Beleodaq® (belinostat)
(Intravenous)

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Document Number: MODA-0381

Last Review Date: 04/06/2021
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I. Length of Authorization

Coverage will be provided for 6 months and may be renewed.

II. Dosing Limits

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

- Beleodaq 500 mg powder for injection: 25 vials per 21 days

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

- All indications: 1,250 billable units every 21 days

III. Initial Approval Criteria [1]

Coverage is provided in the following conditions:

- Patient is at least 18 years of age; **AND**

Universal Criteria [1,2]

- Used as a single agent; **AND**

T-Cell Lymphomas [1,2,4]

- Peripheral T-Cell Lymphoma (PTCL) † Φ [3,6,7,10]
  (Including: Angioimmunoblastic T-cell lymphoma ‡; Peripheral T-cell lymphoma not otherwise specified ‡; Anaplastic large cell lymphoma (ALK-negative only) ‡)
  - Used as subsequent therapy for relapsed or refractory disease

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-labeled indication(s); ‡ Compendia Recommended Indication(s); Φ Orphan Drug

IV. Renewal Criteria [1,4,5]

Coverage can be renewed based upon the following criteria:

- Patient continues to meet universal and other indication-specific relevant criteria such as concomitant therapy requirements (not including prerequisite therapy), performance status, etc. identified in section III; **AND**
- Disease response with treatment as defined by stabilization of disease or decrease in size of tumor or tumor spread; **AND**
- Absence of unacceptable toxicity from the drug. Examples of unacceptable toxicity include: hematologic toxicity (e.g., thrombocytopenia, leukopenia, and/or anemia), severe infections, hepatotoxicity, tumor lysis syndrome, severe gastrointestinal toxicity, etc.

V. Dosage/Administration [1,4,5]

Indication	Dose
All indications	Administer 1,000 mg/m² intravenously daily on days 1-5 of a 21 day cycle until disease progression or unacceptable toxicity.

VI. Billing Code/Availability Information

HCPCS Code:

- J9032 - Injection, belinostat, 10 mg; 1 billable unit = 10 mg

NDC:

- Beleodaq 500 mg single dose vial (30 mL): 72893-0002-xx

VII. References (STANDARD)

1. Beleodaq [package insert]. Acrotech Biopharma, East Windsor, NJ; January 2020. Accessed March 2021.
2. Referenced with permission from the NCCN Drugs & Biologics Compendium (NCCN Compendium®) for belinostat. 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 March 2021.

3. O'Connor OA, Masszi T, Savage KJ, et al. Belinostat, a novel pan-histone deacetylase inhibitor (HDACi), in relapsed or refractory peripheral T-cell lymphoma (R/R PTCL): Results from the BELIEF trial. Journal of Clinical Oncology 2013 31:15_suppl, 8507-8507.
4. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) T-Cell Lymphomas, Version 1.2021. 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 March 2021.
5. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Primary Cutaneous Lymphomas 1.2021. National Comprehensive Cancer Network, 2021. 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 Guidelines, go online to NCCN.org. Accessed March 2021.

VIII. References (ENHANCED)

1e. Pro B, Advani R, Brice P, et al. Brentuximab vedotin (SGN-35) in patients with relapsed or refractory systemic anaplastic large-cell lymphoma: results of a phase II study. J Clin Oncol. 2012 Jun 20;30(18):2190-6.

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Appendix 1 – Covered Diagnosis Codes

ICD-10	ICD-10 Description
C84.40	Peripheral T-cell lymphoma, not classified, unspecified site
C84.41	Peripheral T-cell lymphoma, not classified, lymph nodes of head, face and neck
C84.42	Peripheral T-cell lymphoma, not classified, intrathoracic lymph nodes
C84.43	Peripheral T-cell lymphoma, not classified, intra-abdominal lymph nodes
C84.44	Peripheral T-cell lymphoma, not classified, lymph nodes of axilla and upper limb
C84.45	Peripheral T-cell lymphoma, not classified, lymph n odes of inguinal region of lower limb
C84.46	Peripheral T-cell lymphoma, not classified, intrapelvic lymph nodes
C84.47	Peripheral T-cell lymphoma, not classified, spleen
C84.48	Peripheral T-cell lymphoma, not classified, lymph nodes of multiple sites
C84.49	Peripheral T-cell lymphoma, not classified, extranodal and solid organ sites
C84.70	Anaplastic large cell lymphoma, ALK-negative, unspecified site
C84.71	Anaplastic large cell lymphoma, ALK-negative, lymph nodes of head, face and neck
C84.72	Anaplastic large cell lymphoma, ALK-negative, intrathoracic lymph nodes
C84.73	Anaplastic large cell lymphoma, ALK-negative, intra-abdominal lymph nodes
C84.74	Anaplastic large cell lymphoma, ALK-negative, lymph nodes of axilla and upper limb
C84.75	Anaplastic large cell lymphoma, ALK-negative, lymph nodes of inguinal region and lower limb
C84.76	Anaplastic large cell lymphoma, ALK-negative, intrapelvic lymph nodes
C84.77	Anaplastic large cell lymphoma, ALK-negative, spleen
C84.78	Anaplastic large cell lymphoma, ALK-negative, lymph nodes of multiple sites
C84.79	Anaplastic large cell lymphoma, ALK-negative, extranodal and solid organ sites
C86.5	Angioimmunoblastic T-cell lymphoma

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, AZ	Noridian Healthcare Solutions, LLC
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; AE = adverse event; LCT = large cell transformation

T-Cell Lymphomas

Peripheral T-cell lymphoma (PTCL) – Subsequent Therapy							
Regimen	**NCCN Category**	**FDA Approved**	**Trial Design**	**Comparator**	**Primary End-Point**	**Line of Therapy**	**Conclusion**
Belinostat	2A preferred (not preferred for ALCL)	Yes	Phase 2 (BELIEF), non-randomized, open-label	N/A	ORR	After at least one prior therapy	• Belinostat induced responses across all types of PTCL • Response rates were significantly higher for AITL than other subtypes • A response was not seen in patients with Anaplastic large cell lymphoma ALK-positive disease (2 patients) and Enteropathy-associated TCL (2 patients).
Brentuximab vedotin	1 (ALCL) 2A preferred for CD30+ PTCL	Yes (ALCL only)	Phase 2 (NCT00866047), multicenter, open-label, single-arm Long-term follow-up	N/A	ORR	After at least one prior therapy	• Brentuximab vedotin induced an ORR of 86% and CRs in more than half of patients with recurrent systemic ALCL

Brentuximab vedotin	1 (ALCL) 2A preferred for CD30+ PTCL	Yes (ALCL only)	Phase 2, open-label, multicenter	N/A	ORR	After at least one prior therapy	• Brentuximab vedotin showed antitumor activity in patients with relapsed PTCL with an ORR of 41%, particularly AITL (ORR 54%)
Pralatrexate	2A preferred (not preferred for AITL and ALCL)	Yes	Phase 2 (PROPEL), single-arm, open-label, multicenter	N/A	ORR	After at least one prior therapy	• Pralatrexate induced durable responses with an ORR of 29% in relapsed or refractory PTCL
Romidepsin	2A preferred (not preferred for ALCL)	Yes	Phase 2, open-label, single-arm	N/A	CR	After at least one prior therapy	• Single-agent romidepsin induced complete and durable responses with manageable toxicity in patients with relapsed or refractory PTCL across all major PTCL subtypes, regardless of the number or type of prior therapies
Adult T-Cell Leukemia/Lymphoma – Subsequent Therapy							
Regimen	**NCCN Category**	**FDA Approved**	**Trial Design**	**Comparator**	**Primary End-Point**	**Line of Therapy**	**Conclusion**
Belinostat	2A	No	No clinical literature evidence to support use.				
Brentuximab	2A preferred (CD30+)	No	No clinical literature evidence to support use.				
Lenalidomide	2A preferred	No	Phase 2 (ATLL-002), multicenter, single-arm, open-label	N/A	ORR	After at least one prior therapy	• Lenalidomide demonstrated clinically meaningful antitumor activity with an ORR of 42% and an acceptable toxicity profile in patients with relapsed or recurrent aggressive ATL
Mogamulizumab	2A preferred	No	Phase 2, multicenter	N/A	ORR	After at least one prior therapy	• Mogamulizumab monotherapy may improve PFS and OS in some patients with relapsed aggressive ATL, especially those who develop

			Follow-up analysis				a skin rash as a moderate immune-related adverse event
Mogamulizumab	2A preferred	No	Phase 2 (NCT01626664)	Investigator choice (IC) (GEMOX, DHAP, pralatrexate) Cross-over was allowed	ORR	After at least one prior therapy	• In patients with aggressive R/R ATL commonly used cytotoxic regimens provided limited therapeutic benefit whereas treatment with mogamulizumab resulted in an ORR that supports its therapeutic potential in this setting
Alemtuzumab	2A	No	Phase 2, open-label, non-randomized	N/A	ORR	All lines of therapy	• Alemtuzumab induced responses with an ORR of 52% in patients with ATLL
Pralatrexate	2A	No	Retrospective analysis	N/A	----------	After at least one prior therapy	• Pralatrexate demonstrated limited activity in patients with relapsed or refractory ATLL
Bortezomib	2A	No	Phase 2, multicenter, two-stage, single-arm	N/A	ORR	After at least one prior therapy	• Bortezomib demonstrated limited activity in patients with relapsed or refractory ATLL
Extranodal NK/T-cell Lymphoma (Nasal type) – Relapsed or Refractory							
Regimen	**NCCN Category**	**FDA Approved**	**Trial Design**	**Comparator**	**Primary End-Point**	**Line of Therapy**	**Conclusion**
Belinostat	2A certain circumstances	No	Phase 2 (BELIEF), non-randomized, open-label	N/A	ORR	After at least one prior therapy	• Belinostat induced responses across all types of PTCL including 2 patients with Extranodal NK/T-cell Lymphoma, nasal type. • Response rates were significantly higher for AITL than other subtypes

							• A response was not seen in patients with Anaplastic large cell lymphoma ALK-positive disease (2 patients) and Enteropathy-associated TCL (2 patients).
Pembrolizumab	2A preferred	No	Retrospective study	N/A	-----	Relapsed or refractory disease after asparaginase-based regimens	• Pembrolizumab induced high response rates in patients with relapsed or refractory extranodal NK/T-cell lymphoma following treatment with asparaginase-based regimens.
Hepatosplenic Gamma-Delta T-Cell Lymphoma – Subsequent Therapy							
Regimen	**NCCN Category**	**FDA Approved**	**Trial Design**	**Comparator**	**Primary End-Point**	**Line of Therapy**	**Conclusion**
Belinostat	2A preferred	No	Phase 2 (BELIEF), non-randomized, open-label	N/A	ORR	After at least one prior therapy	• Belinostat induced responses across all types of PTCL, including 2 patients with Hepatosplenic T-cell Lymphoma. • Response rates were significantly higher for AITL than other subtypes • A response was not seen in patients with Anaplastic large cell lymphoma ALK-positive disease (2 patients) and Enteropathy-associated TCL (2 patients).
Breast Implant-Associated Anaplastic Large Cell Lymphoma (ALCL) – Subsequent Therapy							
Regimen	**NCCN Category**	**FDA Approved**	**Trial Design**	**Comparator**	**Primary End-Point**	**Line of Therapy**	**Conclusion**
Belinostat	2A	No	No clinical literature evidence to support use.				

Peripheral Cutaneous Lymphomas

Mycosis Fungoides (MF)/Sezary Syndrome (SS) – Primary Therapy							
Regimen	**NCCN Category**	**FDA Approved**	**Trial Design**	**Comparator**	**Primary End-Point**	**Line of Therapy**	**Conclusion**
Belinostat	2A preferred (primary therapy for stage IV non-Sezary or visceral disease, or LCT)	No	No clinical literature evidence to support use.				
Gemcitabine	2A preferred	No	Phase 2	N/A	-----	Untreated	• Phase II study demonstrated the activity of gemcitabine as a single agent in untreated CTCL patients
Mycosis Fungoides (MF)/Sezary Syndrome (SS) – Relapsed, Persistent, or Refractory							
Regimen	**NCCN Category**	**FDA Approved**	**Trial Design**	**Comparator**	**Primary End-Point**	**Line of Therapy**	**Conclusion**
Belinostat	2A preferred 2A (relapsed or refractory disease)	No	No clinical literature evidence to support use.				
Brentuximab vedotin	2A preferred (primary therapy and for relapsed or refractory disease)	Yes (CD30+ MF relapsed or refractory disease only)	Phase 3 (ALCANZA), international, open-label, randomized, multicenter	Physician's Choice (methotrexate or bexarotene)	ORR ≥ 4 months	After at least one prior therapy	• Significant improvement in objective response lasting at least 4 months was seen with brentuximab vedotin versus physician's choice of methotrexate or bexarotene
Brentuximab vedotin	2A preferred (primary therapy	Yes (CD30+ MF relapsed	Phase 2, open-label	N/A	----------	After at least one prior therapy	• Brentuximab vedotin is both active and well tolerated in

	and for relapsed or refractory disease)	or refractory disease only)					cutaneous T-cell lymphoma with an ORR of 73% and CR of 35%.
Brentuximab vedotin	2A preferred (primary therapy and for relapsed or refractory disease)	Yes (CD30+ MF relapsed or refractory disease only)	Phase 2, investigator-initiated, multi-institution	N/A	ORR	After at least one prior therapy	• Brentuximab vedotin demonstrated significant clinical activity with an ORR of 70% in treatment-refractory or advanced MF or SS with a wide range of CD30 expression levels
Liposomal doxorubicin	2A preferred (stage IV non-Sezary or visceral disease, or LCT – both primary therapy and relapsed or refractory disease)	No	Phase 2	N/A	----------	After at least one prior therapy	• Liposomal doxorubicin resulted an ORR 84% with minimal toxicity.
Liposomal doxorubicin	2A preferred (stage IV non-Sezary or visceral disease, or LCT – both primary therapy and relapsed or refractory disease)	No	Prospective multicenter study	N/A	ORR	After at least two prior therapies or transformed CTCL	• Liposomal doxorubicin demonstrated to be effective in treating CTCL with an ORR of 56%
Liposomal doxorubicin	2A preferred (stage IV non-Sezary or visceral disease, or LCT – both primary therapy and	No	Phase 2, multicenter	N/A	ORR	After at least two prior therapies	• Liposomal doxorubicin demonstrated to be effective with an ORR of 41% in patients with advanced MF

	relapsed or refractory disease)						
Pralatrexate	2A preferred (stage IV non-Sezary or visceral disease, or LCT – both primary therapy and relapsed or refractory disease)	No	Multicenter dose-finding study	N/A	---------	After at least one prior therapy	• Pralatrexate showed high activity with an ORR of 41% with acceptable toxicity if patients with relapsed or refractory CTCL
Pralatrexate	2A preferred (stage IV non-Sezary or visceral disease, or LCT – both primary therapy and relapsed or refractory disease)	No	Retrospective analysis of phase 2 (PROPEL) study	N/A	ORR	After at least one prior therapy	• Pralatrexate demonstrated clinical activity in patients with transformed MF.
Mogamulizumab	2A preferred (primary or subsequent treatment of stage IA-III MF and stage IV Sezary syndrome)	Yes (relapsed or refractory MF/SS only)	Phase 3 (MAVORIC), randomized, open-label, multicenter	Vorinostat	PFS	After at least one prior therapy	• Mogamulizumab significantly prolonged progression-free survival compared with vorinostat
Primary Cutaneous CD30+ T-Cell Lymphoproliferative Disorders – Relapsed or Refractory							
Regimen	**NCCN Category**	**FDA Approved**	**Trial Design**	**Comparator**	**Primary End-Point**	**Line of Therapy**	**Conclusion**
Belinostat	2A	No	No clinical literature evidence to support use.				

Brentuximab vedotin	2A preferred (primary treatment) 2A (relapsed or refractory disease)	Yes (for Anaplastic Large Cell Lymphoma)	Phase 3 (ALCANZA), international, open-label, randomized, multicenter	Physician's Choice (methotrexate or bexarotene)	ORR ≥ 4 months	After at least one prior therapy	• Significant improvement in objective response lasting at least 4 months was seen with brentuximab vedotin versus physician's choice of methotrexate or bexarotene
Methotrexate (low-dose)	2A	No	Retrospective study	N/A	-----	--------	• Low-dose methotrexate demonstrated to be effective (ORR 87%) in patients with primary cutaneous CD30+ lymphoproliferative disease