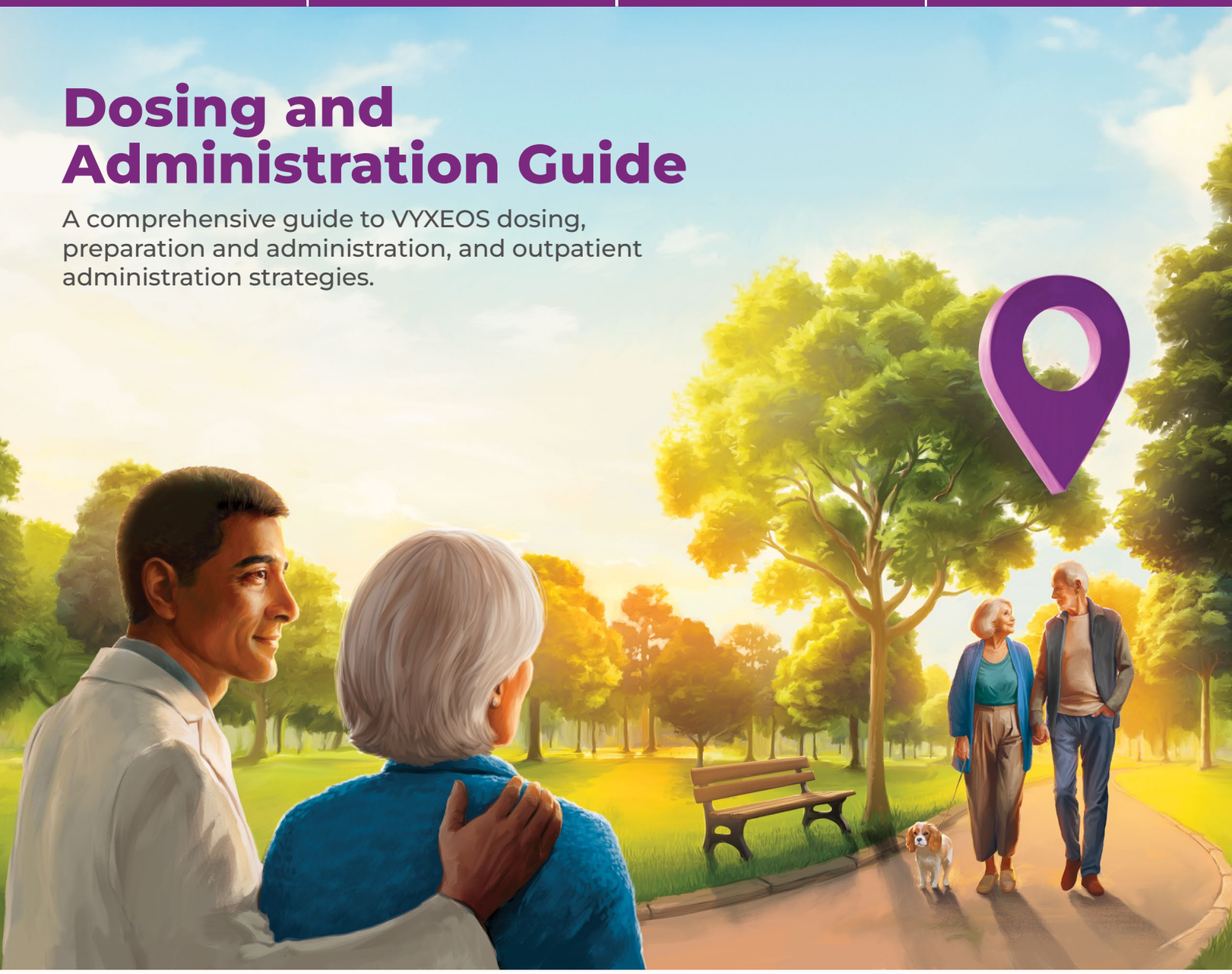
Vyxeos®
(daunorubicin and cytarabine) 44 mg/100 mg per vial
liposome for injection

Dosing and Administration Guide

A comprehensive guide to VYXEOS dosing, preparation and administration, and outpatient administration strategies.



INDICATION

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

IMPORTANT SAFETY INFORMATION

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

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

Contraindications

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

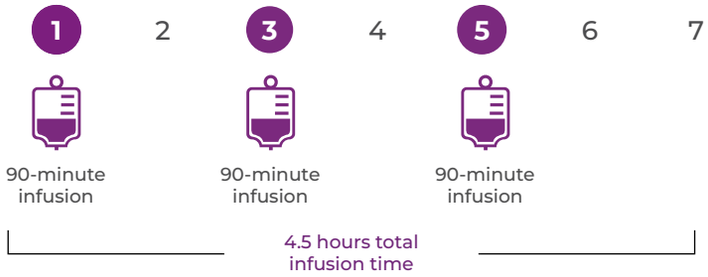
Please see additional Important Safety Information throughout and full Prescribing Information, including BOXED Warning.

VYXEOS PROVIDES A FINITE TREATMENT DURATION[1,a]

VYXEOS is administered through up to 2 cycles of induction and consolidation[1]

FIRST INDUCTION

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



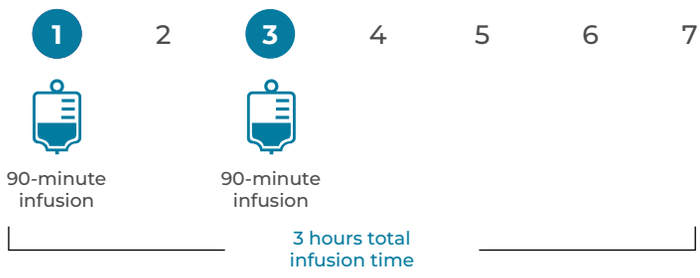
Second induction (if needed)
Daunorubicin 44 mg/m^2 and cytarabine 100 mg/m^2 liposome on Days 1 and 3

For patients who do not achieve a response after first induction, a **second induction** may be started **2 to 5 weeks later** at the same dose on Days 1 and 3.

CONSOLIDATION

Patients could receive consolidation or proceed to HSCT.

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



Second consolidation (if needed)
Daunorubicin 29 mg/m^2 and cytarabine 65 mg/m^2 liposome on Days 1 and 3

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

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

HSCT=hematopoietic stem cell transplantation.
[a]All infusions administered intravenously.

IMPORTANT SAFETY INFORMATION (cont'd)

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.

Please see additional Important Safety Information throughout and full Prescribing Information, including BOXED Warning.

DOSING CONSIDERATIONS

Consider patient fitness before beginning treatment[1]

- 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 >0.5 Gi/L and the platelet count recovers to >50 Gi/L in the absence of unacceptable toxicity
- In the Phase 3 study, VYXEOS was evaluated in patients aged 60-75 years

THE DOSING SCHEDULE FOR VYXEOS ALLOWS FOR FLEXIBLE ADMINISTRATION THROUGH[1,2]:

- A fixed induction and consolidation dosing regimen over the course of therapy
- The opportunity for outpatient treatment with appropriate patients
- On-site infusion with VYXEOS that ensures patients are receiving treatment

- In the Phase 3 study, site of induction and consolidation administration—inpatient vs outpatient—was not defined. The decision was left to the discretion of the investigators according to the standard practices of their institution[3]
  - Almost all patients in the Phase 3 study received induction in an inpatient setting
- Outpatient administration may decrease the number of days a patient needs to be hospitalized for treatment[2]

IMPORTANT SAFETY INFORMATION (cont'd)

Warnings and Precautions (cont'd)

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.

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.

Please see additional Important Safety Information throughout and full Prescribing Information, including BOXED Warning.

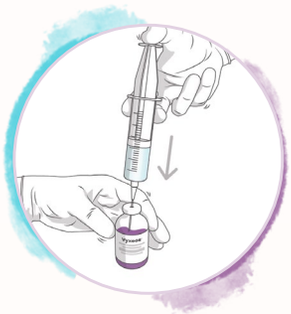
PREPARATION AND ADMINISTRATION

VYXEOS is straightforward to prepare for infusion by following these 3 steps[1]

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

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

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

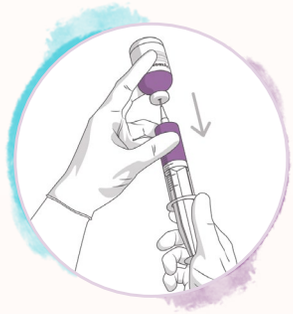
After reconstitution, let product rest for 15 minutes

VYXEOS is reconstituted when the product is 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.

Calculate the appropriate volume of VYXEOS for intravenous infusion.



2

Use the formula on the next page to calculate how much VYXEOS needs to be administered to your patient

- **The number of VYXEOS vials needed is based on the daunorubicin dose and the patient's body surface area (BSA)**

Gently invert each vial 5 times prior to withdrawing the reconstituted product for further dilution.

GO TO STEP 3

IMPORTANT SAFETY INFORMATION (cont'd)

Warnings and Precautions (cont'd)

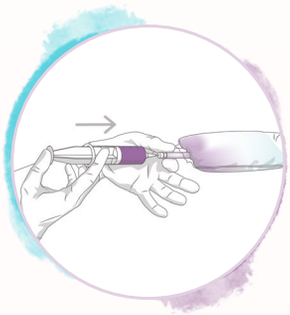
Copper Overload
VYXEOS contains copper. Consult with a hepatologist and nephrologist with expertise in managing acute copper toxicity in patients with Wilson's disease treated with VYXEOS. Monitor total serum copper, serum non-ceruloplasmin-bound copper, 24-hour urine copper levels, and serial neuropsychological 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.

Please see additional Important Safety Information throughout and full Prescribing Information, including BOXED Warning.

PREPARATION AND ADMINISTRATION

VYXEOS is straightforward to prepare for infusion by following these 3 steps[1]

Aseptically withdraw the calculated volume of the reconstituted VYXEOS and transfer to an infusion bag.



3

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, transluscent, homogenous 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 refer to the full Prescribing Information for VYXEOS for complete preparation and handling instructions, including BOXED Warning.

Calculate the number of vials of VYXEOS needed based on the daunorubicin dose and the patient's BSA using the following equation:

Dose of daunorubicin (mg/m^2) **X** **Patient's BSA (m^2)** **÷** **2.2 mg/mL** **=** **Volume required (mL)**

Each vial contains 20 mL of solution after reconstitution.[4]

IMPORTANT SAFETY INFORMATION (cont'd)

Warnings and Precautions (cont'd)

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.

Please see additional Important Safety Information throughout and full Prescribing Information, including BOXED Warning.

OUTPATIENT STRATEGIES

Real-world strategies for outpatient administration of VYXEOS[5]

Outpatient administration of VYXEOS was used for some patients in the Phase 3 study, and multiple institutions have evaluated its use in real-world practice.[3,6-8,a]

PREPARATION

- **Designate** a team of healthcare professionals, including registered nurses, pharmacists, advanced practice providers, and physicians, to run the outpatient center
- **Train** all personnel in managing outpatient care
- **Dedicate** a space specifically for outpatient care, if possible

ASSESS PATIENT ELIGIBILITY

- **Ensure** patients are compliant and/or have a suitable caregiver
- **Limit** a patient's commute to a treatment center to no more than 60 minutes
- **Evaluate** patient's overall health fitness (eg, ECOG PS, risk for complications, comorbidities, etc)

PATIENT EDUCATION

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

PATIENT MONITORING

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

ECOG PS=Eastern Cooperative Oncology Group Performance Status.

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

IMPORTANT SAFETY INFORMATION (CONT'D)

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 throughout and full Prescribing Information, including BOXED Warning.

PATIENT ASSESSMENT

Patient assessment should happen before, during, and after treatment[5]

BEFORE TREATMENT

- **Assess patient's suitability for outpatient therapy**
- **Laboratory tests:**
  - CMP
  - CBC with differential
  - Magnesium
  - Uric acid
  - Phosphate
  - LDH levels

DURING TREATMENT

- **Patient assessments (Days 2-5)**
  - Conduct patient assessment daily to evaluate for signs of disease- or treatment-related toxicities, such as TLS and/or infection
- **Laboratory tests (Days 1-5):**
  - CMP
  - CBC with differential
  - Magnesium
  - Uric acid
  - Phosphate
  - LDH levels
- **Hospital admission**
  - During Days 1-5, if any complications arise, such as infections, fever, uncontrolled pain, or syncope
  - Planned for Day 6 to carefully monitor patient with laboratory testing until ANC[a] recovery is achieved[b]

AFTER TREATMENT

- **Repeat bone marrow biopsy to evaluate response to therapy (Day 14)**
- **After patient is discharged, outpatient patient monitoring visits with laboratory testing should be conducted at least 2x weekly[c]**

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

[a]ANC >0.5 x 10^9/L.
[b]The admission stay typically lasts an average of 30 days (ranging between 25 and 50 days).
[c]Frequency of assessment may be modified based on patient need.

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 throughout and full Prescribing Information, including BOXED Warning.

SUPPORTIVE CARE

Ensure timely access to supportive care

Supportive care may include[5]

Blood and platelet transfusion support

- Patients may require frequent transfusions during outpatient care care

Prophylactic antimicrobial implementation

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

Wellness support

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

Additional considerations for outpatient treatment

- Inpatient access allows for unplanned admission due to urgent adverse events or if a patient requires frequent monitoring and/or transfusion support[9]
- Some institutions may prefer preplanned admission to monitor patients more closely[7]
- A patient who does not experience any major complications may be able to complete all treatment in an outpatient setting[5]

IMPORTANT SAFETY INFORMATION (cont'd)

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.

Please see additional Important Safety Information throughout and full Prescribing Information, including BOXED Warning.

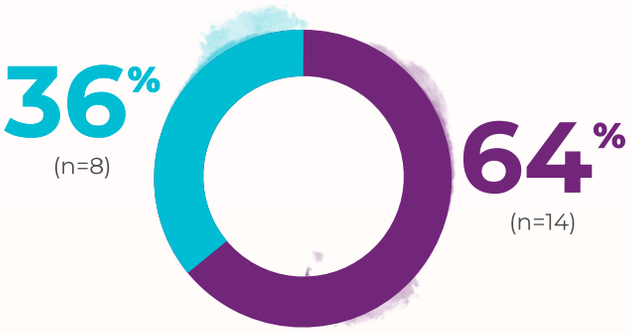
PATIENT SETTING

Institutions have evaluated administering VYXEOS in the outpatient setting[7,8]

In 2 small, postapproval, single-institution studies, more than half of patients initiated VYXEOS induction in the outpatient setting.

INPATIENT OUTPATIENT

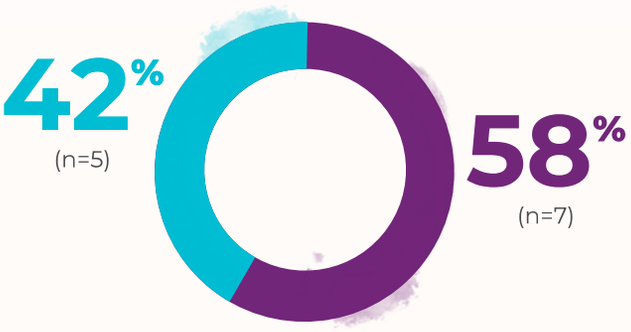
Kubal et al[7]



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

- Patients were evaluated each day with CBC, CMP, and uric acid and phosphorus measures
- Planned admission occurred on Day 6 for continued care
- 64% (n=14; median age 69 years) received induction in an IPOP setting, and 93% of those patients (n=13) were admitted for continued care on Day 6, as planned
- One patient was admitted on Day 2 of induction

Deutsch et al[8]



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

- Patients were monitored at least every other day until count recovery and admitted for continued care if complications occurred
- 58% (n=7; median age 72 years) received induction in an IPOP setting
- Of these 7 patients, 86% (n=6) were eventually admitted for continued care; all admissions were due to infection complications
- One patient was admitted prior to completing the third induction dose

These 2 studies assessed the feasibility of patients receiving VYXEOS induction in the inpatient/outpatient setting[7,8]

STUDY EXCLUSION CRITERIA

IPOP=inpatient/outpatient.

IMPORTANT SAFETY INFORMATION (cont'd)

Warnings and Precautions (cont'd)

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.

Please see additional Important Safety Information throughout and full Prescribing Information, including BOXED Warning.

PATIENT SETTING

Institutions have evaluated administering VYXEOS in the outpatient setting[7,8]

Exclusion criteria for outpatient administration were similar across these 2 studies[7,8]

Kubal et al Study (n=22)[7]
Increased risk for tumor lysis including white count >50K
Active cardiopulmonary symptoms
ECOG PS >2
Lacked a caregiver or were unable to reside within 60 minutes of the treating facility
Increased creatinine or uric acid

Deutsch et al Study (n=12)[8]
At risk for tumor lysis syndrome
Signs or symptoms of active infection or cardiopulmonary disease
ECOG PS >2
Lacked an appropriate caregiver or transportation to the cancer center

Treatment in an IPOP setting enables appropriate patients to receive induction in an outpatient setting, with inpatient admission scheduled as needed for continued monitoring and care or for treatment for adverse reactions.[7,8]

IMPORTANT SAFETY INFORMATION (cont'd)

Warnings and Precautions (cont'd)

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.

Please see additional Important Safety Information throughout and full Prescribing Information, including BOXED Warning.

ORDERING

VYXEOS reimbursement information and patient support

J code issued for VYXEOS

Permanent, product-specific HCPCS J code for VYXEOS		
	Dosage	**Billing**
J9153	Injection, liposomal, 1 mg daunorubicin and 2.27 mg cytarabine	Units per dose: 1 Units per vial: 44

ORDERING

Order VYXEOS through our distribution partners

Specialty Distributors

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

- Orders can be placed Monday-Thursday, 7 AM-6:30 PM CT; Friday, 7 AM-6 PM CT
- For emergency orders after hours of service, call 1-800-746-6273

ONCOLOGY SUPPLY

Online: https://www.oncologysupply.com

Phone: 1-800-633-7555

Fax: 1-800-248-8205

Email: custserv@oncologysupply.com

- Orders can be placed Monday-Friday, 9 AM-8 PM CT
- If orders are placed after hours via Oncology Supply's email address, they will be managed on the morning of the next business day

NEXT

IMPORTANT SAFETY INFORMATION (cont'd)

Warnings and Precautions (cont'd)

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.

Please see additional Important Safety Information throughout and full Prescribing Information, including BOXED Warning.

Cardinal Health

CARDINAL SPECIALTY PHARMACEUTICAL DISTRIBUTION

Online:
Order Express (hospitals)
https://orderexpress.cardinalhealth.com

Specialty Online (clinics)
https://specialtyonline.cardinalhealth.com

Phone: 1-800-746-6273

Fax: 1-800-547-9413

Email: SPDOncologyTeam@cardinalhealth.com

- Orders can be placed Monday-Friday, 8 AM -7 PM CT
- For emergency orders after hours of service, call 1-877-453-3972

McKesson

MCKESSON PLASMA AND BIOLOGICS

Online: https://connect.mckesson.com

Phone: 1-877-625-2566

Fax: 1-888-752-7626

Email: MPBOrders@mckesson.com

- Orders can be placed Monday-Friday, 9 AM-7:30 PM ET
- Email for all other information requests: MPB@mckesson.com
- For emergency orders after hours of service, call 1-877-625-2566

MCKESSON SPECIALTY HEALTH

Online: https://mscs.mckesson.com

Phone: 1-800-482-6700

Fax: 1-800-289-9285

Email: MSH-CustomerCare@mckesson.com

- Orders can be placed Monday-Friday, 8 AM-8 PM ET
- If orders are placed after hours via MSH's email address, they will be managed on the morning of the next business day

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

- VON (Vizient Oncology Network)
- Intersectta
- ION (Cencora)
- Unity GPO (McKesson Specialty Health)
- VitalSource (Cardinal Health)
- ON Solutions (AmerisourceBergen)

Please contact your GPO representative to learn more about purchasing VYXEOS.

IMPORTANT SAFETY INFORMATION (CONT'D)

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 throughout and full Prescribing Information, including BOXED Warning.

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

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.

Please see additional Important Safety Information throughout and full Prescribing Information, including BOXED Warning.

Important Safety Information (cont'd)

Warnings and Precautions (cont'd)

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%).

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. 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.** Kolitz JE, Strickland SA, Cortes JE, et al. Efficacy by consolidation administration site: subgroup analysis of a phase 3 study of CPX-351 versus 7+3 in older adults with newly diagnosed, high-risk acute myeloid leukemia (AML). Presented at: American Society of Clinical Oncology Annual Meeting; June 2-6, 2017; Chicago, IL. Poster 7036. **4.** Data on File (VYX-2022-022). Jazz Pharmaceuticals, Inc. **5.** Talati C, Frantz D, Lubas A, et al. How I treat newly diagnosed acute myeloid leukemia in an outpatient setting: a multidisciplinary team perspective. *Future Oncol*. 2020;16(7):281-291. **6.** 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. **7.** Kubal TE, Salamanca C, Komrokji RS, et al. Safety and feasibility of outpatient induction chemotherapy with CPX-351 in selected older adult patients with newly diagnosed AML. *J Clin Oncol*. 2018;36(15)(suppl):e19013. **8.** Deutsch YE, Presutto JT, Brahim A, et al. Safety and feasibility of outpatient liposomal daunorubicin and cytarabine (Vyxeos) induction and management in patients with secondary AML. *Blood*. 2018:132(suppl 1):3559. **9.** 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.