Synribo® (omacetaxine mepesuccinate)
(Subcutaneous)

-E-

Document Number: IC-0488

Last Review Date: 02/04/2020
Date of Origin: 08/05/2019
Dates Reviewed: 08/2019, 02/2020

I. Length of Authorization

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

II. Dosing Limits

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

Synribo 3.5 mg for injection SDV:
- Induction: 28 vials every 28 days (*until hematologic response is achieved, then begin maintenance*)
- Maintenance: 14 vials every 28 days

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

Induction:
- 9,800 billable units every 28 days until hematologic response is achieved, then begin maintenance

Maintenance:
- 4,900 billable units every 28 days

III. Initial Approval Criteria[1,2,3]

Coverage is provided in the following conditions:

- Patient is at least 18 years old; **AND**
- Patient's disease is confirmed by either a Philadelphia chromosome-positive (Ph+) or *BCR-ABL1* positive laboratory test result; **AND**

Chronic myelogenous leukemia (CML) †

- Used as single agent therapy for patients resistant, intolerant, or had an inadequate response after at least 3 months of therapy to TWO or more tyrosine kinase inhibitor (TKI) therapies (e.g., bosutinib, imatinib, dasatinib, ponatinib or nilotinib); **AND**
  - Patient has chronic phase CML; **OR**
  - Patient has advanced disease that has progressed to accelerated phase; **OR**
  - Patient has T315I mutation positive 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 Approved Indication(s)

IV. Renewal Criteria[1,3]

Coverage can be renewed based upon the following criteria:

- Patient continues to meet the criteria identified in Section III; **AND**
- Absence of unacceptable toxicity from the drug. Examples of unacceptable toxicity include: myelosuppression (e.g., severe neutropenia, thrombocytopenia, or anemia), hemorrhage (including cerebral and gastrointestinal), uncontrolled hyperglycemia, etc.; **AND**
- Patient has been adherent to therapy; **AND**
- Treatment response as indicated by one of the following:
  - Patient has *BCR-ABL1* (IS) transcript levels:
    - ≤ 10% at 3 months; **OR**
    - ≤ 10% at 6 months; **OR**
    - ≤ 0.1% or a ≥ 3-log reduction in *BCR-ABL1* mRNA from the standardized baseline, if qPCR (IS) is not available

    Note: cytogenetic assessment of response may be used if quantitative RT-PCR (QPCR) using International Scale (IS) for *BCR-ABL1* is not available

V. Dosage/Administration

Indication	Dose
Chronic myelogenous leukemia	Induction Dose: 1.25 mg/m² administered by subcutaneous injection twice daily for 14 consecutive days of a 28-day cycle. Repeat until a hematologic response is achieved, then begin maintenance. Maintenance Dose: 1.25 mg/m² administered by subcutaneous injection twice daily for 7 consecutive days of a 28-day cycle. Treatment should continue as long as patients are clinically benefiting from therapy.
– Synribo should be prepared/reconstituted in a healthcare facility by a healthcare professional – Synribo may be administered by the patient or caregiver with appropriate training and storage of the reconstituted product	

VI. Billing Code/Availability Information

HCPCS Code:

- J9262 – Injection, omacetaxine mepesuccinate, 0.01 mg; 1 billing unit = 0.01 mg

NDC:

- Synribo 3.5 mg single-use vial for injection: 63459-0177-xx

VII. References

1. Synribo [package insert]. North Wales, PA; Teva Pharmaceuticals USA, Inc.; November 2019. Accessed January 2020.
2. Referenced with permission from the NCCN Drugs & Biologics Compendium (NCCN Compendium®) for omacetaxine. National Comprehensive Cancer Network, 2019. 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 January 2020.
3. Referenced with permission from the NCCN Drugs & Biologics Compendium (NCCN Compendium®) for Chronic Myeloid Leukemia 2.2020. National Comprehensive Cancer Network, 2019. 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 January 2020.
4. Khoury HJ, Cortes J, Baccarani M, et al. Omacetaxine mepesuccinate in patients with advanced chronic myeloid leukemia with resistance or intolerance to tyrosine kinase inhibitors. Leuk Lymphoma. 2015 Jan;56(1):120-7.
5. Cortes JE, Kantarjian HM, Rea D, et al. Final analysis of the efficacy and safety of omacetaxine mepesuccinate in patients with chronic- or accelerated-phase chronic myeloid leukemia: Results with 24 months of follow-up. Cancer. 2015;121(10):1637–1644.
6. Talpaz M, Silver RT, Druker BJ, et al. Imatinib induces durable hematologic and cytogenetic responses in patients with accelerated phase chronic myeloid leukemia: results of a phase 2 study. Blood. 2002 Mar 15;99(6):1928-37.
7. Palandri F, Castagnetti F, Alimena G, et al. The long-term durability of cytogenetic responses in patients with accelerated phase chronic myeloid leukemia treated with imatinib 600 mg: the GIMEMA CML Working Party experience after a 7-year follow-up. Haematologica. 2009;94(2):205–212.
8. Kantarjian H, Cortes J, Kim DW, et al. Phase 3 study of dasatinib 140 mg once daily versus 70 mg twice daily in patients with chronic myeloid leukemia in accelerated phase resistant or intolerant to imatinib: 15-month median follow-up. Blood. 2009;113(25):6322–6329.
9. le Coutre PD, Giles FJ, Hochhaus A, et al. Nilotinib in patients with Ph+ chronic myeloid leukemia in accelerated phase following imatinib resistance or intolerance: 24-month follow-up results. Leukemia. 2012 Jun;26(6):1189-94.
10. Gambacorti-Passerini C, Kantarjian HM, Kim DW, et al. Long-term efficacy and safety of bosutinib in patients with advanced leukemia following resistance/intolerance to imatinib and other tyrosine kinase inhibitors. Am J Hematol. 2015;90(9):755–768.

11. Cortes J, Lipton JH, Rea D, et al. Phase 2 study of subcutaneous omacetaxine mepesuccinate after TKI failure in patients with chronic-phase CML with T315I mutation. Blood. 2012;120(13):2573–2580.
12. Cortes J, Digumarti R, Parikh PM, et al. Phase 2 study of subcutaneous omacetaxine mepesuccinate for chronic-phase chronic myeloid leukemia patients resistant to or intolerant of tyrosine kinase inhibitors. Am J Hematol. 2013;88(5):350–354.
13. Cortes JE, Kim DW, Pinilla-Ibarz J, et al. Ponatinib efficacy and safety in Philadelphia chromosome-positive leukemia: final 5-year results of the phase 2 PACE trial. Blood. 2018;132(4):393–404.
14. Kantarjian HM, O'Brien S, Cortes JE, et al. Imatinib mesylate therapy for relapse after allogeneic stem cell transplantation for chronic myelogenous leukemia. Blood. 2002 Sep 1;100(5):1590-5.
15. Magellan Health, Magellan Rx Management. Synribo Clinical Literature Review Analysis. Last updated January 2020. Accessed January 2020.

Appendix 1 – Covered Diagnosis Codes

ICD-10	ICD-10 Description
C92.10	Chronic myeloid leukemia, BCR/ABL-positive, not having achieved remission
C92.11	Chronic myeloid leukemia, BCR/ABL-positive, in remission
C92.12	Chronic myeloid leukemia, BCR/ABL-positive, in relapse

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) and Local Coverage Determinations (LCDs) 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): 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.

Medicare Part B Administrative Contractor (MAC) Jurisdictions		
Jurisdiction	**Applicable State/US Territory**	**Contractor**
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

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; TKI = tyrosine kinase inhibitor; HR = hematologic response; CHR = complete hematologic response; MaHR = major hematologic response; MCyR = major cytogenetic response; CCyR = complete cytogenetic response; MMR = major molecular response; GVHD = graft versus host disease

Chronic myelogenous leukemia (CML)

Accelerated Phase CML (AP-CML)							
Regimen	**NCCN Category**	**FDA Approved**	**Trial Design**	**Comparator**	**Primary End-Point**	**Line of Therapy**	**Conclusion**
Omacetaxine mepesuccinate	2A	Yes (chronic or accelerated phase CML with resistance and/or intolerance to 2 or more TKIs)	Phase 2	N/A	MaHR	After multiple TKIs	• Omacetaxine demonstrates activity with a MaHR of 37% in pretreated patients with AP-CML, irrespective of mutational status
Omacetaxine mepesuccinate	2A	Yes (chronic or accelerated phase CML with resistance and/or intolerance to 2 or more TKIs)	Phase 2 (CML 300)	N/A	MCyR	After prior imatinib and at least 1 other TKI	• In patients with AP-CML, 14% achieved or maintained major hematologic response for a median of 4.7 months.
Imatinib	2A	Yes (after interferon-alpha therapy)	Phase 2	N/A	-----	All lines of therapy	• Orally administered imatinib is an effective treatment for patients with CML in accelerated phase inducing a hematologic response of 82%.

Imatinib	2A	Yes (after interferon-alpha therapy)	Phase 2, multi-center	N/A	-----	All lines of therapy	• Imatinib may induce durable responses, associated with prolonged survival, in patients with accelerated phase chronic myeloid leukemia.
Dasatinib (twice daily dosing)	2A	Yes (after prior imatinib therapy)	Phase 3, randomized, multi-center, open-label	Dasatinib (once daily dosing)	MaHR	After prior imatinib therapy	• These results demonstrate that dasatinib 140 mg once daily has similar efficacy to dasatinib 70 mg twice daily but with an improved safety profile.
Nilotinib	2A	Yes (after prior imatinib therapy)	Phase 2, open-label	N/A	HR	After prior imatinib therapy	• Nilotinib treatment resulted in a high overall survival rate at 2 years (70%) and was generally well tolerated in this heavily pretreated AP-CML patient population.
Bosutinib	2A	Yes (after prior therapy)	Phase 1/2	N/A	HR	After prior imatinib therapy	• Responses were durable in ~50% AP-CML responders at 4 years
Chronic Phase CML (CP-CML)							
Regimen	**NCCN Category**	**FDA Approved**	**Trial Design**	**Comparator**	**Primary End-Point**	**Line of Therapy**	**Conclusion**
Omacetaxine mepesuccinate	2A	Yes (chronic or accelerated phase CML with resistance and/or intolerance to 2 or more TKIs)	Phase 2 (CML 202)	N/A	CHR	After prior imatinib	• Omacetaxine mepesuccinate is an effective treatment for CML patients with T315I mutation after TKI failure demonstrating a CHR of 77%.
Omacetaxine mepesuccinate	2A	Yes (chronic or accelerated phase CML with resistance and/or	Phase 2 (CML 203), open-label, multi-center	N/A	MCyR	After ≥ 2 prior TKI (all had received imatinib)	• Subcutaneous omacetaxine demonstrated a MCyR of 22% and CCyR of 4% in patients with chronic-phase CML with resistance or intolerance to multiple TKI therapies.

		intolerance to 2 or more TKIs)					
Ponatinib	2A	Yes (when no other TKI therapy is indicated or T315I CML; not for newly diagnosed CML)	Phase 2 (PACE)	N/A	MCyR	Previously treated with dasatinib or nilotinib OR T315I mutation positive	• These final PACE results demonstrate ponatinib provides durable and clinically meaningful responses (MCyR 56%) in this population of heavily pretreated CP-CML patients
Post-transplant							
Regimen	**NCCN Category**	**FDA Approved**	**Trial Design**	**Comparator**	**Primary End-Point**	**Line of Therapy**	**Conclusion**
Omacetaxine mepesuccinate	2A	No	No clinical evidence to support use.				
Imatinib	2A	No	Clinical trial	N/A	-----	Relapsed after ASCT	• Imatinib mesylate effectively controlled CML that recurred after ASCT, but it was associated with side effects including myelosuppression and recurrence of severe GVHD.