OMACETAXINE MEPESUCCINATE

Generic	Brand	HICL	GCN	Exception/Other
OMACETAXINE MEPESUCCINATE	SYNRIBO	24243		

This drug requires a written request for prior authorization.

GUIDELINES FOR USE

1. Does the patient have a diagnosis of chronic myeloid leukemia (CML)?

   If yes, continue to #2.
   If no, do not approve.
   DENIAL TEXT: See the denial text at the end of the guideline.

2. Is this for induction therapy?

   If yes, continue to #3.
   If no, continue to #5.

3. Has the patient previously tried at least two of the following or does the patient have a contraindication to Gleevec, Sprycel, Tasigna, Bosulif, or Iclusig?

   If yes, continue to #4.
   If no, do not approve.
   DENIAL TEXT: See the denial text at the end of the guideline.

4. Has the patient received less than 6 fills for Synribo?

   If yes, **approve for 3 fills by HICL with a quantity limit of #28 vials per 28 days supply.**
   PAC Note: Patient should receive a maximum of 6 fills of Synribo when used as induction therapy.
   If no, do not approve.
   DENIAL TEXT: See the denial text at the end of the guideline.

5. Has the patient achieved a hematologic response (defined as an absolute neutrophil count (ANC) greater than or equal to 1.5 x 10(9)/L, AND platelets greater than or equal to 100 x 10(9)/L, AND no blood blasts; OR bone marrow blasts less than 5 percent)?

   If yes, **approve for 12 fills by HICL with a quantity limit of #14 vials per 28 days supply.**
   If no, **approve for 3 fills by HICL with a quantity limit of #28 vials per 28 days supply.**

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GUIDELINES FOR USE (CONTINUED)

DENIAL TEXT: Our guideline for **OMACETAXINE** requires a diagnosis of chronic myeloid leukemia (CML) and a trial of at least two of the following therapies: Gleevec, Sprycel, Tasigna, Bosulif, or Iclusig. Approval of Synribo beyond 6 treatment cycles requires evidence of a hematologic response.

RATIONALE

Ensure appropriate utilization of Synribo based on FDA approved indication and dosage.

Synribo should be prepared in a healthcare facility and must be reconstituted by a healthcare professional. Before a decision is made to allow Synribo to be administered by someone other than a healthcare professional, ensure that the patient 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 that patients receive the necessary supplies for home administration. At minimum these should include:

- Reconstituted Synribo in syringe with a capped needle for subcutaneous injection. Syringe(s) should be filled to the patient-specific dose.
- Protective eyewear.
- Gloves.
- An appropriate biohazard container.
- Absorbent pad(s) for placement of administration materials and for accidental spillage.
- Alcohol swabs.
- Gauze pads.
- Ice packs or cooler for transportation of reconstituted Synribo syringes

If a patient or caregiver cannot be trained for any reason, then in such patients, Synribo should be administered by a healthcare professional.

DOSAGE

The recommended induction dosing schedule is 1.25 mg/m^2 administered subcutaneously twice daily for 14 consecutive days every 28 days, over a 28-day cycle, and should be repeated every 28 days until patients achieve a hematologic response.

The recommended maintenance schedule is 1.25 mg/m^2 administered subcutaneously twice daily for 7 consecutive days every 28 days, over a 28-day cycle, and should continue as long as patients are clinically benefiting from therapy.

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RATIONALE (CONTINUED)
Complete blood counts (CBCs) should be performed weekly during induction and initial maintenance cycles followed by every two weeks thereafter, or as clinically indicated. If a patient experiences Grade 4 neutropenia (absolute neutrophil count (ANC) <0.5 x 10^9/L) or Grade 3 thrombocytopenia (platelet counts <50 x 10^9/L) during a cycle, the next cycle should be delayed until the ANC is >1.0 x 10^9/L and platelet count is >50 x 10^9/L, and the number of dosing days should be reduced by two days (for example to 12 or 5 days).

Synribo is a first-in-class cephalotaxine that functions as a protein synthesis inhibitor in CML. CML is a malignant clonal disorder that results in rapid growth of myeloid stem cells in the bone marrow. It is usually associated with a chromosomal abnormality that results from the fusion of the BCR and ABL1 genes, called the Philadelphia (Ph) chromosome. Normally, the ABL1 gene produces a protein with tyrosine kinase catalytic activity that is tightly regulated. The fused BCR-ABL1 gene in the Ph chromosome however, produces a protein with deregulated and constitutively active kinase activity that is fundamental to the pathogenesis of CML. The mainstay of treatment in CML over the last decade has been inhibition of the enzymatic activity of those proteins, and thus the TKIs Gleevec, Sprycel, and Tasigna are designated as first line treatment of CML in the National Comprehensive Cancer Network clinical practice guidelines. Another TKI, Bosulif, was approved earlier this year for treatment-resistant patients. It is currently being studied in a phase III open-label trial versus Gleevec for patients with newly diagnosed CML. However, because there are patients that fail, cannot tolerate, or are resistant to TKI therapy, new therapies, such as Synribo, are being explored. Synribo is unique in that it inhibits protein synthesis independently of direct BCR-ABL1 binding, and therefore, provides a different mechanism to help control the cancer and delay its progression to an acute leukemia for those who have already tried TKI based therapy.

Synribo was approved under the FDA's accelerated approval program. The accelerated approval allows the FDA to approve a drug to treat a serious disease based on clinical data showing that the drug has an effect on a surrogate endpoint that is reasonably likely to predict a clinical benefit to patients. All accelerated approvals come with the caveat that the manufacturer must conduct additional clinical studies to confirm the drug's clinical benefit and safe use.

Effectiveness was based on data from two Phase II, open-label, multicenter, single-arm trials enrolling a combined cohort of 111 patients with chronic phase CML or accelerated phase CML who had received 2 or more approved TKIs and had, at a minimum, documented evidence of resistance or intolerance to dasatinib and/or nilotinib.

The efficacy endpoint for the 76 patients in chronic phase CML was major cytogenetic response (MCyR) as demonstrated by a reduction in the percentage of cells expressing the Philadelphia chromosome genetic mutation. MCyR was achieved in 14 out of 76 patients (18.4 percent) with a mean onset time of 3.5 months and Kaplan-Meier estimated median reduction duration of 12.5 months.

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RATIONALE (CONTINUED)
For the 35 patients in accelerated phase CML, the efficacy endpoints of MCyR or major hematologic response (MaHR) as demonstrated by either normalization of white blood cell counts (complete hematologic response [CHR]) or no evidence of leukemia (NEL) were evaluated. Five out of the 35 patients (14.3 percent) achieved MaHR with a mean response onset time of 2.3 months and Kaplan-Meier estimated median duration of 4.7 months. MCyR was not achieved in any of the 35 patients.

Warnings and precautions for Synribo include: myelosuppression, including severe and fatal thrombocytopenia, neutropenia and anemia; bleeding, including fatal cerebral hemorrhage and severe, non-fatal gastrointestinal hemorrhage; hyperglycemia, including glucose intolerance and hyperosmolar non-ketotic hyperglycemia; and embryo-fetal toxicity.

The most common adverse reactions observed in clinical trials include thrombocytopenia, anemia, neutropenia, including febrile neutropenia, diarrhea, nausea, weakness and fatigue, injection site reaction, and lymphopenia. Synribo is pregnancy category D and may cause fetal harm. Females of reproductive potential should avoid pregnancy while undergoing Synribo treatment. Clinical drug interaction trials were not performed on Synribo based on the lack of interactions seen during in vitro studies.

FDA APPROVED INDICATIONS
Treatment of adult patients with chronic or accelerated phase chronic myeloid leukemia (CML) with resistance and/or intolerance to two or more tyrosine kinase inhibitors (TKI) based upon response rate. There are no trials verifying an improvement in disease-related symptoms or increased survival with Synribo.

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REFERENCES

- Synribo [Prescribing Information]. North Wales, PA: Teva Pharmaceuticals USA, Inc.; April 2014.
- FDA News Release. FDA approves Synribo for chronic myelogenous leukemia. Available at: http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm325895.htm [Accessed November 19, 2012].
- National Comprehensive Cancer Network. Chronic Myelogenous Leukemia 4.2013. Available at: http://www.nccn.org/professionals/physician_gls/pdf/cml.pdf [Accessed April 23, 2013]
- Teva News Release. Teva Receives Approval For SYNRIBO™ (Omacetaxine Mepesuccinate) for Injection. Available at http://ir.tevapharm.com/phoenix.zhtml?c=73925&p=irol-newsArticle&ID=1750668&highlight [Accessed November 20, 2012].
- Omacetaxine: issues you may want to know. Available at: http://www.omacetaxine.info/ [Accessed November 20, 2012].
- Van Etten, RA. Clinical manifestations and diagnosis of chronic myeloid leukemia. In: UpToDate, Larson, RA (Ed), UpToDate, Waltham, MA, 2012.
- Tefferi, A. Overview of the myeloproliferative neoplasms. In: UpToDate, Schrier, SL (Ed), UpToDate, Waltham, MA, 2012.
- Negrin, RS., Schiffer, CA. Overview of the treatment of chronic myeloid leukemia. In: UpToDate, Larson, RA (Ed), UpToDate, Waltham, MA, 2012.

Library	Commercial	NSA
Yes	Yes	No

Part D Effective: N/A
Commercial Effective: 07/01/14
Created: 12/12
Client Approval: 05/14
P&T Approval: 05/13