Omacetaxine Mepesuccinate (Synribo)

National Drug Monograph

October 2015

VA Pharmacy Benefits Management Services, Medical Advisory Panel, and VISN Pharmacist Executives

The purpose of VA PBM Services drug monographs is to provide a focused drug review for making formulary decisions. Updates will be made when new clinical data warrant additional formulary discussion. Documents will be placed in the Archive section when the information is deemed to be no longer current.

FDA Approval Information	
Description/Mechanism of Action	Omacetaxine mepesuccinate (referred to as omacetaxine for the remainder of this document) is a semisynthetic formulation of homoharringtonine, a cytotoxic plant alkaloid that functions independent of direct BCR-ABL binding. The drug binds to the A-site cleft of ribosomes, resulting in transient inhibition of protein synthesis. Preclinical studies noted selective reduction of BCR-ABL levels and other oncoproteins upregulated in leukemic cells, thereby inducing apoptosis in CML cell lines. The action of omacetaxine is not targeted.
Indication(s) Under Review in this document (may include off label)	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).
Dosage Form(s) Under Review	Single-use vial containing 3.5 mg of omacetaxine as a lyophilized powder
REMS	☐ REMS ☐ No REMS ☐ Postmarketing Requirements *See Other Considerations for additional REMS information*
Pregnancy Rating	Category D

Executive Summary	
Efficacy	• FDA-approval for omacetaxine is based upon two open-label, single-arm, phase 2 trials that included populations of patients with CP-CML and AP-CML who had already received two or more TKIs with evidence of resistance or intolerance to therapy. • Accelerated approval was granted based upon the positive trial results in the absence of any approved drug in the third-line setting for the treatment of CML. • There have been no direct comparisons between omacetaxine and TKI therapy. • Omacetaxine is active against the T315I kinase mutation and is active in patients who have resistance/intolerance to 3 prior TKIs
Safety	• Myelosuppression (thrombocytopenia, neutropenia, anemia) can be severe. Severity can be worse in patients aged ≥ 65 years. • Thrombocytopenia may increase risk of bleed. • Home administration considerations are provided; FDA concerns await completion of study to analyze safety data related to home administration. • Severe hyperglycemia noted in 11% of the study population.
Other Considerations	• Dosing is complex; drug requires reconstitution, subcutaneous administration and twice daily dosing on 28-day cycles identified as either induction (7 treatment days) vs. maintenance therapy (14 treatment days). Dose adjustments can involve reduction in volume of drug administered and/or reduction in treatment-days.

	Outcome in clinically significant area	CP: MCyR (R/I; T315I) AP: CHR
	Effect Size	CP: MCyR 22% (R/I); 18.4% (T315I+); Duration 12.5 mos [95% CI, 3.5 – NR] AP: MaHR 14% [95% CI, 4.5-30.3]; Duration 4.7 mos;
	Potential Harms	CP: Thrombocytopenia (85%), neutropenia (81%), anemia (62%) AP: Thrombocytopenia (88%), neutropenia (71%), anemia (80%), Safety concerns with home administration
	Net Clinical Benefit	Moderate (high benefit with high risk of harm)
Potential Impact	• Omacetaxine has activity against the T315I mutation. • Current evidence also supports consideration of use in patients who have not responded to two or more TKIs, but efficacy and safety follow-up are limited at this point. It provides a different mechanism in the CML armamentarium. • Education of safety profile is important for providers and patients; cautious patient selection with diligent monitoring is necessary for safe use. • Logistics associated with clinic or home administration are complex and require careful patient selection and planning.	

Background

Purpose for review

Accelerated FDA approval in October 2012;
Full FDA approval in February 2014.

Issues to be determined:
Does omacetaxine offer advantages to currently available alternatives?
What safety issues need to be considered?

Other therapeutic options

(1) 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).

CML chronic myeloid leukemia;
Ph+ Philadelphia chromosome positive
CP chronic phase
AP accelerated phase
BC blast crisis
W/P warnings/precautions
BMS bone marrow suppression
PAH pulmonary arterial hypertension
TKIs tyrosine kinase inhibitors
CHF congestive heart failure
LV left ventricle
CV cardiovascular
HTN hypertension

Formulary Alternatives	Other Considerations
None	

Non-formulary Alternative	Other Considerations
Ponatinib	Oral formulation; approved in T315I-positive CML in CP, AP or BC; Boxed warning: Vascular occlusion, heart failure, hepatotoxicity W/P: HTN, pancreatitis, neuropathy, ocular toxicity, hemorrhage, fluid retention, cardiac arrhythmias, BMS, impaired wound healing/GI perforation
Dasatinib	Oral formulation; approved in newly diagnosed Ph+ CML in CP; also in CP, AP or BC with resistance/intolerance to prior therapy including imatinib; W/P: fluid retention, QT prolongation, PAH, CV toxicity
Nilotinib	Oral formulation; approved in newly diagnosed Ph+ CML in CP; also in CP and AP with resistance/intolerance to prior therapy including imatinib; Boxed warning: QT prolongation, sudden death W/P: BMS, cardiac/arterial vascular occlusive events, pancreatitis, hepatotoxicity, electrolyte abnormalities, hemorrhage, fluid retention
Bosutinib	Oral formulation; Approved in chronic, accelerated or blast phase Ph+ chronic myelogenous leukemia (CML) with resistance or intolerance to prior therapy; W/P: GI toxicity, BMS, hepatotoxicity, renal toxicity, fluid retention

Efficacy (FDA Approved Indications)

Literature Search Summary

A literature search was performed on PubMed/Medline (1966 to August 2015) using the search terms omacetaxine and Synribo. The search was limited to studies performed in humans and published in the English language. Reference lists of review articles and the manufacturer's AMCP dossier were searched for relevant clinical trials. All randomized controlled trials published in peer-reviewed journals were included.

Review of Efficacy

A. Response Definitions

Table 2. Omacetaxine Response Criteria

Response by Disease	Definitions
CP-CML	**Complete Hematologic Response (CHR)** • WBC < 10×10^9 /L • Basophils < 20% in peripheral blood • Myelocytes + metamyelocytes < 5%; no blasts or promyelocytes • Platelet count < 450×10^9 /L • No extra-medullary disease • Response lasting ≥ 8 weeks **Major hematologic response (MHR)** • **Complete Hematologic Response (CHR)** maintained ≥ 4 weeks **OR** • **No Evidence of Leukemia (NEL)**
AP-CML	**Complete Hematologic Response (CHR) maintained ≥ 4 weeks** • WBC ≤ ULN • ANC ≥ 1500/mm^3 • Platelets ≥ 100,000/mm^3 • No blasts on peripheral blood • Marrow blasts ≤ 5% • No extramedullary involvement (no hepatomegaly or splenomegaly) • Response lasting ≥ 4 weeks **No Evidence of Leukemia (NEL)** • WBC ≤ ULN • No blasts or promyelocytes on peripheral blood • Marrow blasts ≤ 5% • < 5% myelocytes + metamyelocytes in peripheral blood • Basophils < 5% in peripheral blood • No extramedullary involvement (no hepatomegaly or splenomegaly) • At least one of the following: -Platelets 20-100,000/mm^3 -ANC 500-1000/mm^3
All phases CML	**Cytogenetic** **Major (MCyR):** 0-35% Ph+ metaphases (complete + partial) **Complete (CCyR):** No Ph+ metaphases **Partial:** 1-35% Ph+ metaphases

B. Summary of Evidence

Review of Efficacy

Trial/design	Inclusion/Exclusion/Demo	Intervention	Results
Cortes 2012 Omacetaxine 202 Study Group Prospective, MC, Single-arm, OL N=62 (T315I+) IMA imatinib DAS dasatinib NIL nilotinib CV cardiovascular NYHA New York Heart Assoc. ECOG PS Eastern Cooperative Oncology Group Performance Status TKI tyrosine kinase inhibitor ULN upper limit of normal Ph+ Philadelphia chromosome positive R/I resistance/intolerance	Inclusion Ph+ CML with history of T315I mutation, failed imatinib, ECOG PS 0-2 Exclusion NYHA (III or IV); CV ischemia or MI in 12 wks; Uncontrolled active infection; HIV+ Prior TKI: IMA 100% DAS 55% NIL 36%	Omacetaxine at home Induction: 1.25 mg/m^2 subq BID x 14 days; repeat every 28 days to CHR or max 6 cycles After CHR, Maintenance: 1.25 mg/m^2 subq BID x 7 days; repeat every 28 days Assessments: Induction q 7d Maintenance q 14d, then q 3 mos	Primary endpoint: CHR or MCyR CHR 48 (77%) No response 12 (19%) MCyR 14 (23%) CCyR 10 (16%) Partial 4 (6%) No response 23 (37%) Median #cycles to CHR: 1 (range, 1-5) Time 0.46 mos Duration 9.1 mos (2-46+) Median #cycles MCyR 2.5 (range 2-5) Time 4.2 mos Duration 6.6 (2.1-30+) Follow-up at 19 mos: Median PFS 7.7 mos Median OS Not reached
Cortes 2013 Omacetaxine 203 Study Group OL, Single-arm N=46 DAS dasatinib NIL nilotinib CV cardiovascular NYHA New York Heart Assoc. ECOG PS Eastern Cooperative Oncology Group Performance Status TKI tyrosine kinase inhibitor ULN upper limit of normal Ph+ Philadelphia chromosome positive R/I resistance/intolerance	Inclusion Ph+CML in CP with R/I to prior treatment with ≥ 2 TKIs (≥ 1 TKI if from India) Tbili ≤ 2x ULN; ALT ≤ 3x ULN; SCr ≤ 1.5x ULN; ECOG PS 0-2 Exclusion NYHA (III or IV heart disease); Active CV ischemia; MI in prior 12 weeks; Interfering concurrent illness (malignancy, infection) Lymphoid Ph+ blast phase Median age 58 yrs (20-78); Median time from diagnosis 6.2 yrs (0.66-18.4); Mutation analysis on 33 pts; 13 with BCR-ABL mutations; F395V (n=4); V299L (n=3); Rec'd ≥ 2 prior TKIs: 85%; Rec'd ≥ 3 prior TKIs: 59%; DAS 83%; NIL 57%	Omacetaxine at home Induction: 1.25 mg/m^2 subq BID x 14 days; repeat every 28 days to CHR or max 6 cycles After CHR, Maintenance: 1.25 mg/m^2 subq BID x 7 days; repeat every 28 days Assessments: Induction q 7d Maintenance q 14d, then q 3 mos	Primary endpoint: CHR > 8 weeks or MCyR CHR 31 (67%); partial 0 No response 10 (22%) Med response duration 7 mos MCyR 10 (22%); CCyR 2 (4%) No response 18 (39%) Median PFS 7.0 mos [95% CI, 5.9-8.9] Median OS 30.1 mos [95% CI, 20.3 – NR] Median 4.5 treatment cycles (1-36) Median duration 5.1 mos (0.2-33.3)
Cortes 2015 Omacetaxine 300 (202 + 203) CP-CML (n=76) AP-CML (N=35)	Inclusion Ph+CML in CP with R/I to prior treatment with ≥ 2 TKIs (≥ 1 TKI if from India) Tbili ≤ 2x ULN; ALT ≤ 3x ULN; SCr ≤ 1.5x ULN; ECOG PS 0-2 Exclusion NYHA (III or IV heart disease); Active CV ischemia; MI in prior 12 weeks;	Omacetaxine at home Induction: 1.25 mg/m^2 subq BID x 14 days; repeat every 28 days to CHR or max 6 cycles After CHR, Maintenance: 1.25 mg/m^2 subq BID x 7 days; repeat every 28 days Assessments: Induction q 7d Maintenance q 14d, then q 3 mos	Final analysis at 24 months Results as overall and Primary endpoint: CP-CML: MCyR AP-CML: MHR ≥ 4 wks or NEL and/or MCyR CP-CML MCyR (14/76) 18%; CCyR (7/76) 8% Duration 12.5 mos [95% CI, 3.5-NR] OS 40.3 mos [95% CI, 23.8-NR] 50 CP-CML > 3 cycles; MCyR 22% 3 CP-CML ≥ 12 mos

	Interfering concurrent illness (malignancy, infection) Lymphoid Ph+ blast phase		16 T315I+; 19% MCyR 21 CP-CML > 12 cycles; MCyR 29% CP-CML > 3 cycles PFS 9.9 mos; OS 49.3 mos Overall PFS 9.6 mos; OS 40.3 mos AP-CML MHR (5/35) 14%; CHR 4; NEL 1 Duration MHR 4.7 mos MCyR 0 PFS 3.6 mos; OS 14.3 mos 14 AP-CML > 3 cycles; MHR 29% 3 AP-CML > 12 cycles; MHR 3-5 mos 1 AP-CML = 22 cycles; MHR 11.4 mos PFS 7 mos; OS 24.6 mos CP-CML rec'd > 3 cycles: Median OS 49.3 mos [95% CI, 23.8 mos to NR] AP-CML rec'd > 3 cycles: Median OS 24.6 mos [95% CI, 12-37.2 ms] Median study duration CP-CML 8.8 mos; AP-CML 3.4 mos If > 3 cycles received, a trend of longer PFS and OS was noted. Most responses achieved in 1st 3 months, but some as late as 8.5 mos T315I transcripts undetectable in some responding patients

- FDA-approval for omacetaxine is based upon two open-label, single-arm, phase 2 trials that included populations of patients with CP-CML and AP-CML who had already received two or more TKIs with evidence of resistance or intolerance to therapy. The final study population included both CP- and AP-CML patients. Accelerated approval was granted based upon the positive trial results in the absence of any approved drug in the third-line setting for the treatment of CML.
- The primary efficacy endpoint for the CP-CML population was the proportion achieving MCyR; the primary efficacy endpoint for AP-CML was MHR.
- Most responses are achieved in initial 3 months, but some responses were seen as late as 8.5 months
- T315I transcripts reached undetectable levels in some responding patients. The authors suggest that this may enable re-challenge with second-generation TKIs in the future.
- Improvement in PFS and OS appeared to be correlated with increasing number of cycles

Summary of Major Clinical Trial Endpoints Among Drugs with Activity in Resistant/Intolerant CP-CML[1,2,3,4,5]

Drug/Setting	Point of follow-up	Hematologic Response (%)	Cytogenetic Response (%)	PFS (months)	OS (months)
Omacetaxine/T315I+	12 months	CHR 77	MCyR 23	7.7	N/R
Omacetaxine/≥ 2 TKIs	12 months	CHR 67	MCyR 22 CCyR 2	7.0	30.1
	24 months	N/A	MCyR 18 CCyR 8	9.6	40.3
Bosutinib/≥ 2 TKIs	6 months	CHR 73	MCyR 32 CCyR 24	At 24 mos: 73%	At 24 mos: 83%
Ponatinib/ T315I+	15 months	N/A	MCyR 70	At 12 mos: 80%	At 12 mos: 94%
Ponatinib/≥ 2 TKIs	15 months	N/A	MCyR 51		

1. Cortes J, Lipton JH, Rea D, et al for the Omacetaxine 202 Study Group. Phase 2 study of subcutaneous omacetaxine mepesuccinate after TKI failure in patients with chronic phase CML with T315I mutation. Blood 2012; 120: 2573.
2. Cortes J, Digumarti R, Parikh PM, et al. for the Omacetaxine 203 Study Group. 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: 350.
3. 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: 1637.
4. Khoury HJ, Cortes JE, Kantarjian HM, et al. Bosutinib is Active in Chronic Phase Chronic Myeloid Leukemia after Imatinib and Dasatinib and/or Nilotinib Therapy Failure. Blood 2012; 119: 3403-3412.
5. Cortes JE, Kim DW, Pinilla-Ibarz P, et al. for the PACE Investigators. A Phase 2 Trial of Ponatinib in Philadelphia Chromosome-Positive Leukemias. N Engl J Med 2013; 369: 1783.

Potential Off-Label Use

Research with omacetaxine mepesuccinate is ongoing in the following areas:

- Omacetaxine mepesuccinate and Decitabine in Acute Myelogenous Leukemia (AML) and Myelodysplastic Syndrome (MDS)
- Omacetaxine mepesuccinate with standard AML induction of cytarabine and idarubicin
- Omacetaxine mepesuccinate as AML consolidation and maintenance therapy

Safety

(for more detailed information rfer to th product package insert)

Comments

Boxed Warning

- None

Contraindications

- None

Warnings/Precautions

- Myelosuppression. Severe and fatal thrombocytopenia, neutropenia and anemia have occurred in patients with chronic and accelerated phase CML.

Event (Grade 3 or 4)	CP	AP
Thrombocytopenia	85	88
Neutropenia	81	71
Anemia	62	80

Overall, fatalities due to myelosuppression occurred in 3% of the safety population (n=163). Monitor CBC weekly during induction and initial maintenance cycles then every 2 weeks during later maintenance cycles, as clinically indicated. Myelosuppression was generally reversible and managed by delaying cycles and/or dose-reduction.

- Bleeding. Severe thrombocytopenia increases the risk of bleed.

Event	Severity	Incidence (%)
Cerebral hemorrhage	Fatal	2
GI bleed	Non-fatal	2

Monitor platelet counts with CBC as recommended above. Avoid anticoagulants, aspirin and NSAIDs when platelet count < 50,000/µL as risk of bleed may increase.

- Hyperglycemia. Grade 3 or 4 hyperglycemia was reported in 11% of the safety population. Monitor blood glucose levels frequently, especially in patients with diabetes or risk factors for diabetes. Avoid drug in patients with poorly controlled diabetes mellitus until good glucose control is established.
- Embryo-fetal toxicity. Fetal harm can occur when administered to a pregnant woman, as evidenced by death in animals. Females should avoid becoming pregnant while receiving treatment. If used during pregnancy, the patient should be informed of the potential hazard to the fetus.

Safety Considerations

- Safety data was obtained from 3 clinical trials that enrolled 163 patients (n=108 chronic phase; n=55 accelerated phase).
- Myelosuppression (thrombocytopenia, neutropenia, anemia) can be severe. Patients over age 65 years are more likely than younger counterparts to experience this toxicity. Diligent CBC monitoring and patient education about their increased risk of infection is necessary.
- Thrombocytopenia increases the potential risk for bleeding. Some reported bleeding events have been fatal. Monitoring platelet count and signs and symptoms of potential bleeding along with patient education about avoiding drugs that may increase bleed risk is necessary.
- Evaluation of blood glucose in patients with diabetes or those at risk of diabetes should occur at baseline and periodically, throughout the course of therapy.

Summary of Omacetaxine Exposure and Tolerability

Phase	Duration (months)	Median # cycles	Median total dose (mg/m^2)	Received cycle[a] #1 (%)	Received cycle[a] #2 (%)	Received cycle[a] #3 (%)
CP-CML	7.4	6	131	87	42	16
AP-CML	1.9	2	70	86	55	44

[a] Indicates percentage of patients receiving 14 days of treatment

- Since approval in 2012, the FDA became aware of a signal of serious adverse events that could result from incorrect home administration of the drug. Therefore, the manufacturer is required to conduct a study to analyze data related to home administration to assess the potential for serious safety risks of incorrect dose administration and serious adverse events arising from improper distribution, transport, storage and handling. Study completion is set for May 2017.
- Refer to Prescribing Information or Dosing and Administration section for Considerations for Home Administration.

Adverse Reactions

Common adverse reactions	Incidence $\geq$ 20%: thrombocytopenia, anemia, neutropenia, diarrhea, nausea, fatigue, asthenia, injection site reaction, pyrexia, infection, lymphopenia
Death/Serious adverse reactions	CP-CML: Serious adverse reactions in 51%; deaths 5% (2 cerebral hemorrhage, 1 multi-organ failure; 1 progressive disease; 1 unknown cause) AP-CML: Serious adverse reactions in 60%; deaths 9% (2 cerebral hemorrhage; 3 progressive disease)
Discontinuations due to adverse reactions	CP-CML: 18% due to pancytopenia, thrombocytopenia, ↑ ALT AP-CML: 33% due to leukocytosis, thrombocytopenia

Drug Interactions

Drug-Drug Interactions

- No clinically significant interactions have been identified.

Risk Evaluation

As of August 2015:

	Comments
Sentinel event advisories	• None • Sources: ISMP, FDA, TJC
Look-alike/sound-alike error potentials	•

NME Drug Name	Lexi-Comp	First DataBank	ISMP	Clinical Judgment
!Omacetaxine Mepesuccinate 3.5mg soln for SC Inj	None	None	None	Olmesartan Omalizumab OnabotulinumtoxinA Obinutuzumab
Synribo	None	None	None	Symbyax Synagis Sebivo (Canadian) Synbio Marqibo

- ! **High alert medication:** The Institute for Safe Medication Practices (ISMP) includes this medication among its list of drug classes which have a heightened risk of causing significant patient harm when used in error
- Sources: Based on clinical judgment and an evaluation of LASA information from three data sources (Lexi-Comp, First Databank, and ISMP Confused Drug Name List)

Other Considerations

- Chronic myeloid leukemia (CML) is a myeloproliferative disorder characterized by the Philadelphia chromosome (Ph), a translocation between chromosomes 9 and 22 that result in the production of the BCR-ABL fusion oncoprotein. This product, BCR-ABL, is a constitutively active tyrosine kinase. CML accounts for 10% of adult leukemias. The median age of onset is 64 years. An estimated 5980 new diagnoses and 810 deaths from CML were reported in the U.S. in 2014. Estimated number of unique patients within the VA with the diagnosis of CML ~ 4500.
- Response rates are high in the early stages of disease, also known as Chronic Phase (CP). Overall survival in the CP of CML ranges from 6-9 years. Patients in CP are at risk for progression into the advanced phases, also known as Accelerated Phase (AP) and Blast Phase (BP), which are more difficult to control and portend a poor survival rate.
- An estimated 25% of patients have disease that does not initially respond to front-line treatment with imatinib, or responds initially, then progresses. Secondary resistance is thought to be caused by the T315I mutation.
- The T315I mutation of BCR-ABL is present in up to 20% of patients with TKI-resistant disease; the presence of this mutation confers resistance to all other FDA-approved BCR-ABL tyrosine kinase inhibitors, except ponatinib.

Outcome in clinically significant area	CP: MCyR (R/I; T315I) AP: CHR
Effect Size	CP: MCyR 22% (R/I); 18.4% (T315I+) Duration 12.5 mos [95% CI, 3.5 – NR] AP: MaHR 14% [95% CI, 4.5-30.3]; Duration 4.7 mos;
Potential Harms	CP: Thrombocytopenia (85%), neutropenia (81%), anemia (62%) AP: Thrombocytopenia (88%), neutropenia (71%), anemia (80%), Safety concerns with home administration
Net Clinical Benefit	Moderate (high benefit with high risk of harm)

Definitions

Outcome in clinically significant area: morbidity, mortality, symptom relief, emotional/physical functioning, or health- related quality of life

Effect Size: odds ratio, relative risk, NNT, absolute risk reduction, relative risk reduction, difference in size of outcomes between groups, hazard ratio

Potential Harms: Low risk (Grade 3 or 4 toxicity in <20%) versus High risk (Grade 3 or 4 toxicity in ≥20%)

Net Clinical Benefit: Substantial (high benefit with low risk of harm), moderate (high benefit with high risk of harm), minimal (low benefit with low risk of harm), negative (low benefit with high risk of harm)

Dosing and Administration

Omacetaxine is a cytotoxic drug. Special handling and disposal procedures should be followed. Protective eyewear and gloves should be worn during handling and administration of the product. Proper aseptic technique should be used.

Induction schedule.

- Recommended starting schedule for induction is 1.25 mg/m^2 administered subcutaneously twice daily at approximately 12-hour intervals for 14 consecutive days every 28 days, over a 28-day cycle.
- Cycles should be repeated every 28 days until patients achieve a hematologic response.
- Patients received a minimum of 1 to a maximum of 6 induction cycles. Those with no evidence of clinical response after 6 induction cycles were considered for removal from the study.

Maintenance Dosing.

- Recommended maintenance schedule is 1.25 mg/m^2 administered subcutaneously twice daily at approximately 12-hour intervals for 7 consecutive days every 28 days, over a 28-day cycle.
- Treatment should continue as long as patients are clinically benefitting from therapy.

Dose adjustment and modifications.

- **Hematologic Toxicity.** Treatment cycles may be delayed and/or the number of days of dosing during the cycle reduced for hematologic toxicities.
- Complete Blood Counts (CBCs) should be performed weekly during induction and initial maintenance cycles. After initial maintenance cycles, monitor CBCs every 2 weeks or as clinically indicated.
- If a patient experiences Grade 4 neutropenia (ANC < 0.5 x 10^9/L) or Grade 3 thrombocytopenia (platelet count < 50 x 10^9/L) during a cycle, delay starting the next cycle until ANC $\geq$ 1.0 x 10^9/L and platelet count $\geq$ 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).
- **Non-hematologic Toxicity.** Manage other clinically significant non-hematologic toxicity symptomatically. Interrupt and/or delay omacetaxine mepesuccinate until toxicity is resolved.

Reconstitution Instructions and Handling Precautions

- Drug should be prepared in a healthcare facility and must be reconstituted by a healthcare professional, although considerations for home administration are provided.
- **Drug preparation.**
  - Reconstitute vial with one ml of 0.9% Sodium Chloride Injection, USP, prior to subcutaneous injection.
  - After addition of diluent, gently swirl until a clear solution is obtained. The lyophilized powder should be completely dissolved in less than one minute. The resulting clear solution contains 3.5 mg/mL.
  - Observe parenteral drugs visually for particulate matter and discoloration.
  - Drug does not contain antimicrobial preservatives; use caution to ensure contamination does not occur during preparation.
  - Drug is cytotoxic. Follow special handling and disposal procedures. Wear protective eyewear and gloves during handling and administration.
  - Proper aseptic technique should be used. Avoid skin and eye contact. If drug comes into contact with skin, immediately and thoroughly wash affected area with soap and water. If contact with eyes occurs, thoroughly flush with water.
- **Storage conditions and storage time after preparation of syringes.**
  - If drug is not used immediately after reconstitution, follow in-use storage conditions and allowable storage times prior to use as instructed in table.

Storage conditions	Storage time
Room temperature (20°C to 25°C [68°F to 77°F])	Use within 12 hours of reconstitution
Refrigerated (2°C to 8°C [36°F to 46°F])	Use within 6 days (144 hours) of reconstitution

Considerations for home administration

- Before a decision is made to allow drug 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 omacetaxine mepesuccinate in syringe with capped needle for subcutaneous injection; syringe 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 drug syringes
- If a patient or caregiver cannot be trained for any reason, then in such patients, drug should be administered by a healthcare professional.

Disposal and Accidental Spillage Procedures

- After administration, any unused solution should be discarded properly. Instruct patients planning home administration on the following: do not recap or clip the used needle, and do not place used needles, syringes, vials and other used supplies in a household trash or recycling bin. Used needles, syringes, vials and other used supplies should be disposed of in an appropriate biohazard container.
- If accidental spillage occurs, continue to use protective eyewear and gloves, wipe the spilled liquid with the absorbent pad and was the area with water and soap. Then, place the pad and gloves into the biohazard container and wash hands thoroughly. Return the biohazard container to the clinic or pharmacy for final disposal.

Special Populations (Adults)

	Comments
Elderly	• CP-CML efficacy population included 23 (30%) patients age ≧ 65 years; AP-CML efficacy population included 16 (46%) • Patients < 65 years of age had higher rates of MCyRs than older population in CP-CML (23 vs. 9%, respectively) • Similarly, those < 65 years had higher rates of MaHRs than the older population in AP-CML (31 vs. 0%, respectively) • Patients ≥ 65 years were more likely to experienced toxicity, especially hematologic toxicity
Pregnancy	• Category D. Based upon animal studies, omacetaxine mepesuccinate can cause fetal harm when given to a pregnant woman. Advise women to avoid becoming pregnant while taking drug. If used during pregnancy, or if the patient becomes pregnant while taking this drug, apprise patient of the potential hazard to a fetus.
Lactation	• It is unknown if omacetaxine mepesuccinate is excreted in human milk, therefore a decision to discontinue nursing or discontinue therapy should be made, taking into account the importance of drug to the mother.
Renal Impairment	• No data identified
Hepatic Impairment	• No data identified
Pharmacogenetics/genomics	• No data identified

Projected Place in Therapy

- Omacetaxine provides a mechanism different from tyrosine kinase inhibition and has shown activity in patients that have disease progression despite multiple TKIs as well as patients that harbor the T315I kinase domain mutation. Patients who have failed treatment with TKIs due to resistance or intolerance, may be candidates for omacetaxine.
- Follow-up of patients receiving omacetaxine is of shorter duration than other commercial agents.
- The logistics of omacetaxine therapy are complicated and cumbersome, which may be a factor that limits use in some patients.
- NCCN Guidelines, Version 1.2016, give omacetaxine a Category 2A recommendation for those patients with the T315I mutation or patients who are resistant or intolerant to 2 or more TKIs.

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National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology, Chronic Myelogenous Leukemia (version 1.2016). http://www.nccn.org/professionals/physician_gls/pdf/cml.pdf (Accessed October 2015).

Cortes J, Lipton JH, Rea D, et al for the Omacetaxine 202 Study Group. Phase 2 study of subcutaneous omacetaxine mepesuccinate after TKI failure in patients with chronic phase CML with T315I mutation. Blood 2012; 120: 2573.

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Appendix A: GRADEing the Evidence

Designations of Quality

Quality of evidence designation	Description
High	Evidence includes consistent results from well-designed, well-conducted studies in representative populations that directly assess effects on health outcomes (2 consistent, higher-quality randomized controlled trials or multiple, consistent observational studies with no significant methodological flaws showing large effects).
Moderate	Evidence is sufficient to determine effects on health outcomes, but the number, quality, size, or consistency of included studies; generalizability to routine practice; or indirect nature of the evidence on health outcomes (1 higher-quality trial with > 100 participants; 2 higher-quality trials with some inconsistency; 2 consistent, lower-quality trials; or multiple, consistent observational studies with no significant methodological flaws showing at least moderate effects) limits the strength of the evidence.
Low	Evidence is insufficient to assess effects on health outcomes because of limited number or power of studies, large and unexplained inconsistency between higher-quality studies, important flaws in study design or conduct, gaps in the chain of evidence, or lack of information on important health outcomes.

Please refer to Qaseem A, et al. The development of clinical practice guidelines and guidance statements of the American College of Physicians: Summary of Methods. Ann Intern Med 2010;153:194-199.

Appendix B: Approval Endpoints

Table 1. A Comparison of Important Cancer Approval Endpoints

Endpoint	Regulatory Evidence	Study Design	Advantages	Disadvantages
Overall Survival	Clinical benefit for regular approval	• Randomized studies essential • Blinding not essential	• Universally accepted direct measure of benefit • Easily measured • Precisely measured	• May involve larger studies • May be affected by crossover therapy and sequential therapy • Includes noncancer deaths
Symptom Endpoints (patient-reported outcomes)	Clinical benefit for regular approval	• Randomized blinded studies	• Patient perspective of direct clinical benefit	• Blinding is often difficult • Data are frequently missing or incomplete • Clinical significance of small changes is unknown • Multiple analyses • Lack of validated instruments
Disease-Free Survival	Surrogate for accelerated approval or regular approval*	• Randomized studies essential • Blinding preferred • Blinded review recommended	• Smaller sample size and shorter follow-up necessary compared with survival studies	• Not statistically validated as surrogate for survival in all settings • Not precisely measured; subject to assessment bias, particularly in open-label studies • Definitions vary among studies
Objective Response Rate	Surrogate for accelerated approval or regular approval*	• Single-arm or randomized studies can be used • Blinding preferred in comparative studies • Blinded review recommended	• Can be assessed in single-arm studies • Assessed earlier and in smaller studies compared with survival studies • Effect attributable to drug, not natural history	• Not a direct measure of benefit in all cases • Not a comprehensive measure of drug activity • Only a subset of patients with benefit
Complete Response	Surrogate for accelerated approval or regular approval*	• Single-arm or randomized studies can be used • Blinding preferred in comparative studies • Blinded review recommended	• Can be assessed in single-arm studies • Durable complete responses can represent clinical benefit • Assessed earlier and in smaller studies compared with survival studies	• Not a direct measure of benefit in all cases • Not a comprehensive measure of drug activity • Small subset of patients with benefit
Progression- Free Survival (includes all deaths) or Time to Progression (deaths before progression censored)	Surrogate for accelerated approval or regular approval*	• Randomized studies essential • Blinding preferred • Blinded review recommended	• Smaller sample size and shorter follow-up necessary compared with survival studies • Measurement of stable disease included • Not affected by crossover or subsequent therapies • Generally based on objective and quantitative assessment	• Not statistically validated as surrogate for survival in all settings • Not precisely measured; subject to assessment bias particularly in open-label studies • Definitions vary among studies • Frequent radiological or other assessments • Involves balanced timing of assessments among treatment arms

*Adequacy as a surrogate endpoint for accelerated approval or regular approval is highly dependent upon other factors such as effect size, effect duration, and benefits of other available therapy. See text for details.

Guidance for Industry: Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics. U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER), Center for Biologics Evaluation and Research (CBER), May 2007.