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Date of request: September 4, 2012
NCCN Guidelines Panel: Chronic Myelogenous Leukemia

Dear Ms. McClure,

On behalf of the Oncology Business Unit at Pfizer Inc, I respectfully request the NCCN *Chronic Myelogenous Leukemia* Guideline Panel to review the enclosed for consideration of inclusion of bosutinib in the NCCN Compendia listings.

- **Request for NCCN Guidelines Panel to consider review of data for a specific indication**
 - BOSULIF (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.
- **Specific changes recommended within the NCCN Guidelines**
 - For patients with chronic, accelerated, or blast phase Ph+ chronic myelogenous leukemia with resistance, or intolerance to prior therapy, recommend that treatment with BOSULIF (bosutinib) be listed as a treatment option (category 1).
- **Statement of whether the submitted use is or is not FDA approved for that indication**
 - The submitted use was approved by the FDA for this indication on September 4, 2012.
- **Rationale for recommended change**
 - BOSULIF is a new treatment option that helps to fulfill a need for CML patients who develop resistance or intolerance to prior therapies.
- **Citation of literature support and complete articles supporting recommended change:**
 - 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(17):4567-76.
 - 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(15):3403-12.

On September 4, 2012, the FDA approved BOSULIF (bosutinib) for the treatment of adult patients with chronic, accelerated, or blast phase Ph+ chronic myelogenous leukemia (CML) with resistance, or intolerance to prior therapy. The basis for the approval was a single-arm Phase 1/2 open-label, multicenter trial conducted to evaluate the efficacy and safety of BOSULIF 500 mg once daily in patients with imatinib-resistant or -intolerant CML with separate cohorts for chronic, accelerated, and blast phase disease previously treated with imatinib only or more than one TKI (imatinib followed by dasatinib and/or nilotinib).

The efficacy endpoints for patients with CP CML previously treated with imatinib only were the rate of attaining MCyR at week 24 and the duration of MCyR. The efficacy endpoints for patients with CP CML previously treated with both imatinib and at least 1 additional TKI were the cumulative rate of attaining MCyR by week 24 and the duration of MCyR. The efficacy endpoints for patients with previously treated AP and BP CML were complete hematologic response (CHR) and overall hematologic response (OHR).

The trial enrolled 546 patients with CP, AP or BP CML, of whom 73% were imatinib-resistant and 27% were imatinib-intolerant. Among evaluable patients (n=503), there were 266 patients with CP CML previously treated with imatinib only, 108 patients with CP CML previously treated with both imatinib and at least 1 additional TKI, and 129 patients with advanced phase CML previously treated with at least one TKI. Median duration of BOSULIF treatment was 22 months in patients with CP CML previously treated with imatinib only, 8 months in patients with CP CML previously treated with imatinib and at least 1 additional TKI, 10 months in patients with AP CML previously treated with at least imatinib, and 3 months in patients with BP CML previously treated with at least imatinib.

At week 24, the MCyR rate for CP CML treated with imatinib only and with imatinib and an additional TKI were 33.8% and 26.9%, respectively. The minimum follow-up was 23 months for patients with CP CML treated with imatinib only and 13 months for patients with CP CML treated with imatinib and at least one additional TKI. For the 53.4% of patients with CP CML treated with imatinib only who achieved a MCyR at any time, the median duration of MCyR was not reached. Among these patients, 52.8% of them had a MCyR lasting at least 18 months. For the 32.4% of patients with CP CML treated with imatinib and at least one additional TKI who achieved a MCyR at any time, the median duration of MCyR was not reached. Among these patients, 51.4% of them had a MCyR lasting at least 9 months. Of the 374 evaluable patients with CP CML, 16 patients had confirmed disease transformation to AP or BP while on treatment with BOSULIF. Of the 69 evaluable patients with AP CML, 4 patients had confirmed disease transformation to BP while on BOSULIF treatment.. Bosutinib demonstrated preclinical activity against most imatinib-resistant mutants of Bcr-Abl, with the exception of T315I and V299L. Clinically, hematologic and/or cytogenetic responses were observed across several Bcr-Abl mutations, except for T315I (examples include F317L, Y253H, F359C/I/V).

AEs were generally tolerable and clinically manageable. The safety population included 546 CML patients. The most common adverse reactions (incidence greater than 20%) were diarrhea, nausea, thrombocytopenia, vomiting, abdominal pain, rash, anemia, pyrexia, and fatigue. Serious adverse reactions reported include anaphylactic shock, myelosuppression, gastrointestinal toxicity (diarrhea), fluid retention, hepatotoxicity and rash.

We appreciate the Panel's thorough consideration of Pfizer's submission for BOSULIF (bosutinib) for the treatment of adult patients with chronic, accelerated, or blast phase Ph+ CML with resistance, or intolerance to prior therapy.

Kind regards,



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