Vyxeos® (daunorubicin and cytarabine) liposome
(Intravenous)

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Last Review Date: 05/03/2021
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I. Length of Authorization

Coverage will be provided for a maximum of 2 cycles of induction (5 doses total) and 2 cycles of consolidation (4 doses total) within 6 months. Coverage may not be renewed.

II. Dosing Limits

A. Quantity Limit (max daily dose) [NDC Unit]:

- Vyxeos single-dose vial: 23 vials total

B. Max Units (per dose and over time) [HCPCS Unit]:

- Induction: 132 billable units per dose (3 vials per dose; 5 doses total)
- Consolidation: 88 billable units per dose (2 vials per dose; 4 doses total)

III. Initial Approval Criteria [1]

Coverage is provided in the following conditions:

- Baseline left ventricular ejection fraction (LVEF) is within normal limits and will be reassessed prior to consolidation and as clinically required; **AND**
- Cumulative lifetime anthracycline (e.g., daunorubicin, etc.) dose does not exceed 550 mg/m^2 (or 400 mg/m^2 in patients who received radiation to the mediastinum); **AND**
- Will not be used in combination with other chemotherapy; **AND**

Acute Myeloid Leukemia (AML) † ‡ Φ [1-3]

- Patient has one of the following sub-types of disease:
  - Therapy-related acute myeloid leukemia (t-AML)
  - AML with myelodysplasia-related changes (AML-MRC)
  - Antecedent myelodysplastic syndrome/chronic myelomonocytic leukemia (antecedent MDS/CMML); **AND**

- Patient is at least 1 year of age with newly diagnosed disease (*Note: For antecedent MDS/CMML, use is only allowed in patients age ≥ 60 years of age that are candidates for intensive remission induction therapy*)

Preferred therapies and recommendations are determined by review of clinical evidence. NCCN category of recommendation is taken into account as a component of this review. Regimens deemed equally efficacious (i.e., those having the same NCCN categorization) are considered to be therapeutically equivalent.

† FDA Approved Indication(s); ‡ Compendia recommended indication(s); Φ Orphan Drug

IV. Renewal Criteria [1,3]

Authorizations may not be renewed.

V. Dosage/Administration [1,3]

Indication	Dose
t-AML, antecedent MDS/CMML & AML-MRC	<u>First induction</u> • daunorubicin 44 mg/m² and cytarabine 100 mg/m² liposome intravenously days 1, 3 and 5 <u>Second induction</u> • daunorubicin 44 mg/m² and cytarabine 100 mg/m² liposome intravenously days 1 and 3 o Only for patients who fail to respond to the first induction cycle o May be administered 2 to 5 weeks after the first induction cycle if there was no unacceptable toxicity <u>Consolidation</u> • daunorubicin 29 mg/m² and cytarabine 65 mg/m² liposome intravenously days 1 and 3 o Administer the first consolidation cycle 5 to 8 weeks after the start of the last induction cycle o Administer the second consolidation cycle 5 to 8 weeks after the start of the first consolidation cycle if there was no unacceptable toxicity or disease progression

VI. Billing Code/Availability Information

<u>HCPCS Code:</u>

- J9153 – Injection, liposomal, 1 mg daunorubicin and 2.27 mg cytarabine: 1 billable unit = 1 1 mg daunorubicin and 2.27 mg cytarabine

<u>NDC:</u>

- Vyxeos (44 mg daunorubicin and 100 mg cytarabine) liposome, single-dose vial: 68727−0745−xx

VII. References (STANDARD)

1. Vyxeos [package insert]. Palo Alto, CA; Jazz Pharmaceuticals, Inc., March 2021. Accessed April 2021.
2. Referenced with permission from the NCCN Drugs & Biologics Compendium (NCCN Compendium®) for cytarabine/daunorubicin liposome. National Comprehensive Cancer Network, 2021. The NCCN Compendium® is a derivative work of the NCCN Guidelines®. NATIONAL COMPREHENSIVE CANCER NETWORK®, NCCN®, and NCCN GUIDELINES® are trademarks owned by the National Comprehensive Cancer Network, Inc. To view the most recent and complete version of the Compendium, go online to NCCN.org. Accessed April 2021.
3. Referenced with permission from the NCCN Drugs & Biologics Compendium (NCCN Compendium®) Acute Myeloid Leukemia. Version 3.2021. National Comprehensive Cancer Network, 2021. The NCCN Compendium® is a derivative work of the NCCN Guidelines®. NATIONAL COMPREHENSIVE CANCER NETWORK®, NCCN®, and NCCN GUIDELINES® are trademarks owned by the National Comprehensive Cancer Network, Inc. To view the most recent and complete version of the Compendium, go online to NCCN.org. Accessed April 2021.
4. Lin TL, Ryan RJ, Fadert S, et al. Outcomes in older patients with high-risk/secondary AML who achieved remission with CPX-351 versus 7+3 but did not undergo transplant: Phase 3 exploratory analysis. J Clin Onco; DOI: 10.1200/JCO.2020.38.15_suppl.7537 Journal of Clinical Oncology38, no. 15_suppl(May 20, 2020)7537-7537.

VIII. References (ENHANCED)

1e. Lancet JE, Uy, GL, Cortes JE, et al. Final results of a phase III randomized trial of CPX-351 versus 7+3 in older patients with newly diagnosed high risk (secondary) AML. Journal of Clinical Oncology 2016 34:15_suppl, 7000-7000.

2e. Welch JS, Petti AA, Miller CA, et al. TP53 and Decitabine in Acute Myeloid Leukemia and Myelodysplastic Syndromes. N Engl J Med 2016; 375:2023-2036.

3e. Löwenberg B, Ossenkoppele GJ, van Putten W, et al. High-Dose Daunorubicin in Older Patients with Acute Myeloid Leukemia. N Engl J Med 2009; 361:1235-1248.

4e. Stone RM, Mandrekar S, Sanford BL, et al. The Multi-Kinase Inhibitor Midostaurin (M) Prolongs Survival Compared with Placebo (P) in Combination with Daunorubicin (D)/Cytarabine (C) Induction (ind), High-Dose C Consolidation (consol), and As Maintenance (maint) Therapy in Newly Diagnosed Acute Myeloid Leukemia (AML) Patients (pts) Age 18-60 with FLT3 Mutations (muts): An International Prospective Randomized (rand) P-Controlled Double-Blind Trial (CALGB 10603/RATIFY [Alliance]). Blood 2015; 126:6.

5e. Mayer RJ, Davis RB, Schiffer CA, et al. Intensive Postremission Chemotherapy in Adults with Acute Myeloid Leukemia. N Engl J Med 1994; 331:896-903.

6e. Cooper TM, Absalon MJ, Alonzo TA, et al. Phase I/II Study of CPX-351 Followed by Fludarabine, Cytarabine, and Granulocyte-Colony Stimulating Factor for Children With Relapsed Acute Myeloid Leukemia: A Report From the Children's Oncology Group. J Clin Oncol. 2020 Jul 1;38(19):2170-2177. doi: 10.1200/JCO.19.03306.

7e. Magellan Health, Magellan Rx Management. Vyxeos Clinical Literature Review Analysis. Last updated April 2021. Accessed April 2021.

Appendix 1 – Covered Diagnosis Codes

ICD-10	ICD-10 Description
C92.00	Acute myeloblastic leukemia not having achieved remission
C92.01	Acute myeloblastic leukemia in remission
C92.50	Acute myelomonocytic leukemia not having achieved remission
C92.51	Acute myelomonocytic leukemia in remission
C92.60	Acute myeloid leukemia with 11q23-abnormality not having achieved remission
C92.61	Acute myeloid leukemia with 11q23-abnormality in remission
C92.A0	Acute myeloid leukemia with multilineage dysplasia not having achieved remission
C92.A1	Acute myeloid leukemia with multilineage dysplasia in remission
C93.00	Acute monoblastic/monocytic leukemia not having achieved remission
C93.01	Acute monoblastic/monocytic leukemia in remission
C94.00	Acute erythroid leukemia not having achieved remission
C94.01	Acute erythroid leukemia in remission
C94.20	Acute megakaryoblastic leukemia not having achieved remission
C94.21	Acute megakaryoblastic leukemia in remission

Appendix 2 – Centers for Medicare and Medicaid Services (CMS)

Medicare coverage for outpatient (Part B) drugs is outlined in the Medicare Benefit Policy Manual (Pub. 100-2), Chapter 15, §50 Drugs and Biologicals. In addition, National Coverage Determination (NCD), Local Coverage Determinations (LCDs), and Local Coverage Articles (LCAs) may exist and compliance with these policies is required where applicable. They can be found at: http://www.cms.gov/medicare-coverage-database/search/advanced-search.aspx. Additional indications may be covered at the discretion of the health plan.

Medicare Part B Covered Diagnosis Codes (applicable to existing NCD/LCD/LCA): N/A

Medicare Part B Administrative Contractor (MAC) Jurisdictions		
Jurisdiction	**Applicable State/US Territory**	**Contractor**
E (1)	CA, HI, NV, AS, GU, CNMI	Noridian Healthcare Solutions, LLC
F (2 & 3)	AK, WA, OR, ID, ND, SD, MT, WY, UT,	Noridian Healthcare Solutions, LLC

Medicare Part B Administrative Contractor (MAC) Jurisdictions		
Jurisdiction	**Applicable State/US Territory**	**Contractor**
5	KS, NE, IA, MO	Wisconsin Physicians Service Insurance Corp (WPS)
6	MN, WI, IL	National Government Services, Inc. (NGS)
H (4 & 7)	LA, AR, MS, TX, OK, CO, NM	Novitas Solutions, Inc.
8	MI, IN	Wisconsin Physicians Service Insurance Corp (WPS)
N (9)	FL, PR, VI	First Coast Service Options, Inc.
J (10)	TN, GA, AL	Palmetto GBA, LLC
M (11)	NC, SC, WV, VA (excluding below)	Palmetto GBA, LLC
L (12)	DE, MD, PA, NJ, DC (includes Arlington & Fairfax counties and the city of Alexandria in VA)	Novitas Solutions, Inc.
K (13 & 14)	NY, CT, MA, RI, VT, ME, NH	National Government Services, Inc. (NGS)
15	KY, OH	CGS Administrators, LLC

Appendix 3 – CLINICAL LITERATURE REVIEW

OS = overall survival; PFS = progression-free survival; ORR = objective response rate; CR = complete response; PR = partial response; DoR = duration of response; TTP = time to progression; FFS = failure-free survival; EFS = event-free survival; PFR = progression free rate; CRp = compete response with partial recovery of platelet count; HSCT = hematopoietic stem cell transplantation

Therapy-related Acute Myeloid Leukemia (t-AML) or AML with myelodysplasia-related changes (AML-MRC)

Induction, Re-induction, and Post-remission therapy							
Regimen	**NCCN Category**	**FDA Approved**	**Trial Design**	**Comparator**	**Primary End-Point**	**Line of Therapy**	**Conclusion**
Daunorubicin and cytarabine liposome (CPX-351)	1 2B (< 60 years old re-induction therapy)	Yes for newly diagnosed AML	Phase 3, open-label, randomized (1:1), multi-center, active-controlled	Standard daunorubicin + cytarabine (7+3)	OS	Up to 2 inductions and up to 2 consolidations in patients with t-AML or AML-MRC	• CPX-351 treatment is associated with significantly longer survival compared with conventional 7+3 in older adults (60-75 years old) with newly diagnosed secondary AML
Daunorubicin and cytarabine liposome (CPX-351)	2A	Yes for newly diagnosed AML	Phase 1-2 (AAML 1421)	N/A	Dose ORR	Relapsed or refractory	• The liposomal preparation of daunorubicin and cytarabine was effective with a CR of 54% in children with relapsed or refractory AML.
Decitabine	2A	No	Prospective, uncontrolled trial	N/A	Correlate clinical responses with mutation status	All lines of therapy	• Patients with AML and MDS who had cytogenetic abnormalities associated with unfavorable risk, TP53 mutations, or both had favorable clinical responses and robust (but incomplete) mutation

							clearance after receiving serial 10-day courses of decitabine.
Standard-dose cytarabine + standard-dose daunorubicin (45mg/m^2 daily for 3 days)	2A	Yes	Phase 3 (HOVON trial), randomized	Standard-dose cytarabine + dose-escalated daunorubicin (90mg/m^2 daily for 3 days)	EFS	First-line induction therapy	• In patients with AML who are older than 60 years of age, escalation of the dose of daunorubicin to twice the conventional dose, with the entire dose administered in the first induction cycle, effects a higher CR rate, 2-year EFS rate, and 2-year OS rate in patients aged 60-65 years, without additional toxic effects.
Standard-dose cytarabine + daunorubicin + oral midostaurin	2A (for FLT3-mutated AML	Yes	Phase 3 (RATIFY), randomized, placebo-controlled, double-blind	Standard-dose cytarabine + daunorubicin + placebo (induction and consolidation)	OS	First-line; re-treatment with a second course was allowed if residual AML was noted on day 21; consolidation	• The addition of midostaurin to standard chemotherapy significantly improved overall survival in patients with FLT3-mutation positive AML.
HiDAC (3g/m^2 q 12h days 1, 3, 5)	2A	No	CALGB study	Cytarabine (100mg/m^2 x5d or 400mg/m^2 x5d)	---------	Post-remission	• These data support the concept of a dose-response effect for cytarabine in patients with AML who are 60 years of age or younger.