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Subject: Omacetaxine Mepesuccinate (Synribo®) Injection

THIS MEDICAL COVERAGE GUIDELINE IS NOT AN AUTHORIZATION, CERTIFICATION, EXPLANATION OF BENEFITS, OR A GUARANTEE OF PAYMENT, NOR DOES IT SUBSTITUTE FOR OR CONSTITUTE MEDICAL ADVICE. ALL MEDICAL DECISIONS ARE SOLELY THE RESPONSIBILITY OF THE PATIENT AND PHYSICIAN. BENEFITS ARE DETERMINED BY THE GROUP CONTRACT, MEMBER BENEFIT BOOKLET, AND/OR INDIVIDUAL SUBSCRIBER CERTIFICATE IN EFFECT AT THE TIME SERVICES WERE RENDERED. THIS MEDICAL COVERAGE GUIDELINE APPLIES TO ALL LINES OF BUSINESS UNLESS OTHERWISE NOTED IN THE PROGRAM EXCEPTIONS SECTION.

DESCRIPTION:

Omacetaxine mepesuccinate (Synribo) is a cephalotaxine ester that inhibits protein synthesis by binding to the A-site in the peptidyl-transferase center of the large ribosomal subunit. It reduces protein levels of Bcr-Abl and Mcl-1 independent of direct Bcr-Abl binding. Omacetaxine was given orphan designation status for the treatment of chronic myelogenous leukemia (CML) in March 2006 and was subsequently approved by the FDA in October 2012 for treatment of chronic phase (CP) or accelerated phase (AP) chronic myeloid leukemia (CML) that is resistant and/or intolerant to two or more tyrosine kinase inhibitors (TKI). In a pooled analysis of two studies, treatment with omacetaxine resulted in a major cytogenetic response rate of 18.4% in patients with CP-CML (n = 76) and a complete hematologic response rate or no evidence of leukemia (composite endpoint) of 14.3% in patients with AP-CML (n = 35). Omacetaxine has demonstrated efficacy in CML patients with the T315I mutation who had failed previous TKI therapy in a phase II study (n = 62). In May 2014, the FDA approved revised labeling to include home administration in patients appropriate for self-administration or for administration by a caregiver.

Chronic myeloid leukemia is a hematopoietic stem cell disease characterized by a reciprocal translocation between chromosomes 9 and 22, resulting in the formation of the Philadelphia

chromosome. CML occurs in three different phases (chronic, accelerated, and blast phase) and is usually diagnosed in the chronic phase. Untreated chronic phase CML will eventually progress to advanced phase disease in 3 to 5 years. The National Comprehensive Cancer Network (NCCN) CML guidelines provide treatment recommendations for all three phases. The National Comprehensive Cancer Network (NCCN) guidelines for CML (Version 1.2019) list imatinib, bosutinib, nilotinib, and dasatinib as category 1 options for the initial first-line treatment of chronic-phase CML in patients with a low-risk Sokal or Hasford score. For CP-CML patients with an intermediate- or high-risk score, imatinib is listed as category 2A option, while bosutinib, nilotinib, and dasatinib are listed as category 1 options. In addition, bosutinib, dasatinib and nilotinib have a footnote stating "Based on long-term follow-up data from the DASISION and ENESTnd trials and preliminary data from the BFORE trial, second generation TKIs (dasatinib, nilotinib, or bosutinib) are preferred for patients with an intermediate- or high-risk Sokal or Hasford score , especially for young women whose goal is to achieve a deep and rapid molecular response and eventual drug discontinuation of TKI therapy for fertility purposes." The imatinib listing for intermediate- or high-risk scores includes a footnote stating, "Imatinib may be preferred for older patients with comorbidities such as cardiovascular disease." Age, toxicity profile of the TKI, tolerance of adverse effects, and comorbid conditions also may affect initial choice of treatment. Allogenic hematopoietic cell transplantation (HCT) is no longer recommended as first-line treatment option for patient with CP-CML. If the 3-month response milestone (i.e., early molecular response) is not achieved after first-line TKI therapy, patients are considered to be a high risk for disease progression and alternative treatment options should be considered. Evaluation for allogenic HCT is recommended if the response milestones are not achieved at 3, 6, and 12 months. For patients who do not achieve response milestone or those with a loss of response, BCR-ABL1 mutational analysis is recommended, as it is helpful in the selection of subsequent TKI therapy. One important mutation, the T315I, is known as the "gatekeeper" mutation, as it displays resistance to all TKIs, with the exception of ponatinib. In patient with a T315I mutation, the NCCN lists the following as category 2A treatment options: ponatinib, omacetaxine, allogenic HCT, or clinical trial. Omacetaxine includes a footnote stating, "Omacetaxine is a treatment option for patients with disease that is resistant and/or intolerant to 2 or more TKIs." For the treatment of accelerated phase CML, the NCCN list the following category 2A treatment options: clinical trial, TKI, or omacetaxine. Omacetaxine includes a footnote stating, "Omacetaxine is a treatment option for patients with disease progression to accelerated phase CML. Omacetaxine is not a treatment option for patients who present with accelerated phase CML."

POSITION STATEMENT:

Comparative Effectiveness

Initiation of omacetaxine mepesuccinate (Synribo) meets the definition of **medical necessity** when **ALL** of the following criteria are met ("1" to "4"):

1. **EITHER** of the following ("a" or "b"):
    a. **BOTH** of the following ("i" and "ii"):
        i. Member has a diagnosis of Philadelphia-chromosome positive (Ph+) or BCR-ABL1-positive chronic myeloid leukemia (CML)
        ii. **ANY** of the following ("1, "2", "3", or "4"):

1. Member has chronic phase CML
2. Member has had disease progression to accelerated phase CML
3. Member has had an inadequate response to an allogeneic hematopoietic stem cell transplant (HCT)
4. Member has had disease relapse following an allogeneic HCT

b. **BOTH** of the following ("i" and "ii"):

i. Member has an FDA-approved or NCCN-supported diagnosis other than CML

ii. **EITHER** of the following is met:

1. Member is diagnosed with a condition that is consistent with an indication listed in the product's FDA-approved prescribing information (or package insert) AND member meets any additional requirements listed in the "Indications and Usage" section of the FDA-approved prescribing information (or package insert)
2. Indication **AND** usage is recognized in NCCN Drugs and Biologics Compendium as a Category 1 or 2A recommendation

2. **EITHER** of the following ("a" or "b"):

a. Member has tested positive for the T315I BCR-ABL kinase domain mutation (confirmatory laboratory documentation must be submitted)

b. Member meets any of the following ("i", "ii", or "iii") in reference to **TWO or more** TKI therapies (i.e., imatinib, dasatinib, nilotinib, or bosutinib)

i. Inadequate therapeutic response after at least 3 months of continuous treatment

ii. Persistent intolerable adverse effects despite appropriate dose modification (the specific adverse effect must be provided)

iii. FDA-labeled contraindication (the specific contraindication must be provided)

3. Member is **NOT** taking a TKI (i.e., imatinib, dasatinib, nilotinib, ponatinib, or bosutinib) concurrently with omacetaxine
4. Dosage of omacetaxine does not exceed 1.25 mg/m^2 twice daily for 14 consecutive days every 28 days

Approval duration: 6 months

Continuation omacetaxine (Synribo) meets the definition of **medical necessity** when **ALL** of the following criteria are met ("1", "2", "3" and "4"):

1. The member has been previously approved by Florida Blue or another health plan in the past 2 years for the treatment of CML or other FDA-approved or NCCN-supported diagnosis, **OR** the member has previously met all indication-specific criteria.
2. Member's disease has not progressed during treatment with omacetaxine.
3. Member is **NOT** taking a TKI (i.e., imatinib, dasatinib, nilotinib, ponatinib, or bosutinib) concurrently with omacetaxine.

4. The dosage does not exceed the following ("a" or "b") based on phase of treatment:
    a. Members still receiving initiation therapy (i.e., hematologic response has not yet been achieved): 1.25 mg/m^2 twice daily for 14 consecutive days every 28 days
    b. Members receiving maintenance therapy (i.e., hematologic response has been achieved): 1.25 mg/m^2 twice daily for 7 consecutive days every 28 days

Approval duration: 1 year

NOTE: Quest Diagnostics® can perform the BCR-ABL kinase domain mutation test. Current NCCN guidelines recommend checking mutational analysis in the following situations: if there is inadequate initial response, any sign of loss of response, and in disease progression to accelerate-phase or blast-phase CML (CML-AP and CML-BP, respectively).

DOSAGE/ADMINISTRATION:

THIS INFORMATION IS PROVIDED FOR INFORMATIONAL PURPOSES ONLY AND SHOULD NOT BE USED AS A SOURCE FOR MAKING PRESCRIBING OR OTHER MEDICAL DETERMINATIONS. PROVIDERS SHOULD REFER TO THE MANUFACTURER'S FULL PRESCRIBING INFORMATION FOR DOSAGE GUIDELINES AND OTHER INFORMATION RELATED TO THIS MEDICATION BEFORE MAKING ANY CLINICAL DECISIONS REGARDING ITS USAGE.

FDA-approved: omacetaxine is indicated for the treatment of adults with chronic or accelerated phase chronic myeloid leukemia (CML) with resistance and/or intolerance to two or more tyrosine kinase inhibitors. The induction dose is 1.25 mg/m^2 subcutaneously twice daily for 14 days repeated every 28 days, over a 28-day cycle. Cycles should be repeated every 28 days until a hematologic response is achieved. The recommended maintenance dose is 1.25 mg/m^2 subcutaneously twice daily for seven days repeated every 28 days, over a 28 day cycle. Treatment should be continued for as long as a clinical benefit is observed. In clinical trials, the median duration of therapy was 7.4 months (median of 6 treatment cycles) in patients with chronic phase CML and 1.9 months (median of 2 treatment cycles) in those with accelerated phase CML.

Before a decision is made to allow home administration ensure that the member is an appropriate candidate for self-administration or for administration by a caregiver. Provide training on proper handling, storage conditions, administration, disposal, and clean-up of accidental spillage of the product. Ensure the member receives the necessary supplies for home administration. At minimum these should include:

- Reconstituted patient-specific dose in syringe with a capped needle for subcutaneous injection
- Protective eyewear and gloves
- An appropriate biohazard container
- Absorbent pad(s) for placement of administration materials and for accidental spillage
- Alcohol swabs and gauze pads
- Ice packs or cooler for transportation of reconstituted syringes

Dose Modifications:

- Hematologic Toxicity: treatment cycles may be delayed and/or the number of days of dosing during the cycle reduced for hematologic toxicities (e.g. neutropenia, thrombocytopenia). If a patient experiences Grade 4 neutropenia (absolute neutrophil count (ANC) less than 0.5 x 10^9/L) or Grade 3 thrombocytopenia (platelet counts less than 50 x 10^9/L) during a cycle, delay starting the next cycle until ANC is greater than or equal to 1 x 10^9/L and platelet count is greater than or equal to 50 x 10^9/L. Also, for the next cycle, reduce the number of dosing days by 2 days (e.g., to 12 or 5 days).

Drug Availability: supplied as a sterile, preservative-free, single-use vial containing 3.5 mg of omacetaxine mepesuccinate as a lyophilized powder.

PRECAUTIONS:

CONTRAINDICATIONS

- None

PRECAUTIONS/WARNINGS

- **Myelosuppression:** Severe and fatal thrombocytopenia, neutropenia and anemia. Monitor hematologic parameters frequently (i.e., weekly during induction and initial maintenance cycles, then every 2 weeks thereafter or as clinically indicated).
- **Bleeding:** Severe thrombocytopenia and increased risk of hemorrhage. Fatal cerebral hemorrhage and severe, non-fatal gastrointestinal hemorrhage.
- **Hyperglycemia:** Glucose intolerance and hyperglycemia including hyperosmolar non-ketotic hyperglycemia.
- **Embryo-fetal toxicity:** Can cause fetal harm. Advise females of reproductive potential to avoid pregnancy.

BILLING/CODING INFORMATION:

The following codes may be used to describe:

HCPCS Coding

J9262	Injection, omacetaxine mepesuccinate, 0.01 mg

ICD-10 Diagnosis Codes That Support Medical Necessity

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

REIMBURSEMENT INFORMATION:

Refer to section entitled **POSITION STATEMENT**.

PROGRAM EXCEPTIONS:

Federal Employee Program (FEP): Follow FEP guidelines.

State Account Organization (SAO): Follow SAO guidelines.

Medicare Advantage Products: No National Coverage Determination (NCD) and/or Local Coverage Determination (LCD) were found at the time of the last guideline review date.

Medicare Part D: Florida Blue has delegated to Prime Therapeutics authority to make coverage determinations for the Medicare Part D services referenced in this guideline.

If this Medical Coverage Guideline contains a step therapy requirement, in compliance with Florida law 627.42393, members or providers may request a step therapy protocol exemption to this requirement if based on medical necessity. The process for requesting a protocol exemption can be found at Coverage Protocol Exemption Request.

DEFINITIONS:

Accelerated Phase CML: is a phase of chronic myelogenous leukemia in which the disease is progressing.

Blast Phase CML: is the final phase in the evolution of CML, and behaves like an acute leukemia, with rapid progression and short survival.

Chronic Phase CML: approximately 85% of members with CML are in the chronic phase at the time of diagnosis. During this phase, members are usually asymptomatic or have only mild symptoms of fatigue, left side pain, joint and/or hip pain, or abdominal fullness.

Chronic Myelogenous Leukemia (CML): also known as chronic granulocytic leukemia (CGL), is a cancer of the white blood cells. It is a form of leukemia characterized by the increased and unregulated growth of predominantly myeloid cells in the bone marrow and the accumulation of these cells in the blood.

Cytogenetic: is a branch of genetics that is concerned with the study of the structure and function of the cell, especially the chromosomes. It includes routine analysis of G-banded chromosomes, other cytogenetic banding techniques, as well as molecular cytogenetics such as fluorescent in situ hybridization (FISH) and comparative genomic hybridization (CGH).

Induction Chemotherapy: the use of drug therapy as the initial treatment for patients presenting with advanced cancer that cannot be treated by other means.

Philadelphia chromosome or Philadelphia translocation: is a specific chromosomal abnormality that is associated with chronic myelogenous leukemia (CML).

RELATED GUIDELINES:

Allogeneic Bone Marrow and Stem Cell Transplantation, 02-38240-01

Cytogenetic Studies (Chromosomal Studies), 05-82000-18

Dasatinib (Sprycel) Tablets, 09-J1000-43

Imatinib Mesylate (Gleevec) Tablets, 09-J1000-46

Nilotinib (Tasigna) Capsules, 09-J1000-48

Bosutinib (Bosulif) Tablets, 09-J1000-84

Ponatinib (Iclusig) Tablets, 09-J1000-89

OTHER:

None applicable.

REFERENCES:

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2. 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 May 15;121(10):1637-44.
3. 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 Sep 27;120(13):2573-80.
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8. National Comprehensive Cancer Network. Clinical Practice Guidelines in Oncology Version 1.2019. Chronic Myelogenous Leukemia. Available at http://www.nccn.org/professionals/physician_gls/PDF/cml.pdf. Accessed 12/31/18.
9. Synribo (omacetaxine mepesuccinate) [package insert]. Teva Pharmaceuticals, Inc. North Wales (PA): November 2018.

COMMITTEE APPROVAL:

This Medical Coverage Guideline (MCG) was approved by the Florida Blue Pharmacy Policy Committee on 02/11/26.

GUIDELINE UPDATE INFORMATION:

03/15/13	New Medical Coverage Guideline.
01/01/14	Revision to guideline; consisting of code update.
03/15/14	Review and revision to guideline; consisting of reformatting position statement, updated dosage/administration section, program exceptions, and references.
03/15/15	Review and revision to guideline; consisting of revising position statement, and updating the description, dosage/administration, and references.

11/01/15	Revision: ICD-9 Codes deleted.
03/15/16	Review and revision to guideline consisting of description, position statement, definitions, and references.
03/15/17	Review and revision to guideline consisting of removal of the age requirement in the position statement, and updates to description section, definitions, and references.
02/15/18	Review and revision to guideline consisting of updates to description, position statement, definitions, related guidelines and references sections.
02/15/19	Review and revision to guideline consisting of updates to description, position statement, and references sections.
3/15/26	Retire MCG. Synribo was withdrawn from the US market.