March 22, 2018

Submission Request
National Comprehensive Cancer Network® (NCCN®)

RE: Clinical Evidence in Support of Tasigna® (nilotinib) in Pediatric Patients With Newly Diagnosed Philadelphia Chromosome-Positive Chronic Myeloid Leukemia in Chronic Phase (Ph+ CML-CP) and in Pediatric Patients With Ph+ CML-CP Resistant or Intolerant to Prior Tyrosine-Kinase Inhibitor (TKI) Therapy

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Date of request:	March 22, 2018
NCCN Guidelines Panel:	Chronic Myeloid Leukemia (CML)

To Whom It May Concern:

As the NCCN CML Panel reviews the NCCN Clinical Practice Guidelines in Oncology® (NCCN Guidelines®) for CML v.4.2018 and the associated Drugs and Biologics Compendium™, we have enclosed data regarding Tasigna® (nilotinib) for your consideration:

- Data in support of nilotinib use in pediatric patients with newly diagnosed Ph+ CML-CP or Ph+ CML-CP resistant or intolerant to prior TKI therapy

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Nilotinib in pediatric patients with Ph+ CML-CP
This request is for the Panel to consider including nilotinib as a treatment option for pediatric patients greater than or equal to 1 year of age with newly diagnosed Ph+ CML-CP or Ph+ CML-CP resistant or intolerant to prior TKI therapy within the CML Guidelines® and the associated NCCN Drugs and Biologics Compendium™.

Pediatric patients from 2 years to less than 18 years of age with either newly diagnosed Ph+ CML-CP or imatinib/dasatinib resistant or intolerant Ph+ CML-CP received the recommended dose of nilotinib of 230 mg/m^2 twice daily in two studies (N = 69). The median time on treatment with nilotinib was 13.8 months (range: 0.7-30.9 months); the median actual dose intensity was 435.5 mg/m^2/day (range: 149-517 mg/m^2/day) and the median relative dose intensity was 94.7% (range: 32-112%). Forty patients (58%) had relative dose intensity superior to 90%.[1]

In pediatric patients with Ph+ CML-CP, the most common (> 20%) non-hematologic adverse events (AEs) were headache, rash, hyperbilirubinemia, increased alanine aminotransferase (ALT), pyrexia, nausea, upper respiratory tract infection, increased aspartate aminotransferase (AST) and vomiting. The most common (> 5%) Grade 3/4 non-hematologic AEs were increased ALT and hyperbilirubinemia. Lab abnormalities of hyperbilirubinemia (Grade 3/4: 13%) and increased AST and ALT (Grade 3/4: 1% and 9%, respectively) were reported at higher frequency than in adults.[1]

The most common any-Grade hematologic AEs (≥ 30%) were decreases in total white blood cells (54%), platelet count (44%), absolute neutrophils (41%), absolute lymphocytes (32%) and hemoglobin (30%). Discontinuation due to AEs occurred in 9 patients (13%); AEs leading to discontinuation included hyperbilirubinemia (6%) and rash (4%). Increase in QTcF > 30 msec from baseline was observed in 17 patients (25%). No patient had an absolute QTcF > 500 msec or QTcF

> 60 msec from baseline.[1]
In patients with resistant or intolerant CML, major molecular response (MMR; BCR-ABL/ABL ≤0.1% IS) rate was 40.9% (18/44, 95% CI: 26.3%, 56.8%) at 12 cycles (28 days per cycle). In patients with newly diagnosed CML, the MMR rate was 60% (15/25, 95% CI: 38.7%, 78.9%) at 12 cycles. In patients with resistant or intolerant CML, the cumulative MMR rate was 47.7% (21/44) by cycle 12. In patients with newly diagnosed CML, the cumulative MMR rate was 64% (16/25) by cycle 12.[1]

Among the 21 patients with resistant or intolerant CML who were in MMR at any time on treatment, median time to first MMR was 2.8 months (range: 0-11.3). For the 17 patients with newly diagnosed CML who achieved MMR, median time to first MMR was 5.6 months (range: 2.7-16.6). Among patients with resistant or intolerant CML, 4.5% achieved BCR-ABL/ABL ≤0.0032% IS (MR4.5) by the cut-off date. Among patients with newly diagnosed CML, 28% of patients achieved MR4.5.[1]

None of the 21 patients with resistant or intolerant CML who were in MMR on treatment had confirmed loss of MMR, with a median follow-up of 11.3 months. Among the 17 patients with newly diagnosed CML who achieved MMR, one had confirmed loss of MMR 3 months after achieving this response; in these patients, the median follow-up was 11.1 months. One patient with resistant or intolerant CML progressed to advance phase/blast crisis after about 10 months on treatment.[1]

Specific changes recommended for the Guidelines & Compendium
Please consider including nilotinib as an FDA-approved treatment option for pediatric patients greater than or equal to 1 year of age with newly diagnosed Ph+ CML-CP or Ph+ CML-CP resistant or intolerant to prior TKI therapy within the discussion section under special considerations for children with CML (MS-24).

FDA status
Tasigna is a kinase inhibitor indicated for the treatment of:

- Adult and pediatric patients greater than or equal to 1 year of age with newly diagnosed Ph+ CML-CP
- Adult patients with chronic phase and accelerated phase Ph+ CML resistant to or intolerant to prior therapy that included imatinib
- Pediatric patients greater than or equal to 1 year of age with Ph+ CML-CP resistant or intolerant to prior TKI therapy

Rationale for recommended change
Based on the recent FDA-approved indication and clinical evidence, nilotinib has demonstrated safety and efficacy in certain pediatric patients greater than or equal to 1 year of age with newly diagnosed Ph+ CML-CP or Ph+ CML-CP resistant or intolerant to prior TKI therapy.

Literature support
1. Tasigna [prescribing information]. East Hanover, NJ: Novartis Pharmaceuticals Corp; 2018.

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We appreciate the opportunity to provide this additional information specific to nilotinib for consideration by the NCCN CML Panel. If you have any questions or require additional information, please do not hesitate to contact me at 1-862-778-5494 or via e-mail at neilda.baron@novartis.com.

Thank you for your time and consideration.

Sincerely,

Neilda Baron, MD
Executive Director, Medical Information Oncology
Novartis Pharmaceuticals Corporation

Enclosure: Copy of Tasigna prescribing information