PDL NEW DRUG REVIEW

Proprietary Name: Bosulif®
Common Name: bosutinib
PDL Category: Antineoplastics- Protein-Tyrosine Kinase Inhibitors

Comparable Products	Preferred Drug List Status
Gleevec	Recommended
Sprycel	Non-Recommended

Summary

Indications and Usage: For the treatment of adult patients with chronic, accelerated, or blast phase Philadelphia chromosome-positive (Ph+) chronic myelogenous leukemia (CML) with resistance or intolerance to prior therapy. This is a pregnancy category D medication. The safety and efficacy of use in children under the age of 18 years have not been established.

Drug Interactions: Concomitant use of strong or moderate CYP3A4 inducers or inhibitors with Bosulif® should be avoided. In a trial with healthy adults, the concomitant use of Bosulif® with lansoprazole resulted in a decreased Bosulif® level (by 46%) and a decreased AUC (by 26%) as compared with those taking Bosulif® as monotherapy. It is therefore recommended that short-acting antacids or H2 blockers be used rather than a PPI if also taking Bosulif®. Furthermore, the antacid or H2 blocker dose should be separated from the Bosulif® dose by more than 2 hours. Lastly, Bosulif® may potentially increase the levels of drugs that are P-gp substances, such as digoxin.

Dosage Forms: Tablets; 100mg, 500mg

Recommended Dosage: Take one 500mg tablet once daily with food, and continue treatment until disease progression or patient intolerance. If a dose is missed beyond 12 hours, that dose should be skipped and then the usual prescribed dose should be taken on the following day. Dose escalation to 600mg once daily may be considered in those who do not reach complete hematological response (CHR) by week 8 or a complete cytogenetic response (CCyR) by week 12, who did not have ≥Grade 3 adverse reactions, and who are currently taking 500mg daily. Dose adjustments are not required in those with renal impairment.

Specific dose adjustment recommendations can be found in the PI for those with non-hematological adverse reactions (eg. elevated liver transaminases, diarrhea) and for those with myelosuppression (severe or persistent neutropenia and thrombocytopenia). Also, the recommended dose of Bosulif® is 200mg once daily in those with pre-existing hepatic impairment, regardless of the severity of the impairment.

Common Adverse Drug Reactions: There was no placebo data to compare. The most commonly reported adverse events with Bosulif® in clinical trials for chronic phase CML include diarrhea (84%), nausea (46%), abdominal pain (40%), vomiting (37%), thrombocytopenia (40%), anemia 23%), neutropenia (16%), fatigue (26%), pyrexia (22%), edema (14%), asthenia (11%), decreased appetite (13%), respiratory tract infection (12%), arthralgia (14%), headache (20%), dizziness (10%), cough (20%), rash (34%), pruritus (11%), low platelet count (25%),

absolute neutrophil count (18%), low hemoglobin (13%), increased alanine aminotransferase (20%), increased aspartate aminotransferase, and SGPT/ALT greater than 5X UNL (10%).

As myelosuppression occurs with Bosulif® use, those who are using this treatment should have a complete blood count performed weekly for the first month and then monthly thereafter as clinically indicated. Monthly hepatic enzyme tests should be performed for the first three months of treatment, as clinically indicated. If there are elevations in transaminases, then liver enzymes should be monitored more frequently. Fluid retention has been reported with Bosulif® and may lead to pericardial effusion, pleural effusion, pulmonary edema, and/or peripheral edema. Patients should be monitored, and the dose should be interrupted, reduced, or discontinued as necessary.

Contraindications: In those with hypersensitivity to bosutinib or any component of the product

Manufacturer: Pfizer Labs

Analysis: Bosutinib, the active ingredient of Bosulif®, is a tyrosine kinase inhibitor. It inhibits the Bcr-Abl kinase that promotes CML. It is also an inhibitor of the Src-family kinases, including Src, Lyn, and Hck. Several warnings exist with Bosulif® use, including GI toxicity, hepatic toxicity, and myelosuppression. If these occur, it is recommended to withhold, reduce the dose, or discontinue Bosulif® treatment to help manage the condition. Furthermore, due to the risk of myelosuppression, it is recommended that a complete blood count be performed weekly for the first month and then monthly thereafter or as clinically indicated. Due to the risk of hepatic toxicity, monthly hepatic enzyme tests should be performed for the first three months of treatment, and as clinically indicated. Liver enzymes should be monitored more frequently in those with transaminase elevations.

There was a single arm, open-label multicenter study that assessed the safety and efficacy of Bosulif® 500mg daily in those with imatinib-resistant or-intolerant CML. The efficacy endpoint for those with chronic phase (CP) CML previously treated with imatinib was the rate of attaining major cytogenetic response (MCyR) at week 24, while for those with CP CML previously treated with both imatinib and at least one additional tyrosine kinase inhibitor (TKI) it was the cumulative rate of attaining MCyR by week 24. The efficacy endpoints for those previously treated accelerated phase (AP) and blast phase (BP) CML were confirmed complete hematologic response (CHR) and overall hematologic response (OHR).

Results suggest that at week 24, the efficacy rate of attaining MCyR in those with CP CML with prior treatment with imatinib only was 33.8%, and was 26.9% for those with prior treatment with imatinib and another TKI (either dasatinib or nilotinib). The CHR by week 48 in the AP CML group was 30.4% and in the BP CML group was 15%, while the OHR was 55.1% in the AP CML group and 28.3% in the BP CML group.

It is recommended that Bosulif® be added to the Recommended Drug List as a non-recommended drug, as it is not intended as a first-line treatment option.

PDL Placement: ☐ **Recommended**
☒ **Non-Recommended**

References

[1] Bosulif [package insert]. New York, NY: Pfizer Labs, a division of Pfizer Inc; 2012.