HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use SYNRIBO safely and effectively. See full prescribing information for SYNRIBO.

SYNRIBO™ (omacetaxine mepesuccinate) for Injection, for subcutaneous use
Initial U.S. Approval: 2012

----------INDICATIONS AND USAGE----------
SYNRIBO for Injection is indicated for the 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). This indication is based upon response rate. There are no trials verifying an improvement in disease-related symptoms or increased survival with SYNRIBO. (1)

----------DOSAGE AND ADMINISTRATION----------
- Induction Dose: 1.25 mg/m^2 administered by subcutaneous injection twice daily for 14 consecutive days of a 28-day cycle. (2.1)
- Maintenance Dose: 1.25 mg/m^2 administered by subcutaneous injection twice daily for 7 consecutive days of a 28-day cycle. (2.2)
- Dose modifications are needed for toxicity. (2.3)

----------DOSAGE FORMS AND STRENGTHS----------
Single-use vial containing 3.5 mg of omacetaxine mepesuccinate as a lyophilized powder. (3)

----------CONTRAINDICATIONS----------
None.

----------WARNINGS AND PRECAUTIONS----------
- Myelosuppression: severe and fatal thrombocytopenia, neutropenia and anemia. Monitor hematologic parameters frequently. (2.3, 5.1)
- Bleeding: severe thrombocytopenia and increased risk of hemorrhage. Fatal cerebral hemorrhage and severe, non-fatal gastrointestinal hemorrhage. (5.1, 5.2)
- Hyperglycemia: glucose intolerance and hyperglycemia including hyperosmolar non-ketotic hyperglycemia. (5.3)
- Embryo-fetal toxicity: Can cause fetal harm. Advise females of reproductive potential to avoid pregnancy. (5.4, 8.1)

----------ADVERSE REACTIONS----------
CML-Chronic Phase and Accelerated Phase: Most common adverse reactions (frequency ≥ 20%): thrombocytopenia, anemia, neutropenia, diarrhea, nausea, fatigue, asthenia, injection site reaction, pyrexia, infection, and lymphopenia. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Teva Pharmaceutical USA, Inc. at 1-800-896-5855 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

See 17 for PATIENT COUNSELING INFORMATION

Revised: 10/2012

FULL PRESCRIBING INFORMATION: CONTENTS*

1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
2.1 Induction Schedule
2.2 Maintenance Dosing
2.3 Dose Adjustments and Modifications
2.4 Preparation and Administration Precautions
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
5.1 Myelosuppression
5.2 Bleeding
5.3 Hyperglycemia
5.4 Embryo-Fetal Toxicity
6 ADVERSE REACTIONS
6.1 Clinical Trials Experience
6.2 Additional Data From Safety Population
7 DRUG INTERACTIONS
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.3 Nursing Mothers
8.4 Pediatric Use
8.5 Geriatric Use
8.6 Renal Impairment
8.7 Hepatic Impairment
8.8 Effect of Gender
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.3 Pharmacokinetics
12.6 Assessment for Risk of QT Prolongation
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
14 CLINICAL STUDIES
14.1 Chronic Phase CML (CP CML)
14.2 Accelerated Phase CML (AP CML)
15 REFERENCES
16 HOW SUPPLIED/STORAGE AND HANDLING
16.1 How Supplied
16.2 Storage and Handling
17 PATIENT COUNSELING INFORMATION

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

SYNRIBO is indicated for the 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). This indication is based upon response rate. There are no trials verifying an improvement in disease-related symptoms or increased survival with SYNRIBO.

2 DOSAGE AND ADMINISTRATION

2.1 Induction Schedule

The recommended starting schedule for induction is 1.25 mg/m^2 administered subcutaneously twice daily 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.

2.2 Maintenance Dosing

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. Treatment should continue as long as patients are clinically benefiting from therapy.

2.3 Dose Adjustments and Modifications

Hematologic Toxicity:

SYNRIBO treatment cycles may be delayed and/or the number of days of dosing during the cycle reduced for hematologic toxicities (e.g. neutropenia, thrombocytopenia). *[see Warnings and Precautions (5.1)]*

Complete blood counts (CBCs) should be performed weekly during induction and initial maintenance cycles. After initial maintenance cycles, monitor CBCs every two weeks or as clinically indicated. 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 1.0 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).

Non-hematologic Toxicity:

Manage other clinically significant non-hematologic toxicity symptomatically. Interrupt and/or delay SYNRIBO until toxicity is resolved.

2.4 Preparation and Administration Precautions

SYNRIBO should be prepared in a healthcare facility and administered by a healthcare professional. Omacetaxine mepesuccinate is an antineoplastic product. Follow special handling and disposal procedures.

Reconstitute SYNRIBO with one mL of 0.9% Sodium Chloride Injection, USP, prior to subcutaneous injection. After addition of the diluent, gently swirl until a clear solution is obtained. The lyophilized powder should be completely dissolved in less than one minute. The resulting solution will contain 3.5 mg/mL SYNRIBO.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit.

Avoid contact with the skin. If SYNRIBO comes into contact with skin, immediately and thoroughly wash affected area with soap and water.

Use SYNRIBO within 12 hours of reconstitution when stored at room temperature and within 24 hours of reconstitution if stored at 2°C to 8 °C (36^{o}F to 46^{o}F). Protect reconstituted solution from light. After administration, any unused solution should be discarded properly[1].

3 DOSAGE FORMS AND STRENGTHS

SYNRIBO for Injection contains 3.5 mg omacetaxine mepesuccinate; as a sterile, preservative-free, white to off-white lyophilized powder in a single-use vial.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Myelosuppression

In uncontrolled trials with SYNRIBO, patients with chronic phase and accelerated phase CML experienced NCI CTC (version 3.0) Grade 3 or 4 thrombocytopenia (85%, 88%), neutropenia (81%, 71%), and anemia (62%, 80%), respectively. Fatalities related to myelosuppression occurred in 3% of patients in the safety population (N=163). Patients with neutropenia are at increased risk for infections, and should be monitored frequently and advised to contact a physician if they have symptoms of infection or fever.

Monitor complete blood counts weekly during induction and initial maintenance cycles and every two weeks during later maintenance cycles, as clinically indicated. In clinical trials myelosuppression was generally reversible and usually managed by delaying next cycle and/or reducing days of treatment with SYNRIBO. *[see Dosage and Administration (2.3) and Adverse Reactions (6.1)]*

5.2 Bleeding

SYNRIBO causes severe thrombocytopenia which increases the risk of hemorrhage. In clinical trials with CP and AP CML patients, a high incidence of Grade 3 and 4 thrombocytopenia (85% and 88%, respectively) was observed. Fatalities from cerebral hemorrhage occurred in 2% of patients treated with SYNRIBO in the safety population. Severe, non-fatal, gastrointestinal hemorrhages occurred in 2% of patients in the same population. Most bleeding events were associated with severe thrombocytopenia.

Monitor platelet counts as part of the CBC monitoring as recommended. *[see Warnings and Precautions (5.1)]* Avoid anticoagulants, aspirin, and non-steroidal anti-inflammatory drugs (NSAIDs) when the platelet count is less than 50,000/µL as they may increase the risk of bleeding.

5.3 Hyperglycemia

SYNRIBO can induce glucose intolerance. Grade 3 or 4 hyperglycemia was reported in 11% of patients in the safety population. Hyperosmolar non-ketotic hyperglycemia occurred in 1 patient treated with SYNRIBO in the safety population. Monitor blood glucose levels frequently, especially in patients with diabetes or risk factors for diabetes. Avoid SYNRIBO in patients with poorly controlled diabetes mellitus until good glycemic control has been established.

5.4 Embryo-Fetal Toxicity

SYNRIBO can cause fetal harm when administered to a pregnant woman. Omacetaxine mepesuccinate caused embryo-fetal death in animals. Females of reproductive potential should avoid becoming pregnant while being treated with SYNRIBO. There are no adequate and well-controlled studies of SYNRIBO in pregnant women. If this drug is used during pregnancy, or if the patient becomes pregnant while receiving this drug, the patient should be apprised of the potential hazard to the fetus. *[see Use in Specific Populations (8.1)]*

6 ADVERSE REACTIONS

The following serious adverse reactions have been associated with SYNRIBO in clinical trials and are discussed in greater detail in other sections of the label.

- Myelosuppression *[see Warnings and Precautions (5.1)]*
- Bleeding *[see Warnings and Precautions (5.2)]*
- Hyperglycemia *[see Warnings and Precautions (5.3)]*

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The safety data for SYNRIBO are from 3 clinical trials which enrolled a total of 163 adult patients with TKI resistant and/or intolerant chronic phase (N=108) and accelerated phase (N=55) CML. All patients were treated with initial induction therapy consisting of a dose of 1.25 mg/m^2 administered subcutaneously twice daily for 14 consecutive days every 28 days (induction cycle). Responding patients were then treated with the same dose and a twice daily schedule for 7 consecutive days every 28 days (maintenance cycle).

6.1 Clinical Trials Experience

Chronic Phase CML

The median duration of exposure for the 108 patients with chronic phase CML was 7.4 months (range 0 to 43 months). The median total cycles of exposure was 6 (range 1 to 41), and the median total dose delivered during the trials was 131 mg/m^2 (range 1.2 to 678). Among the patients with chronic phase CML, 87% received 14 days of treatment during cycle 1. By cycles 2 and 3, the percentage of patients receiving 14 days of treatment decreased to 42% and 16% respectively. Of the 91 patients who received at least 2 cycles of treatment, 79 (87%) had at least 1 cycle delay during the trials. The median number of days of cycle delays was greatest for cycle 2 (17 days) and cycle 3 (25 days) when more patients were receiving induction cycles.

Adverse reactions were reported for 99% of the patients with chronic phase CML. A total of 18% of patients had adverse reactions leading to withdrawal. The most frequently occurring adverse reactions leading to discontinuation were pancytopenia, thrombocytopenia, and increased alanine aminotransferase (each 2%). A total of 87% of patients reported at least 1 Grade 3 or Grade 4 treatment emergent adverse reactions (Table 1).

Table 1: Adverse Reactions Occurring[a] in at Least 10% of Patients (Chronic Myeloid Leukemia – Chronic Phase)

	Number (%) of Patients (N=108)	
Adverse reactions	**All reactions**	**Grade 3 or 4 reactions**
Patients with at least 1 commonly occurring adverse reaction	**107 (99)**	**94 (87)**
Blood and Lymphatic System Disorders		
Thrombocytopenia	80 (74)	72 (67)
Anemia	66 (61)	39 (36)
Neutropenia	54 (50)	49 (45)
Lymphopenia	18 (17)	17 (16)
Bone Marrow Failure	11 (10)	11 (10)
Febrile Neutropenia	11 (10)	11 (10)
Gastrointestinal Disorders		
Diarrhea	45 (42)	1 (1)
Nausea	35 (32)	1 (1)
Constipation	16 (15)	0
Abdominal Pain Upper	15 (14)	0
Vomiting	13 (12)	0
General Disorders and Administration Site Conditions		
Fatigue	28 (26)	5 (5)
Pyrexia	26 (24)	1 (1)
Asthenia	25 (23)	1 (1)
Edema Peripheral	14 (13)	0
Infusion and injection site related reactions	37 (34)	0
Infections and Infestations[b]	50 (46)	12 (11)
Musculoskeletal and Connective Tissue Disorders		
Arthralgia	20 (19)	1 (1)
Pain in Extremity	14 (13)	1 (1)
Back Pain	12 (11)	2 (2)
Nervous System Disorders		
Headache	20 (19)	1 (1)
Psychiatric Disorders		
Insomnia	11 (10)	0
Respiratory, Thoracic and Mediastinal Disorders		
Cough	17 (16)	1 (1)
Epistaxis	16 (15)	1 (1)
Skin and Subcutaneous Tissue Disorders		
Alopecia	16 (15)	0
Rash	11 (10)	0

[a] Occurred in the period between the first dose and 30 days after the last dose.
[b] Infection includes bacterial, viral, fungal, and non-specified.

Serious adverse reactions were reported for 51% of patients. Serious adverse reactions reported for at least 5% of patients were bone marrow failure and thrombocytopenia (each 10%), and febrile neutropenia (6%). Serious adverse reactions of infections were reported for 8% of patients.

Deaths occurred while on study in five (5%) patients with CP CML. Two patients died due to cerebral hemorrhage, one due to multi-organ failure, one due to progression of disease, and one from unknown causes.

Accelerated Phase CML

Median total cycles of exposure was 2 (range 1 to 29), and the median total dose delivered during the trials was 70 mg/m^2. The median duration of exposure for the 55 patients with accelerated phase CML was 1.9 months (range 0 to 30 months). Of the patients with accelerated phase CML, 86% received 14 days of treatment during cycle 1. By cycles 2 and 3, the percentage of patients receiving 14 days of treatment decreased to 55% and 44% respectively. Of the 40 patients who received at least 2 cycles of treatment, 27 (68%) had at least 1 cycle delay during the trials. The median number of days of cycle delays was greatest for cycle 3 (31 days) and cycle 8 (36 days).

Adverse reactions regardless of investigator attribution were reported for 100% patients with accelerated phase CML. A total of 33% of patients had adverse reactions leading to withdrawal. The most frequently occurring adverse reactions leading to withdrawal were leukocytosis (6%), and thrombocytopenia (4%). A total of 84% of patients reported at least 1 Grade 3 or Grade 4 treatment emergent adverse reaction (Table 2).

Table 2: Adverse Reactions Occurring[a] in at Least 10% of Patients (Chronic Myeloid Leukemia – Accelerated Phase)

	Number (%) of Patients (N=55)	
Adverse reactions	**All reactions**	**Grade 3 or 4 reactions**
Patients with at least 1 commonly occurring adverse reaction	**55 (100)**	**46 (84)**
Blood and Lymphatic System Disorders		
Anemia	28 (51)	20 (36)
Febrile Neutropenia	11 (20)	9 (16)
Neutropenia	11 (20)	10 (18)
Thrombocytopenia	31 (56)	27 (49)
Gastrointestinal Disorders		
Diarrhea	19 (35)	4 (7)
Nausea	15 (27)	2 (4)
Vomiting	8 (15)	1 (2)
Abdominal Pain	7 (13)	0
General Disorders and Administration Site Conditions		
Fatigue	17 (31)	5 (9)
Pyrexia	16 (29)	1 (2)
Asthenia	13 (24)	1 (2)
Chills	7 (13)	0
Infusion and injection site related reactions	12 (22)	0
Infections and Infestations[b]	31 (56)	11 (20)
Metabolism and Nutrition Disorders		
Anorexia	7 (13)	1 (2)
Musculoskeletal and Connective Tissue Disorders		
Pain in Extremity	6 (11)	1 (2)
Nervous System Disorders		
Headache	7 (13)	0
Respiratory, Thoracic and Mediastinal Disorders		
Cough	8 (15)	0
Dyspnea	6 (11)	1 (2)
Epistaxis	6 (11)	1 (2)

[a] Occurred in the period between the first dose and 30 days after the last dose.
[b] Infection includes bacterial, viral, fungal, and non-specified.

Serious adverse reactions were reported for 60% of patients. Serious adverse reactions reported for at least 5% of patients were febrile neutropenia (18%), thrombocytopenia (9%), anemia (7%), diarrhea and convulsions (6% each). Serious adverse reactions of infections were reported for 11% of patients. Death occurred while on study in 5 (9%) patients with AP CML. Two patients died due to cerebral hemorrhage and three due to progression of disease.

Laboratory Abnormalities in Chronic and Accelerated Phase CML

Grade 3/4 laboratory abnormalities reported in patients with chronic and accelerated phase CML are described in Table 3. Myelosuppression occurred in all patients treated with SYNRIBO. *[see Warnings and Precautions (5.1)]* Five patients with chronic phase CML and 4 patients with accelerated phase CML permanently discontinued SYNRIBO due to pancytopenia, thrombocytopenia, febrile neutropenia, or bone marrow necrosis. An event of hyperosmolar non-ketotic hyperglycemia was reported in one patient in the safety population and a similar case has been reported in the literature. Two patients with chronic phase CML permanently discontinued SYNRIBO due to elevated transaminases.

Table 3: Grade 3/4 Laboratory Abnormalities in Clinical Studies in Patients with Chronic Phase and Accelerated Phase CML

	Chronic Phase	Accelerated Phase
	%	%
Hematology Parameters		
Hemoglobin Decreased	62	80
Leukocytes Decreased	72	61
Neutrophils Decreased	81	71
Platelets Decreased	85	88
Biochemistry Parameters		
Alanine aminotransferase (ALT) Increased	6	2
Bilirubin Increased	9	6
Creatinine Increased	9	16
Glucose Increased	10	15
Uric Acid Increased	56	57
Glucose Decreased	8	6

6.2 Additional Data From Safety Population

The following adverse reactions were reported in patients in the SYNRIBO clinical studies of patients with chronic phase and accelerated phase CML at a frequency of 1% to less than 10%. Within each category, adverse reactions are ranked on the basis of frequency.

Cardiac Disorders: tachycardia, palpitations, acute coronary syndrome, angina pectoris, arrhythmia, bradycardia, ventricular extrasystoles.

Ear and Labyrinth Disorders: ear pain, ear hemorrhage, tinnitus.

Eye Disorders: cataract, vision blurred, conjunctival hemorrhage, dry eye, lacrimation increased, conjunctivitis, diplopia, eye pain, eyelid edema.

Gastrointestinal Disorders: stomatitis, mouth ulceration, abdominal distension, dyspepsia, gastroesophageal reflux disease, gingival bleeding, aphthous stomatitis, dry mouth, hemorrhoids, gastritis, gastrointestinal hemorrhage, melena, mouth hemorrhage, oral pain, anal fissure, dysphagia, gingival pain, gingivitis.

General Disorders and Administration Site Conditions: mucosal inflammation, pain, chest pain, hyperthermia, influenza-like illness, catheter site pain, general edema, malaise.

Immune System Disorders: hypersensitivity.

Injury, Poisoning and Procedural Complications: contusion, transfusion reaction.

Metabolism and Nutrition Disorders: decreased appetite, diabetes mellitus, gout, dehydration.

Musculoskeletal and Connective Tissue Disorders: bone pain, myalgia, muscular weakness, muscle spasms, musculoskeletal chest pain, musculoskeletal pain, musculoskeletal stiffness, musculoskeletal discomfort.

Nervous System Disorders: dizziness, cerebral hemorrhage, paresthesia, convulsion, hypoesthesia, lethargy, sciatica, burning sensation, dysgeusia, tremor.

Psychiatric Disorders: anxiety, depression, agitation, confusional state, mental status change.

Renal and Urinary Disorders: dysuria.

Respiratory, Thoracic and Mediastinal Disorders: pharyngolaryngeal pain, nasal congestion, dysphonia, productive cough, rales, rhinorrhea, hemoptysis, sinus congestion.

Skin and Subcutaneous Tissue Disorders: erythema, pruritus, dry skin, petechiae, hyperhidrosis, night sweats, ecchymosis, purpura, skin lesion, skin ulcer, rash erythematous, rash papular, skin exfoliation, skin hyperpigmentation.

Vascular Disorders: hematoma, hypertension, hot flush, hypotension.

7 DRUG INTERACTIONS

Based on the findings from in vitro drug interaction studies with SYNRIBO, no clinical drug interaction trials were warranted. *[see Clinical Pharmacology (12.3)]*

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category D *[see Warnings and Precautions (5.4)]*

Based on its mechanism of action and findings from animal studies, SYNRIBO can cause fetal harm when administered to pregnant women. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to a fetus.

In an embryo-fetal development study, pregnant mice were administered omacetaxine mepesuccinate subcutaneously during the period of organogenesis at doses of 0.21 or 0.41 mg/kg/day. Drug-related adverse effects included embryonic death, an increase in unossified bones/reduced bone ossification and decreased fetal body weights. Fetal toxicity occurred at doses of 0.41 mg/kg (1.23 mg/m^2) which is approximately half the recommended daily human dose on a body surface area basis.

8.3 Nursing Mothers

It is not known whether omacetaxine mepesuccinate is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reaction in nursing infants, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

8.4 Pediatric Use

The safety and effectiveness of SYNRIBO in pediatric patients have not been established.

8.5 Geriatric Use

In the chronic and accelerated phase CML efficacy populations 23 (30%) and 16 (46%) patients were ≥65 years of age. For the age subgroups of <65 years of age and ≥65 years of age, there were differences between the subgroups, with higher rates of major cytogenetic responses (MCyRs) in younger patients with CP CML compared with older patients (23% vs. 9%, respectively) and higher rates of major hematologic responses (MaHRs) in older patients with AP CML compared with younger patients (31% vs. 0%, respectively). Patients ≥65 years of age were more likely to experience toxicity, most notably hematologic toxicity.

8.6 Renal Impairment

No formal studies assessing the impact of renal impairment on the pharmacokinetics of omacetaxine mepesuccinate have been conducted.

8.7 Hepatic Impairment

No formal studies assessing the impact of hepatic impairment on the pharmacokinetics of omacetaxine mepesuccinate have been conducted.

8.8 Effect of Gender

Of the 76 patients included in the chronic phase CML population efficacy analysis, 47 (62%) of the patients were men and 29 (38%) were women. For patients with chronic phase CML, the MCyR rate in men was higher than in women (21% vs. 14%, respectively). There were differences noted in the safety profile of omacetaxine mepesuccinate in men and women with chronic phase CML although the small number of patients in each group prevents a definitive assessment. There were inadequate patient numbers in the accelerated phase subset to draw conclusions regarding a gender effect on efficacy.

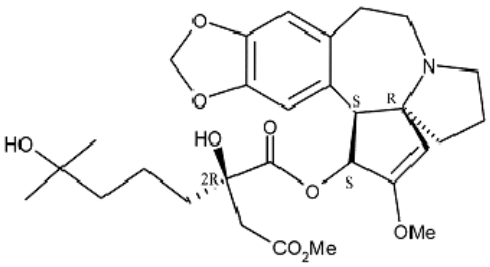
10 OVERDOSAGE

A patient in the clinical program received an overdose of 2.5 mg/m^2 twice daily for 5 days. The patient presented with gastrointestinal disorders, gingival hemorrhage, alopecia, and Grade 4 thrombocytopenia and neutropenia. When SYNRIBO treatment was temporarily interrupted the gastrointestinal disorders and hemorrhagic syndrome resolved, and neutrophil values returned to within normal range. The alopecia and thrombocytopenia (Grade 1) improved, and SYNRIBO was restarted.

11 DESCRIPTION

SYNRIBO contains the active ingredient omacetaxine mepesuccinate, a cephalotaxine ester. It is a protein synthesis inhibitor. Omacetaxine mepesuccinate is prepared by a semi-synthetic process from cephalotaxine, an extract from the leaves of *Cephalotaxus sp*. The chemical name of omacetaxine mepesuccinate is cephalotaxine, 4-methyl (2*R*)-hydroxyl-2-(4-hydroxyl-4-methylpentyl) butanedioate (ester).

Omacetaxine mepesuccinate has the following chemical structure:



The molecular formula is $C_{29}H_{39}NO_9$ with a molecular weight of 545.6 g/mol. SYNRIBO for injection is a sterile, preservative-free, white to off-white, lyophilized powder in a single-use vial. Each vial contains 3.5 mg omacetaxine mepesuccinate and mannitol.

SYNRIBO is intended for subcutaneous administration after reconstitution with 1.0 mL of 0.9% Sodium Chloride Injection, USP. The pH of the reconstituted solution is between 5.5 and 7.0.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

The mechanism of action of omacetaxine mepesuccinate has not been fully elucidated but includes inhibition of protein synthesis and is independent of direct Bcr-Abl binding. Omacetaxine mepesuccinate binds to the A-site cleft in the peptidyl-transferase center of the large ribosomal subunit from a strain of archaeabacteria. In vitro, omacetaxine mepesuccinate reduced protein levels of the Bcr-Abl oncoprotein and Mcl-1, an anti-apoptotic Bcl-2 family member. Omacetaxine mepesuccinate showed activity in mouse models of wild-type and T315I mutated Bcr-Abl CML.

12.3 Pharmacokinetics

The dose proportionality of omacetaxine mepesuccinate is unknown. A 90% increase in systemic exposure to omacetaxine mepesuccinate was observed between the first dose and steady state.

Absorption

The absolute bioavailability of omacetaxine mepesuccinate has not been determined. Omacetaxine mepesuccinate is absorbed following subcutaneous administration, and maximum concentrations are achieved after approximately 30 minutes.

Distribution

The steady-state (mean ± SD) volume of distribution of omacetaxine mepesuccinate is approximately 141 ± 93.4 L following subcutaneous administration of 1.25 mg/m^2 twice daily for 11 days . The plasma protein binding of omacetaxine mepesuccinate is less than or equal to 50%.

Metabolism

Omacetaxine mepesuccinate is primarily hydrolyzed to 4′-DMHHT via plasma esterases with little hepatic microsomal oxidative and/or esterase-mediated metabolism in vitro.

Elimination

The major elimination route of omacetaxine mepesuccinate is unknown. The mean percentage of omacetaxine mepesuccinate excreted unchanged in the urine is less than 15%. The mean half-life of omacetaxine mepesuccinate following subcutaneous administration is approximately 6 hours.

Drug Interactions

Cytochrome P450 Enzymes (CYPs): Omacetaxine mepesuccinate is not a substrate of CYP450 enzymes in vitro. Omacetaxine mepesuccinate and 4′-DMHHT do not inhibit major CYPs in vitro at concentrations that can be expected clinically. The potential for omacetaxine mepesuccinate or 4′-DMHHT to induce CYP450 enzymes has not been determined.

Transporter Systems: Omacetaxine mepesuccinate is a P-glycoprotein (P-gp) substrate in vitro. Omacetaxine mepesuccinate and 4′-DMHHT do not inhibit P-gp mediated efflux of loperamide in vitro at concentrations that can be expected clinically.

12.6 Assessment for Risk of QT prolongation

In an uncontrolled pharmacokinetic study there were no reports of QTcF > 480 ms or ΔQTcF > 60 ms in 21 treated patients who received omacetaxine mepesuccinate 1.25 mg/m^2 BID for 14 consecutive days. There was no evidence for concentration-dependent increases in QTc for omacetaxine mepesuccinate or 4'-DMHHT. Although the mean effect on QTc was 4.2 ms (upper 95% CI: 9.5 ms), QTc effects less than 10 ms cannot be verified due to the absence of a placebo and positive controls.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

No carcinogenicity studies have been conducted with omacetaxine mepesuccinate.

Omacetaxine mepesuccinate was genotoxic in an in vitro chromosomal aberration test system in Chinese hamster ovary (CHO) cells, but was not mutagenic when tested in an in vitro bacterial cell assay (Ames test), and it did not induce genetic damage using an in vivo mouse micronucleus assay.

SYNRIBO may impair male fertility. Studies in mice demonstrated adverse effects on male reproductive organs. Bilateral degeneration of the seminiferous tubular epithelium in testes and hypospermia/aspermia in the epididymides were reported in the highest dose group (2.33 mg/kg/day reduced to 1.67 mg/kg/day; 7 to 5 mg/m^2/day) following subcutaneous injection of omacetaxine mepesuccinate for six cycles over six months. The doses used in the mice were approximately two to three times the clinical dose (2.5 mg/m^2/day) based on body surface area.

14 CLINICAL STUDIES

The efficacy of SYNRIBO was evaluated using a combined cohort of adult patients with CML from two trials. The combined cohort consisted of patients who had received 2 or more approved TKIs and had, at a minimum, documented evidence of resistance or intolerance to dasatinib and/or nilotinib. Resistance was defined as one of the following: no complete hematologic response (CHR) by 12 weeks (whether lost or never achieved); or no cytogenetic response by 24 weeks (i.e., 100% Ph positive [Ph+]) (whether lost or never achieved); or no major cytogenetic response (MCyR) by 52 weeks (i.e., ≥35% Ph+) (whether lost or never achieved); or progressive leukocytosis. Intolerance was defined as one of the following: 1) Grade 3-4 non-hematologic toxicity that does not resolve with adequate intervention; or 2) Grade 4 hematologic toxicity lasting more than 7 days; or 3) any Grade ≥ 2 toxicity that is unacceptable to the patient. Patients with NYHA class III or IV heart disease, active ischemia or other uncontrolled cardiac conditions were excluded.

Patients were treated with omacetaxine mepesuccinate at a dose of 1.25 mg/m^2 administered subcutaneously twice daily for 14 consecutive days every 28 days (induction cycle). Responding patients were then treated with the same dose and twice daily schedule for 7 consecutive days every 28 days (maintenance cycle). Patients were allowed to continue to receive maintenance treatment for up to 24 months. Responses were adjudicated by an independent Data Monitoring Committee (DMC).

14.1 Chronic Phase CML (CP CML)

A total of 76 patients with chronic phase CML were included in the efficacy analysis. The demographics were: median age 59 years, 62% were male, 30% were 65 years of age or older, 80% were Caucasian, 5% were African-American, 4% were Asian and 4% were Hispanic. Thirty-six (47%) patients had failed treatment with imatinib, dasatinib, and nilotinib. Most patients had also received prior non-TKI treatments, most commonly hydroxyurea (54%), interferon (30%), and/or cytarabine (29%).

The efficacy endpoint was based on MCyR (adjudicated by a DMC).

Table 4: Efficacy Results Evaluated by DMC for Patients with CP CML

	Patients (N=76)
Primary Response – MCyR	
Total with MCyR, n (%)	14 (18.4)
95% confidence interval	(10.5% – 29.0%)
Cytogenetic Response, n (%)	
Confirmed complete	6 (7.9)
Confirmed partial	3 (3.9)

Cytogenetic response evaluation is based on standard cytogenetic analysis (at least 20 metaphases).
Complete: 0% Ph+ cells, Partial > 0% to 35% Ph+ cells

The mean time to MCyR onset in the 14 patients was 3.5 months. The median duration of MCyR for the 14 patients was 12.5 months (Kaplan-Meier estimate).

14.2 Accelerated Phase CML (AP CML)

A total of 35 patients with accelerated phase CML were included in the efficacy analysis. The demographics were: median age was 63 years, 57% were male, 46% were 65 years of age or older, 68% were Caucasian, 23% were African-American, 3% were Asian and 3% were Hispanic. Twenty-two (63%) of 35 patients with accelerated phase had failed treatment with imatinib, dasatinib, and nilotinib. Most patients had also received prior non-TKI treatments, most commonly hydroxyurea (43%), interferon (31%), and/or cytarabine (29%). The efficacy endpoint was assessed based on MCyR and MaHR (complete hematologic response [CHR] or no evidence of leukemia [NEL]). The efficacy results for the patients with accelerated phase as adjudicated by the DMC are shown in Table 5.

Table 5: Efficacy Results Evaluated by DMC for Patients with AP CML

	Patients (N=35)
Primary Response – MaHR	
Total with MaHR, n (%)	5 (14.3)
95% confidence interval	(4.5% - 30.3%)
CHR	4 (11.4)
NEL	1 (2.9)
Primary Response – McyR	
Total with MCyR, n (%)	0

MaHR is defined as complete hematologic response (CHR) or no evidence of leukemia (NEL): CHR - absolute neutrophil count $\geq 1.5 \times 10^9$/liter, platelets $\geq 100 \times 10^9$/liter, no blood blasts, bone marrow blasts < 5%, no extramedullary disease; NEL - Morphologic leukemia-free state, defined as <5% bone marrow blasts.

The mean time to response onset in the 5 patients was 2.3 months. The median duration of MaHR for the 5 patients was 4.7 months (Kaplan-Meier estimate).

15 REFERENCES

1. OSHA Hazardous Drugs. *OSHA*. http://www.osha.gov/SLTC/hazardousdrugs/index.html.

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

SYNRIBO (omacetaxine mepesuccinate) for Injection is supplied in 8 mL clear glass single-use vial in individual cartons. Each vial contains 3.5 mg of SYNRIBO (omacetaxine mepesuccinate) for Injection (NDC 63459-177-14).

16.2 Storage and Handling

Store at 20ºC to 25ºC (68º C to 77ºF); excursions permitted from 15ºC to 30ºC (59ºF to 86ºF). Until use, keep product in carton to protect from light.

Omacetaxine mepesuccinate is an antineoplastic product. Follow special handling and disposal procedures[1].

17 PATIENT COUNSELING INFORMATION

- Bleeding
  Advise patients of the possibility of serious bleeding due to low platelet counts. Instruct patients to report immediately any signs or symptoms suggestive of hemorrhage (unusual bleeding, easy bruising or blood in urine or stool; confusion, slurred speech, or altered vision).
- Myelosuppression
  Advise patients of the likelihood that SYNRIBO will cause a decrease in white blood cells, platelets, and red blood cells and that monitoring of these parameters will be needed. Instruct patients to contact a heath care professional if they develop a fever, or other signs/symptoms of infection; shortness of breath, significant fatigue, or bleeding.
- Hyperglycemia
  Advise patients with diabetes of the possibility of hyperglycemia and the need for careful monitoring of blood glucose levels. Patients with poorly controlled diabetes mellitus should not be treated with omacetaxine mepesuccinate until good glycemic control has been established.
- Pregnancy and Nursing
  Advise patients that omacetaxine mepesuccinate can cause fetal harm when administered to a pregnant woman. Advise females of reproductive potential of the potential hazard to the fetus and to avoid becoming pregnant. Advise females to avoid nursing while receiving SYNRIBO.
- Gastrointestinal Complaints
  Advise patients that they may experience nausea, diarrhea, abdominal pain, constipation, and vomiting. If these symptoms persist, they should seek medical attention.
- Fatigue
  Advise patients that SYNRIBO may cause tiredness and to avoid driving any vehicle or operating any dangerous tools or machinery if they experience this side effect.
- Rash
  Advise patients that they may experience skin rash. Advise patients to immediately report severe or worsening rash or itching.
- Alopecia
  Advise patients that they may experience hair loss.

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