Bosutinib (Bosulif)

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 comprehensive 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 Documents will be placed in the Archive section when the information is deemed to be no longer current.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	Bosutinib is a dual SRC/ABL1 tyrosine kinase inhibitor with minimal inhibitory activity against KIT and platelet-derived growth factor (PDGFR).
Indication(s) Under Review	Bosutinib is a kinase inhibitor indicated for the treatment of adult patients with chronic, accelerated or blast phase Ph+ chronic myelogenous leukemia (CML) with resistance or intolerance to prior therapy.
Dosage Form(s) Under Review	100 mg, 500 mg tablets
REMS	☐ REMS ☐ No REMS
Pregnancy Rating	Category D

Executive Summary

Efficacy

- The primary endpoint of Major Cytogenetic Response (MCyR) at week 24 was reached by 31% of chronic phase CML patients that were imatinib-intolerant or imatinib-resistant.
- Two-year follow up of the chronic phase population resulted in 85% of patients achieving Complete Hematologic Response (CHR) while 59% achieved and/or maintained MCyR; at 2-yrs PFS 79%, with 2-yr OS 92%.
- Efficacy in Accelerated phase (AP) and Blast Phase (BP) CML is evidenced by the endpoint of CHR achieved by 30% of patients in AP and 15% of those in BP by week 48; Overall Hematologic Response (OHR) by week 48 was attained by 55% of AP and 28% of BP patients, respectively

Safety

- Common adverse reactions include diarrhea, nausea, vomiting, thrombocytopenia, abdominal pain and rash.
- Serious adverse reactions in the chronic phase CML patients include thrombocytopenia; among the accelerated phase population, severe reactions include thrombocytopenia, anemia and neutropenia.
- Most common reasons for discontinuation include thrombocytopenia, increased AST and ALT and diarrhea.
- Toxicity profile of bosutinib after multiple TKIs does not greatly differ.
- Caution when prescribing bosutinib in patients with prior dasatinib-intolerance as retrospective evaluation notes that prior dasatinib-intolerance may lead patients to experience a more severe version of the same event while receiving bosutinib.
- Dose-adjustments are needed in renal and hepatic impairment.

Other Considerations

Outcome in clinically significant area	CP: MCyR at 24 weeks; 2-yr PFS 79%; 2-yr OS 92% AP, BP: CHR, OHR by week 48
Effect Size	MCyR (2-yr) 58% [95% CI 52-64] CHR (AP) 30.4% [95% CI 19.9-42.7]; (BP) 15% [95% CI 7.1-26.6] OHR (AP) 55% [95% CI 42.6-67.1]; (BP) 28% [95% CI 17.5-41.4]

	Potential Harms	CP: thrombocytopenia (26%) AP, BP: thrombocytopenia (37%), anemia (26%), neutropenia (37%)
	Net Clinical Benefit	CP: Substantial (high benefit w/low risk harm) AP, BP: Moderate (high benefit w/ high risk harm)
Potential Impact	• Projected place in therapy. Bosutinib was evaluated in Chronic, Accelerated and Blast Phases of CML among patients with imatinib resistance or intolerance. • Bosutinib was evaluated in patients that had progressed on multiple TKIs (nilotinib and/or dasatinib) indicating that bosutinib is effective as a second-line TKI and beyond; response rates are lower among patients who have received two prior TKIs. • Patient convenience. Bosutinib is an oral formulation to be taken once daily with food. • As evidenced by the median dose intensity of treatment within the clinical trial setting, bosutinib appears to be well-tolerated. • Bosutinib is not active against the T315I mutation.	

Background

Purpose for review

FDA-approval 2012

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

Other therapeutic options

CML chronic myelogenous 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

Formulary Alternatives	Other Considerations
None	
Non-formulary Alternative (if applicable)	**Other Considerations**
Dasatinib	Oral formulation; dosed once daily approved in newly diagnosed Ph+ CML in CP; also in CP, AP or BC with resistance/intolerance to prior therapy including imatinib; Dosing adjustment not needed in hepatic impairment, use with caution; less than 4% of drug and metabolites excreted renally; CHR 86-92%; CCR 41-45%; 6-yr PFS 49%; 6-yr OS 71% W/P: fluid retention, QT prolongation, PAH, CV toxicity
Nilotinib	Oral formulation; dosed twice daily approved in newly diagnosed Ph+ CML in CP; also in CP and AP with resistance/intolerance to prior therapy including imatinib; Dosing adjustment to lower dose recommended in hepatic impairment; no renal excretion; CHR 90%; MCyR 59% (CCR 44%); MMR 28%; 4-yr PFS 57%; 4-yr OS 78% Boxed warning: QT prolongation, sudden death W/P: BMS, cardiac/arterial vascular occlusive events, pancreatitis, hepatotoxicity, electrolyte abnormalities, hemorrhage, fluid retention
Ponatinib	Oral formulation; dosed once daily; approved in T315I-positive CML in CP, AP or BC; Dosing adjustment to 30 mg once daily in hepatic impairment; renal excretion ~5%; 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
	Omacetaxine	SubQ injectable given twice daily; approved in CP or AP CML with resistance/intolerance to ≥ 2 TKIs Renal excretion < 15%; no studies conducted in renal impairment or hepatic impairment; W/P: BMS, hemorrhage, hyperglycemia

Efficacy (FDA Approved Indications)

Literature Search Summary

A literature search was performed on PubMed/Medline (1966 to April 2015) using the search terms bosutinib and Bosulif. 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 (Refer to Appendix I, Table 2 for definitions of response in CML)

Trial/design	Inclusion/Exclusion/Demo	Intervention	Results
Cortes, 2011 P1/2, OL, 2-part study Part 1: dose-escalation Part 2: safety/efficacy N=288 (200 IR; 88 II) Key: BOS, bosutinib IM, imatinib DAS, dasatinib NIL, nilotinib	Inclusion Ph+ CML or Ph+ ALL with imatinib resistance (IR) or intolerance (II) ECOG PS 0-1, ANC > 1000	BOS 500 mg PO daily	Results: IR vs. II populations Primary endpoint: MCyR @ 24 wks MCyR @ 24 wks: 31% Median time to MCyR: 12 weeks Results at 24 mos: CHR: 86% Median time to CHR: 2 weeks MCyR: 53% (CCyR 41% [MMR 64%]) PFS 79%; OS 92% (89% IR; 98% II) Median duration of f/u: 24.2 mos Duration of treatment: 14.9 mos (IR); 15.3 mos (II) Median dose intensity 484.9 mg (IR); 394.1 mg (II)
Gamacorti-Passerini, 2014 24-month follow-up	Same as above	Same as above	Cumulative cytogenetic, hematologic and molecular response rates at 2 yrs MCyR 59% (CCyR 48%) MMR 35% (CMR 28%) CHR 85% 2-yr PFS 81%; 2-yr OS 91%
Khoury, 2012 P1/2, OL, 2-part study Part 1: dose-escalation Part 2: safety/efficacy N=118 w/CP-CML s/p multiple TKIs Continuation of Cortes, 2011 (above)	Focus on subpopulation of patients with prior treatment with IM followed by DAS and/or NIL; ECOG PS 0, 1 Primary Resistance = failure to achieve/maintain any of the following: hematologic improvement within 4 wks; CHR after 12 wks; any cytogenetic response by 24 wks; or MCyR by 12 months Acquired resistance = loss of a MCyR or any heme response	BOS 500 mg PO daily until PD or toxicity IM + DAS-R (n=37) IM + DAS-I (n=50) IM + NIL-R (n=27) IM + DAS/NIL (n=4) N = 118 total Study was not powered for comparative stats between cohorts.	Primary endpoint: MCyR by 24 wks Median duration follow-up: 28.5 mos (range, 0.3-56.2 mos) Median duration on BOS 8.3 mos Median dose intensity 478 mg/day Dose interruptions in 70%: 57% DAS-R 82% DAS-I; 67% NIL-R 75% NIL-I/prior tx all prior TKIs MCyR: 32% (n=35) CCyR 24% (n=26) Median time to MCyR 12.4 weeks CHR achieved/maintained 73% (n=85) CHR achieved 65% (n=44) Molecular response of 105 patients: MMR 15% (n=16) Overall PFS estimate at 2 yrs: 73% OS estimate at 2 yrs: 83% Hematologic and cytogenetic responses were noted among patients with or without domain mutations, except for T315I
Gambacorti-Passerini C, 2010 P1/2 N=134 (63 AP; 48 BP) AP, accelerated phase BP, blast phase SCT, stem cell transplant	Evaluation of patients with advanced phases (AP, BP or ALL) with resistance/intolerance to IMA. Prior therapy included: IMA, interferon (43 pts), DAS (45 pts), NIL (16 pts), SCT (12 pts) 66 pts baseline sequencing	BOS 500 mg PO daily until PD or toxicity	Follow-up 8.3 mos AP, N (%) / BP, N (%) / ALL, N (%) CHR 21 (64) / 7 (32) / 1 (25) MCyR 13 (48) / 11 (52) / 2 (100) CCyR 9 (33) / 6 (29) / 2 (100) MMR 4 / 7 / 6

	analysis; 16 mutations/40 pts		(15) (28) (46) mPFS 11.6 mos 7.8 mos 2.7 mos Response by mutation status: CHR 50% (w/mutations); 47% (w/o) MCyR 47% (w/mutations); 54% (w/o) 9/10 pts w/T315I – resistant to BOS

- The FDA approval of bosutinib was based upon a single-arm, Phase 1/2 trial that was open-label and multi-centered. The intent was to evaluate safety and efficacy of bosutinib in imatinib-resistant or imatinib-intolerant CML. Separate cohorts existed for chronic, accelerated and blast phase CML. Within each cohort, patients were evaluated based on prior imatinib therapy only or prior imatinib followed by either dasatinib or nilotinib.
- Efficacy in CP (n=288), in patients with CML and either imatinib resistance (n = 200) or intolerance (n = 88), is supported by major cytogenetic responses (MCyR) noted in 31% of patients by week 24. A two-year follow-up report notes that 85% of patients newly achieved or maintained a Complete Hematologic Response (CHR); 59% achieved a MCyR, which included 58% of imatinib-resistant and 61% of imatinib-intolerant patients. The median time to achieve MCyR was 12.3 weeks. The CCyR rate was 48%. The 2-yr PFS was 79%, and 2-yr OS was 92%.
- Efficacy in AP (n = 69) and BP (n = 60) CML, in patients previously treated with at least imatinib, are based upon the endpoints of Complete Hematologic Response (CHR) by week 48 in 21 (30.4%) in AP and 9 (15%) of those in BP. Overall Hematologic Response (OHR) by week 48 was noted in 38 (55.1%) of AP patients and 17 (28.3%) of BP patients.
- Further efficacy data is provided in the Phase 1/2 data of patients with advanced phases of CML and progression on at least imatinib and another therapy that may have included TKIs, interferon or stem cell transplant. Additional evaluation of patients with baseline mutations provided data for response based on mutational status. Hematologic and cytogenetic responses were noted among patients treated with bosutinib with or without BCR-ABL kinase domain mutations, except for T315I.
- Use of bosutinib in the first-line CP-CML setting is under investigation. At this time, bosutinib is FDA-approved as second-line therapy. It appears that there is activity as a third- or fourth-line agent.

Potential Off-Label Use

Research with bosutinib is ongoing in the following area:

- First-line setting of CP CML

<table>
<tr>
<td>Cortes, 2012
BELA (Bosutinib Efficacy and Safety in Newly Diagnosed Chronic Myeloid Leukemia)
OL, R, MN, P3 trial
N=502 (250 BOS; 252 IM)
139 centers; 31 countries</td>
<td><u>Inclusion</u>
New (≤ 6 mos) diagnosis of Ph+ CML in CP;
No prior leukemia treatment (except anagrelide or hydroxyurea);
adequate hepatic, renal function: AST/ALT ≤ 2.5x ULN or < 5x ULN if liver involved; Tbili ≤ 2.0x ULN; SCr ≤ 1.5x ULN; ECOG PS 0-1

<u>Exclusion</u>
CNS leukemia, extramedullary disease, AP or BP CML, meds that prolong QT interval, uncontrolled CV disease

<u>Demographics</u>
Median age 47-48 yrs
11-12% ≥ 65 yrs
18% Sokal high risk</td>
<td>BOS 500 mg PO daily vs.
IM 400 mg PO daily

Assessments every 3 mos x 1 yr</td>
<td>BOS 500 mg PO daily vs.
IM 400 mg PO daily

Primary endpoint: CCyR at 12 mos

Secondary:
MMR, MCyR, CHR, time to transform to AP or BP, time to first response, DOR, response by Sokal risk group, EFS, OS

Results at 12 mos:
CCyR: 70 vs. 68%; p=0.601

Time to first CCyR: 12.9 vs. 24.6 weeks; p<0.001
MMR: 41 vs. 27%; p<0.001;
CMR: 12 vs. 3%; p<0.001;
Time to first MMR: 37.1 vs. 72.3 wks; p<0.001;
Cumulative rate MMR at 12 mos: 47 vs. 32%;p<0.001
CHR: 71 vs. 85%; p>0.999
Time to first CHF: 4.4 vs. 4.6 wks
OS at 12 mos: 99 vs. 97%

Sokal risk on response at 12 mos:
<table>
<tr><th></th><th>CCyR</th><th>MMR</th></tr>
<tr><td>low</td><td>78 vs. 75%; p=0.623</td><td>53 vs. 28%; p<0.001</td></tr>
<tr><td>Intermed</td><td>69 vs. 67%; p=0.708</td><td>31 vs. 24%; p=0.226</td></tr>
<tr><td>high</td><td>56 vs.56%; p>0.999</td><td>33 vs. 28%; p=0.651</td></tr>
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<tr>
<td>Brummendorf, 2014
BELA 24-month results</td>
<td>Same as above</td>
<td>Same as above</td>
<td>BOS 500 mg PO daily vs.
IM 400 mg PO daily

Results at 24 months
CCyR: 58 vs. 65%
Cumulative CCyR: 79 vs. 80%;
MMR 47 vs. 41%;
Cumulative MMR: 59 vs. 49%

No significant interaction between treatment and Sokal risk groups
OS: 97 vs. 95%

Retrospective analysis
BCR-ABL1/ABL1 ratio ≤ 10% at 3 mos: 86 vs. 66%; p<0.001
Cumulative CCyR and MMR rates at both 12 and 24 mos were higher in both treatment arms with ≤ 10% at 3 mos.</td>
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Safety

	Comments
Boxed Warning	• None
Contraindications	• Hypersensitivity to bosutinib; anaphylactic shock occurred in less than 0.2% of clinical trial participants.
Warnings/Precautions	• **Gastrointestinal Toxicity**. Diarrhea, nausea, vomiting and abdominal pain can occur with bosutinib. In the single-arm phase 1/2 trial, the median time to diarrhea onset was 2 days; median duration of diarrhea was 1 day; median number of episodes per patient was 3 (range, 1-221). Management of GI toxicity should involve holding, dose-reducing or discontinuing drug. • **Myelosuppression**. Thrombocytopenia, anemia and neutropenia can occur. Check CBCs weekly for the first month, then monthly thereafter, or as clinically indicated. Management should involve withholding, dose-reducing or discontinuing therapy. • **Hepatic Toxicity**. Among the safety population, the incidence of ALT elevation was 17%; AST elevation was 14%. Twenty percent of patients experienced an increase in either ALT or AST. Most cases occurred early in treatment; more than 80% experienced their first event within the first 3 months. Median time to onset of increased ALT and AST was 30 and 33 days; median duration for each was 21 days. Check hepatic enzyme tests monthly for the first 3 months of treatment and as clinically indicated. Management should involve withholding, dose-reducing or discontinuing therapy. • **Fluid Retention**. Fluid retention may manifest as pericardial effusion, pleural effusion, pulmonary edema and/or peripheral edema. Severe fluid retention was reported in 3% of patients. Monitor and management patients using standard of care and interrupt, dose-reduce or discontinue bosutinib as necessary. • **Renal Toxicity**. Bosutinib has been associated with an on-treatment decline in estimated glomerular filtration rate. Monitor renal function at baseline and throughout therapy with bosutinib. Pay particular attention to those who have pre-existing renal impairment of risk factors for renal dysfunction. Consider dose adjustment in those with baseline and treatment emergent renal impairment. • **Embryofetal Toxicity**. Bosutinib can cause fetal harm when administered to a pregnant woman. Embryofetal toxicity has been noted in the animal model. Females of reproductive potential should be advised to avoid pregnancy while being treated with bosutinib. If used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus.

Safety Considerations

- Bosutinib is generally well-tolerated as evidenced by the median dose intensity. Of 287 patients with CP CML previously treated with imatinib, median duration of bosutinib was 24 months; median dose intensity 484 mg/day; of 119 patients with CP CML previously treated with 2 TKI's, median duration of bosutinib was 9 months; median dose intensity 475 mg/day; of 140 patients with AP and BP CML, median duration of bosutinib was 10 and 3 months, respectively; with median dose intensity of 483 and 500 mg/day.
- Common gastrointestinal adverse events are seen early in the course of therapy (median time to onset: diarrhea 2 days; nausea 5 days; vomiting 8 days).
- At the 2-yr follow-up, the most common toxicities were diarrhea (84%), nausea (45%), vomiting (37%), which were all mild-moderate severity. Thrombocytopenia was the most common severe hematologic toxicity (24%).

- The toxicity profile of bosutinib after treatment with multiple TKIs does not greatly differ from the toxicity profile following one prior TKI. Koury, et al. evaluated use of bosutinib in CP-CML after prior imatinib and dasatinib and/or nilotinib. The most common non-hematologic toxicities seen in these patients were GI in nature (diarrhea 81%; nausea 43%; vomiting 32%). Median duration of any diarrhea was 2 days; grade 3, 4 diarrhea lasted ~7 days. Grade 3, 4 hematologic toxicities included thrombocytopenia 25%, neutropenia 19% and anemia 8%.
- Use caution when prescribing bosutinib in patients with prior dasatinib-intolerance. Retrospective evaluation of cross-intolerance between bosutinib and dasatinib by Koury, et al. led to the discovery that among patients with prior dasatinib-intolerance, 22% had a more severe version of the same event while receiving bosutinib; 8% discontinued bosutinib because of the same event. Most common cross-intolerant event was myelosuppression. A total of 19 patients discontinued dasatinib due to pleural effusions but only 2 patients experienced grade 3, 4 pleural effusions with bosutinib and neither discontinued therapy. Patients with prior dasatinib-intolerance related to cardiovascular events, gastrointestinal events, musculoskeletal or skin events did not experience these toxicities in a more severe form while on bosutinib therapy.
- Dose-adjustments are recommended in renal and hepatic impairment.
- Comparatively, bosutinib has myelosuppressive effects, similar to imatinib, nilotinib and dasatinib; it lacks the risk of QT prolongation as with nilotinib and dasatinib and the risk of fluid retention/edema is less that that noted with dasatinib. GI effects (diarrhea, nausea and vomiting) are greater with bosutinib.

Adverse Reactions

Common adverse reactions	Incidence > 20%: diarrhea (82%), nausea (46%), thrombocytopenia (41%), vomiting (39%), abdominal pain (37%), rash (35%), anemia (27%), pyrexia (25%) and fatigue (24%).
Death/Serious adverse reactions	Incidence Grade 3/4 > 20% in CP CML: thrombocytopenia (26%) Incidence Grade 3/4 > 20% in AP CML: thrombocytopenia (37%), anemia (26%), ANC < 1000 (37%)
Discontinuations due to adverse reactions	21% discontinued due to adverse events: 17% imatinib-resistant; 31% imatinib-intolerant; median time to discontinuation 5.3 months (range, 0.2-19.7 mos); Most common AE leading to DC: thrombocytopenia (4%); increased ALT (2%); increased AST (2%); diarrhea (2%).

Drug Interactions

Drug-Drug Interactions

- **Drugs that may increase bosutinib plasma concentrations**: CYP3A or P-glycoprotein inhibitors. Avoid concomitant use of strong or moderate CYP3A and/or P-gp inhibitors as they may increase bosutinib concentrations.
- **Drugs that may decrease bosutinib plasma concentrations**:
  CYP3A Inducers. Avoid concomitant use of strong or moderate CYP3A inducers with bosutinib, as a larger reduction in exposure is expected.
  Proton Pump Inhibitors: Avoid PPIs with concomitant bosutinib therapy as a reduction in bosutinib exposure is expected. Consider using short-acting antacids or H2 blockers instead of PPIs. Separate antacid or H2 blocker dosing and bosutinib dosing by more than 2 hours.
- **Drugs that may have their plasma concentrations altered by bosutinib**. Substrates of P-glycoprotein. *In vitro* data suggests that bosutinib has the potential to increase plasma concentrations of drugs that are P-gp substrates, such as digoxin.

Risk Evaluation

As of November, 2012:

	Comments
Sentinel event advisories	• None • Sources: ISMP, FDA, TJC
Look-alike/sound-alike error potentials	• LA/SA for BOSULIF: none • LA/SA for BOSUTINIB: bortezomib, bosentan, dasatinib, imatinib, nilotinib, ponatinib, sunitinib, sorafenib • Sources: As part of a JCAHO standard, LASA names are assessed during the formulary selection of drugs. 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.
- NCCN Guidelines, Version 1.2016, list bosutinib as a Category 2A recommendation as a second-line or third-line therapy in CML; it is not recommended as first-line therapy in newly diagnosed patients with CP-CML.
- European LeukemiaNet (ELN) recommendations for management of CP-CML are as follows:
  First-line: imatinib, nilotinib or dasatinib
  Second-line: This line of therapy is guided by patient characteristics (age, comorbidities), AEs from prior TKI, BCR-ABL1 point mutations, drug availability, cost and provider experience.
  Imatinib → dasatinib, nilotinib, bosutinib or ponatinib
  Nilotinib → dasatinib, bosutinib, ponatinib
  Dasatinib → nilotinib, bosutinib, ponatinib
- Health-related quality of life data collected as an exploratory endpoint in chronic phase CML patients on bosutinib therapy noted improvements at week 96 in three summary scales: FACT-General, FACT-Leukemia total and FACT-Trial Outcome Index. Although both imatinib-resistant and imatinib-intolerant patients had statistically significant improvements in the subscales, only the imatinib-intolerant patients had both statistically and clinically significant improvements.

Outcome in clinically significant area	CP: MCyR at 24 weeks; 2-yr PFS 79%; 2-yr OS 92% AP, BP: CHR, OHR by week 48
Effect Size	MCyR (2-yr) 58% [95% CI 52-64] CHR (AP) 30.4% [95% CI 19.9-42.7]; (BP) 15% [95% CI 7.1-26.6] OHR (AP) 55% [95% CI 42.6-67.1]; (BP) 28% [95% CI 17.5-41.4]
Potential Harms	CP: thrombocytopenia (26%) AP, BP: thrombocytopenia (37%), anemia (26%), neutropenia (37%)
Net Clinical Benefit	CP: Substantial (high benefit w/low risk harm) AP, BP: Moderate (high benefit w/ high risk 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

- Bosutinib dose is 500 mg orally once daily with food until disease progression or intolerance. Doses missed beyond 12 hours should be skipped and take the usual prescribed dose on the following day.
- Refer to Prescribing Information for dose escalation and adjustments.

Special Populations (Adults)

	Comments
Elderly	• No overall differences in safety or effectiveness have been observed between patients over age 65 and younger patients.
Pregnancy	• Pregnancy Category D. Bosutinib can cause fetal harm when administered to a pregnant woman; animal studies showed reproductive toxicities. If used during pregnancy, or if the patient becomes pregnant while taking bosutinib, patient should be informed of the potential hazard to the fetus.
Lactation	• Because of the potential for serious adverse reactions in nursing infants, a decision should be made whether to discontinue nursing or discontinue the drug.
Renal Impairment	• Dose-reduce the bosutinib starting dose in patients with moderate or severe renal impairment at baseline. If declining renal function is noted during therapy, follow dose-adjustment recommendations for toxicity. Drug has not been studied in patients undergoing hemodialysis.
Hepatic Impairment	• In a hepatic impairment trial, exposure to bosutinib increased in patients with Child-Pugh classes A, B and C compared to matched healthy volunteers. Treat these patients with a reduced dose.
Pharmacogenetics/genomics	• No data identified.

Projected Place in Therapy

- NCCN Guidelines, Version 1.2016, list bosutinib as a Category 2A recommendation as a second-line or third-line therapy in CML; it is not recommended as first-line therapy in newly diagnosed patients with CP-CML.
- European LeukemiaNet (ELN) recommendations for management of CML
  First-line: imatinib, nilotinib or dasatinib
  Second-line: This line of therapy is guided by patient characteristics (age, comorbidities), adverse effects from prior TKI, BCR-ABL1 point mutations, drug availability, cost and provider experience.
  Imatinib → dasatinib, nilotinib, bosutinib or ponatinib
  Nilotinib → dasatinib, bosutinib, ponatinib
  Dasatinib → nilotinib, bosutinib, ponatinib
- Bosutinib is a once daily formulation that lacks the risk of QT prolongation seen with nilotinib and dasatinib.
- Bosutinib was evaluated in patients that had progressed on multiple TKIs (nilotinib and/or dasatinib) indicating that bosutinib is effective as a second-line TKI and beyond; response rates are lower among patients who have received two prior TKIs.

References

Bosulif (bosutinib) Prescribing Information. New York, New York: Pfizer Labs. December 2014.

Bosulif. Drugs@FDA. Food and Drug Administration Web site. http://www.accessdata.fda.gov/drugsatfda_docs/nda/2012/203341Orig1s000MedR.pdf. Accessed May, 2015.

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).

Baccarani M, Castagnetti F, Gugliotta G, Rosti G. A review of the European LeukemiaNet recommendations for the management of CML. Ann Hematol 2015; 94: S141-S147.

Cortes JE, Kantarjian HM, Brummendorf TH, et al. Safety and Efficacy of Bosutinib (SKI-606) in Chronic Phase Philadelphia Chromosome-Positive Chronic Myeloid Leukemia Patients with Resistance or Intolerance to Imatinib. Blood 2011; 118: 4567-4576.

Cortes JE, Kim DW, K HM, et al. Bosutinib versus Imatinib in Newly Diagnosed Chronic Phase Chronic Myeloid Leukemia: Results from the BELA Trial. J Clin Oncol 2012; 30: 3486.

Brummendorf TH, Cortes JE, de Souza CA, et al. Bosutinib versus Imatinib in Newly Diagnosed Chronic Phase Chronic Myeloid Leukemia: Results from the 24-month Follow-up of the BELA Trial. British Journal of Haematology 2015; 168: 69-81.

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.

Kantarjian HM, Cortes JE, Kim DW, et al. Bosutinib Safety and Management of toxicity in leukemia patients with resistance or intolerance to imatinib and other tyrosine kinase inhibitors. Blood 2014; 123: 1309-1318.

Trask PC, Cella D, Besson N, Kelly V, Masszi T, Kim DW. Health-Related Quality of Life of Bosutinib (SKI-606) in Imatinib-Resistant or Imatinib-Intolerant Chronic Phase Chronic Myeloid Leukemia. Leukemia Research 2012; 36: 438-442.

Gambacorti-Passerini C, Cortes JE, Khoury HJ, et al. Safety and efficacy of bosutinib in patients with AP and BP CML and Ph+ ALL following resistance/intolerance to imatinib and other TKIs: Update from study SKI-200. J. Clin Oncol 2010; 28 (15, suppl): abstract 6509.

Gambacorti-Passerini C, Brummendorf TH, Kim DW, et al. Bosutinib efficacy and safety in chronic phase chronic myeloid leukemia after imatinib resistance or intolerance: Minimum 24-month follow-up. Am J Hematol 2014; 89: 732-742.

Abbas R, Hug BA, Leister C, Sonnichsen D. A randomized, crossover, placebo- and moxifloxacin-controlled study to evaluate the effects of bosutinib (SKI-606), a dual Src/Abl tyrosine kinase inhibitor, on cardiac repolarization in healthy adult subjects. Int J Cancer 2012;131: E304-11

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Appendix 1: 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.

Table 2. Definitions of hematologic, cytogenetic and molecular response in chronic myeloid leukemia[1,2]

Response by type	Definitions
Hematologic	
Complete (CHR)	WBC < 10 x 10^9 /L Basophils < 5% No immature cells such as myelocytes, promyelocytes, myeloblasts in the differential Platelet count < 450 x 10^9 /L Spleen non-palpable
Cytogenetic*	
Major	Major (MCyR): 0-35% Ph+ metaphases (complete + partial) Complete (CCyR): No Ph+ metaphases Partial: 1-35% Ph+ metaphases
Minor	36-65% Ph+ metaphases
Minimal	66-95 % Ph+ metaphases
None	> 95% Ph+ metaphases
Molecular	
Complete (CMR)	Undetectable BCR-ABL with a RT-PCR sensitivity of ≥ 5 log
Major (MMR)	≥ 3 log reduction from standardized baseline

WBC white blood cell; Ph+ Philadelphia chromosome positive; FISH fluorescence in situ hybridization; IS international scale

* Chromosome banding analysis of at least 20 bone marrow cell metaphases is necessary to determine the degree of cytogenetic response. If marrow cell metaphases cannot be obtained or evaluated by chromosome banding analysis, the definition of CCgR may be based on interphase fluorescent in situ hybridization of blood cells, provided that it is performed with BCR-ABL1 extrasignal, dual color, dual fusion, or in situ hybridization probes, and that at least 200 nuclei are scored.

Molecular responses are, in general, reported on the evaluation of blood, not marrow samples. For a standardized assessment of the MoIR, the conversion of each laboratory datum to the international scale is recommended, to correct for the variability of the assays in different laboratories. To allow for intra-laboratory variations, a fluctuation of less than one log requires confirmation.

1. Baccarani M, Cortes J, Pane F, et al. Chronic myeloid leukemia: An update of concepts and management recommendations of European LeukemiaNet. J Clin Oncol 2009; 27: 6041.
2. Baccarani M, Deininger MW, Rosti G, et al. European LeukemiaNet recommendations for the management of chronic myeloid leukemia: 2013. Blood 2013; 122: 872.