
30-DAY

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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VYXEOS safety profile 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 (7+3)[1]

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

ADVERSE REACTION	ALL GRADES[a]		GRADES 3 TO 5[a]	
	VYXEOS (N=153) n (%)	7+3 (N=151) n (%)	VYXEOS (N=153) n (%)	7+3 (N=151) n (%)
Hemorrhage	107 (70)	74 (49)	15 (10)	9 (6)
Febrile neutropenia	104 (68)	103 (68)	101 (66)	102 (68)
Rash	82 (54)	55 (36)	8 (5)	2 (1)
Edema	78 (51)	90 (60)	2 (2)	5 (3)
Nausea	72 (47)	79 (52)	1 (1)	1 (1)
Diarrhea/colitis	69 (45)	100 (66)	4 (3)	10 (7)
Mucositis	67 (44)	69 (46)	2 (1)	7 (5)
Constipation	61 (40)	57 (38)	0	0
Musculoskeletal pain	58 (38)	52 (34)	5 (3)	4 (3)
Abdominal pain	51 (33)	45 (30)	3 (2)	3 (2)
Cough	51 (33)	34 (23)	0	1 (1)
Headache	51 (33)	36 (24)	2 (1)	1 (1)
Dyspnea	49 (32)	51 (34)	17 (11)	15 (10)
Fatigue	49 (32)	58 (38)	8 (5)	8 (5)
Arrhythmia	46 (30)	41 (27)	10 (7)	7 (5)
Decreased appetite	44 (29)	57 (38)	2 (1)	5 (3)
Pneumonia (excluding fungal)	39 (26)	35 (23)	30 (20)	26 (17)
Sleep disorders	38 (25)	42 (28)	2 (1)	1 (1)
Bacteremia (excluding sepsis)	37 (24)	37 (25)	35 (23)	31 (21)
Vomiting	37 (24)	33 (22)	0	0
Chills	35 (23)	38 (25)	0	0
Hypotension	30 (20)	32 (21)	7 (5)	1 (1)
Non-conduction cardiotoxicity	31 (20)	27 (18)	13 (9)	15 (10)

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]

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Time to recovery of absolute neutrophil count and platelets may be prolonged with VYXEOS and require additional monitoring[1]

- Incidences of Grade 3 thrombocytopenia[b] were prolonged in the absence of active leukemia in 28% (16/58) of patients in the VYXEOS arm and 12% (4/34) in the 7+3 arm during Induction 1 and in 25% (12/48) in the VYXEOS arm and 16% (5/32) in the 5+2 arm during Consolidation 1[c]
- Incidences of Grade 4 neutropenia[b] were prolonged in the absence of active leukemia in 17% (10/58) of patients in the VYXEOS arm and 3% (1/34) in the 7+3 arm during Induction 1 and in 10% (5/48) in the VYXEOS arm and 3% (1/32)in the 5+2 arm during Consolidation 1[c]

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

[b]Platelets <50 Gi/L or neutrophils <0.5 Gi/L lasting past cycle day 42 in the absence of active leukemia.[1]

[c]Patients receiving at least 1 consolidation.[1]

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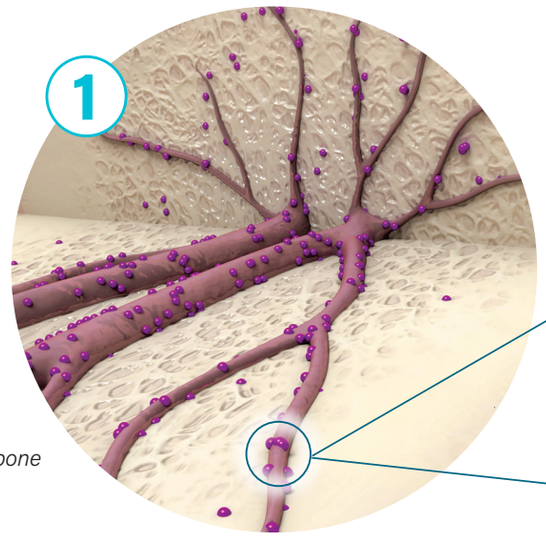
Synergistic combination for coordinated delivery[1,11]

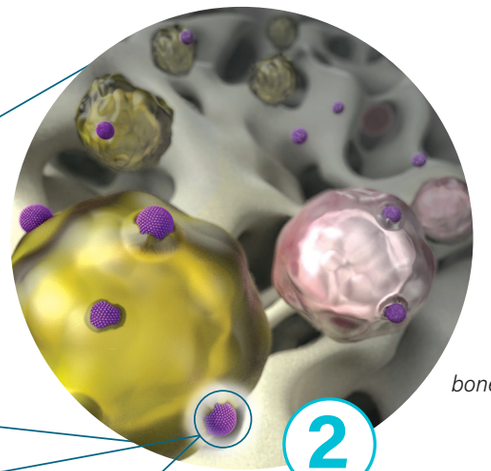
VYXEOS (CPX-351) is a combination liposome that coordinates the pharmacokinetics of 2 drugs to provide delivery at a synergistic 1:5 molar ratio[1,11]

Based on animal studies[a]...

Delivery to the bone marrow

VYXEOS liposomes enter and persist in the bone marrow[1]





Greater leukemia cell uptake and killing of leukemic cells

The synergistic 1:5 molar ratio of daunorubicin and cytarabine has demonstrated increased activity vs free drug in vitro and in murine models, thereby enhancing the killing of leukemia cells[1,11]

Based on pharmacokinetic Phase 1 trial data...

Prolonged exposure

VYXEOS is released into the intracellular environment and has a longer half-life than traditional daunorubicin and cytarabine, which results in greater drug exposure within the plasma and bone marrow than traditional chemotherapy[1,12]

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] The clinical relevance of this is unknown.

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

Neutrophil/platelet recovery in patients who achieved CR+CRi with induction[13]

	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 neutrophil or platelet 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[14]

If myelosuppressive complications occur, consider using these appropriate supportive measures

- Colony-stimulating factors[3,15,16]
- Red blood cell and platelet transfusions[3,15]

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 (CL_{CR} 60 mL/min to 89 mL/min, as estimated by C-G)
Dosage adjustment is not required.

MODERATE (CL_{CR} 30 mL/min to 59 mL/min, as estimated by C-G)
Dosage adjustment is not required. However, comparing to patients with normal renal function (n=7, CL_{CR} ≥90 mL/min), patients with moderate renal impairment (n=8, CL_{CR} 30 to 59 mL/min) showed 8% and 6% decrease, respectively, in the mean AUC_{tau} of total cytarabine and daunorubicin in a dedicated study

SEVERE (CL_{CR} 15 mL/min to 29 mL/min, as estimated by C-G)
Dosage adjustment is not required. However, comparing to patients with normal renal function (n=7, CL_{CR} ≥90 mL/min), patients with severe renal impairment (n=6, CL_{CR} 15 to 29 mL/min) showed 0.4% increase and 3% decrease, respectively, in the mean AUC_{tau} of cytarabine and daunorubicin in a dedicated study

VXYEOS has not been studied in patients with end-stage renal disease on hemodialysis.[1]

Dosing calculation[1]

Calculate the number of vials of VYXEOS needed based on the daunorubicin dose and the patient's BSA[1]

Calculate the required volume using the equation below:

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

Each vial contains 20 mL of solution after reconstitution.[17]

AUC_{tau}=area under concentration-time curve over dosing interval; BSA=body surface area; C-G=Cockcroft-Gault equation; CL_{CR}=creatinine clearance.

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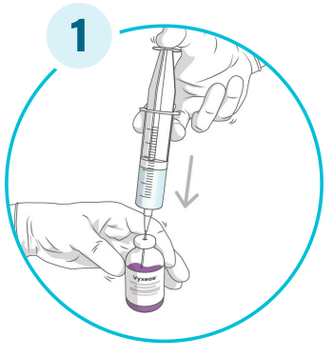
Preparation and handling[1]

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

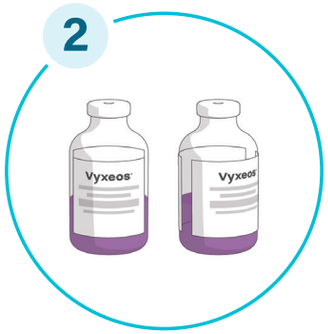
Equilibrate the appropriate number of vials of VYXEOS to room temperature for 30 minutes[1]

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

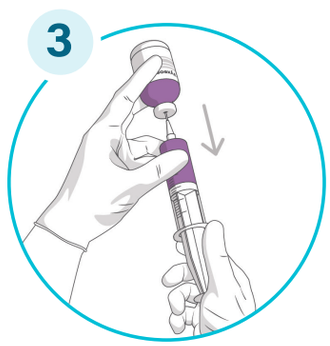
- **Carefully swirl the contents of the vial for 5 minutes** while gently inverting the vial every 30 seconds
- Do not heat, vortex, or shake vigorously



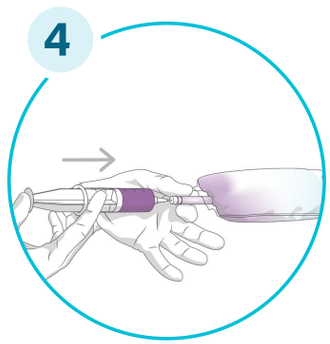
After reconstitution, let rest for 15 minutes

- 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

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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Please see the VYXEOS full Prescribing Information for complete preparation and handling instructions, including BOXED Warning.

USP=United States Pharmacopeia.

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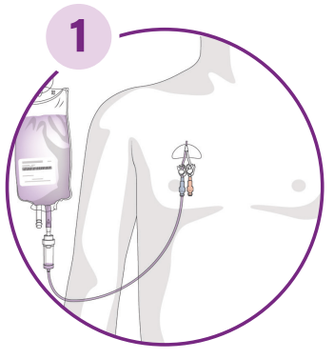
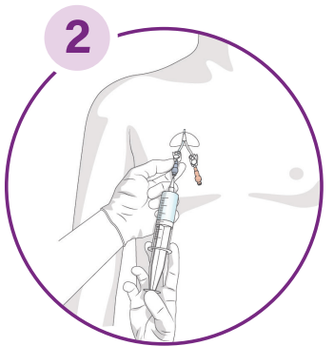
Administration instructions[1]



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%) are 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 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 and support

J code issued for VYXEOS

Permanent, product-specific HCPCS J code for VYXEOS

J9153	**DOSAGE**
	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 vials through your supplier

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 hazardous drug. Follow applicable special handling and disposal procedures

HCPCS=Healthcare Common Procedure Coding System.

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

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

Visit www.jazzcares.com/hcp/vyxeos or 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.

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

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

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

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%) are 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.3.2022. ©National Comprehensive Cancer Network, Inc. 2022. All rights reserved. Accessed January 13, 2023. 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. CPX-351 versus 7+3 cytarabine and daunorubicin chemotherapy in older adults with newly diagnosed high-risk or secondary acute myeloid leukaemia: 5-year results of a randomised, open-label, multicentre, phase 3 trial. *Lancet Haematol.* 2021;8(7):e481-e491. **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.** 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. **13.** 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. **14.** 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. **15.** Data on File (VYX-2018-014). Jazz Pharmaceuticals, Inc. **16.** 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. **17.** Data on File (VYX-2022-022). Jazz Pharmaceuticals, Inc.

Jazz Pharmaceuticals