RXADVANCE
2 Park Central Drive
Southborough, MA 01772

Clinical Policy Title:	daunorubicin/cytarabine
Policy Number:	RxA.564
Drug(s) Applied:	Vyxeos®
Original Policy Date:	03/06/2020
Last Review Date:	12/07/2020
Line of Business Policy Applies to:	All lines of business

Background

Daunorubicin/cytarabine (Vyxeos®) is a liposomal combination of daunorubicin, an anthracycline topoisomerase inhibitor, and cytarabine, a nucleoside metabolic inhibitor.
It is indicated for the treatment of adults with newly-diagnosed therapy-related acute myeloid leukemia (t-AML) or AML with myelodysplasia-related changes (AML-MRC).

Dosing Information

Drug Name	Indication	Dosing Regimen	Maximum Dose
daunorubicin/cytarabine (Vyxeos®)	Therapy-related acute myeloid leukemia or Acute myeloid leukemia with myelodysplasia-related changes	A full Vyxeos® course consists of 1-2 cycles of induction and up to 2 cycles of consolidation. First Induction: Daunorubicin 44 mg/m^2 and cytarabine 100 mg/m^2 liposome intravenous over 90 minutes on days 1, 3 and 5 Second Induction (Only for patients failing to achieve a response with the first induction cycle; administered 2 to 5 weeks after the first): Daunorubicin 44 mg/m^2 and cytarabine 100 mg/m^2 liposome intravenous over 90 minutes on days 1 and 3 • Consolidation: Daunorubicin 29 mg/m^2 and cytarabine 65 mg/m^2 liposome intravenous over 90 minutes on days 1 and 3. Administer the first consolidation cycle 5 to 8 weeks after the start of the last induction; administer the second consolidation cycle 5 to 8 weeks after the start of the first consolidation cycle in patients who do not show disease progression or unacceptable toxicity to Vyxeos®.	See dosing regimens

Dosage Forms

- Single-dose vial: 44 mg daunorubicin and 100 mg cytarabine

Clinical Policy

Provider must submit documentation (such as office chart notes, lab results or other clinical information) supporting that member has met all approval criteria.

I. Initial Approval Criteria

A. Acute Myeloid Leukemia (must meet all):

1. Diagnosis of one of the following secondary AML subtypes (see Appendix D for related information) (a, b, or c):
   a. t-AML;
   b. AML-MRC;
   c. Antecedent myelodysplastic syndrome/chronic myelomonocytic leukemia (antecedent MDS/CMML);
2. Prescribed by or in consultation with an oncologist or hematologist;
3. Age ≥ 18 years;
4. Request meets one of the following* (a, b, or c):
   *Prescribed regimen must be FDA-approved or recommended by NCCN.
   a. Induction (up to 2 cycles): dose does not exceed 44 mg/m^2 daunorubicin liposomal and 100 mg/m^2 cytarabine liposomal on days 1, 3, and 5 of cycle 1, and days 1 and 3 if a second cycle;
   b. Consolidation (up to 2 cycles): dose does not exceed 29 mg/m^2 daunorubicin liposomal and 65 mg/m^2 cytarabine liposomal on days 1 and 3 of each cycle;
   c. Dose is supported by practice guidelines or peer-reviewed literature for the relevant off-label use (prescriber must submit supporting evidence).

Approval Duration
Commercial: 6 months
Medicaid: 6 months

II. Continued Therapy Approval

A. Acute Myeloid Leukemia (must meet all):

1. Member is currently receiving the medication that has been authorized by RxAdvance or member has met initial approval criteria listed in this policy;, or documentation supports that member is currently receiving Vyxeos® for a covered indication and has received this medication for at least 30 days;
2. Member is responding positively to therapy;
3. Member has not yet received ≥ 4 treatment cycles (up 2 to induction and 2 consolidation cycles);
4. If request is for a dose increase, request meets one of the following (a, b, or c):
   *Prescribed regimen must be FDA-approved or recommended by NCCN.
   a. Induction (up to 2 cycles total): new dose does not exceed 44 mg/m^2 daunorubicin liposomal and 100 mg/m^2 cytarabine liposomal on days 1, 3, and 5 of cycle 1, and days 1 and 3 if a second cycle;
   b. Consolidation (up to 2 cycles total): new dose does not exceed 29 mg/m^2 daunorubicin liposomal and 65 mg/m^2 cytarabine liposomal on days 1 and 3 of each cycle;
   c. Dose is supported by practice guidelines or peer-reviewed literature for the relevant off-label use (prescriber must submit supporting evidence).

Approval Duration
Commercial: 6 months
Medicaid: 6 months

III. Appendices

APPENDIX A: Abbreviation/Acronym Key

AML: Acute myeloid leukemia
AML-MRC: acute myeloid leukemia with myelodysplasia-related changes
FDA: Food and Drug Administration
MDS: Myelodysplastic syndrome
NCCN: National Comprehensive Cancer Network
MDS/CMML: Myelodysplastic syndrome/chronic myelomonocytic leukemia
MDS/MPN: Myelodysplastic/ myeloproliferative neoplasm
t-AML: Therapy-related acute myeloid leukemia

APPENDIX B: Therapeutic Alternatives

- Not applicable

APPENDIX C: Contraindications/Boxed Warnings

- Contraindication(s):
  - Hypersensitivity to daunorubicin, cytarabine, or any component of the formulation

- Boxed Warning(s):
  - Do not interchange with other daunorubicin and/or cytarabine-containing products.

APPENDIX D: General Information

The following AML subtypes are categorized as secondary AML:

- t-AML is a clinical syndrome occurring as a late complication following cytotoxic therapy and/ or ionizing radiotherapy for an unrelated disease.
- AML-MRC includes those forms of AML occurring in patients with a history of a myelodysplastic syndrome (MDS) or a myelodysplastic/myeloproliferative neoplasm (MDS/MPN); it also includes those forms of AML with morphologic features or cytogenetic abnormalities characteristic of an MDS.
- The World Health Organization, as discussed in Vardiman et al, defines AML-MRC as cases with 20% or more blasts in the peripheral blood or bone marrow and one or more of the following:
  - history of MDS or MDS/MPN,
  - multilineage dysplasia (dysplasia in ≥ 50% of the cells in at least two lineages), or
  - specific myelodysplasia-related cytogenetic abnormalities - e.g. –7/del(7q), –5/del(5q), i(17q)/t(17p), 13/del(13q), del(13q), del(12p)/t(12p), del(9q), idic(X)(q13), t(11;16)(q23;p13.3), t(3;21)(q26.2;q22.1), t(1;3)(p36.3;q21.1), t(2;11)(p21;q23), t(5;12)(q33;p12), t(5;7)(q33;q11.2), t(5;17)(q33;p13), t(5;10)(q33;q21), t(3;5)(q25;q34).
- Antecedent MDS/CMML.

References

1. Vyxeos Prescribing Information. Palo Alto, CA: Jazz Pharmaceuticals, Inc.; July 2019. Available at: https://vyxeos.com/ . Accessed October 12, 2020.
2. National Comprehensive Cancer Network Drugs and Biologics Compendium. Available at: http://www.nccn.org/professionals/drug_compendium. Accessed October 12, 2020.
3. National Comprehensive Cancer Network. Acute Myeloid Leukemia Version 1.2021. Available at: https://www.nccn.org/professionals/physician_gls/pdf/aml.pdf. Accessed October 14, 2020.
4. Godley LA, Larson RA. Therapy-related Myeloid Leukemia. Seminars in oncology. 2008;35(4):418-429. doi:10.1053/j.seminoncol.2008.04.012.

5. Vardiman J, Reichard K. Acute myeloid leukemia with myelodysplasia-related changes. Am J Clin Pathol. 2015 Jul;144(1):29-43.
6. Lencet 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; 36:2684-2692. Available at https://www.ncbi.nlm.nih.gov/pubmed/30024784.

Review/Revision History	Review/Revision Date	P&T Approval Date
Policy established.	01/2020	03/06/2020
Policy was reviewed: 1. Clinical policy title was updated. 2. Line of Business Policy Applies to was updated to "All lines of business". 3. Dosing regimen abbreviated form of IV is replaced with intravenous. 4. Continued therapy criteria II.A.1 was rephrased to "Currently receiving medication that has been authorized by RxAdvance". 5. HIM approval duration deleted from initial and continued therapy criteria. 6. References were reviewed and updated.	10/14/2020	12/07/2020