June 7, 2010

Submission Request c/o Mary Anne Bergman
National Comprehensive Cancer Network
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RE: Clinical Evidence in Support of Tasigna® (nilotinib) in Newly Diagnosed Philadelphia Chromosome Positive Chronic Myelogenous Leukemia

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Date of request:	June 7, 2010
NCCN Guidelines Panel:	Chronic Myelogenous Leukemia

Dear Ms. Bergman:

As the NCCN Chronic Myelogenous Leukemia Panel reviews the NCCN Clinical Practice Guidelines in Oncology for Chronic Myelogenous Leukemia, v.2.2010 and the associated Drugs and Biologics Compendium™, we have enclosed data relating to treatment with nilotinib. This information is highlighted below:

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Nilotinib for the treatment of newly diagnosed Philadelphia Chromosome Positive Chronic Myelogenous Leukemia (Ph+ CML)

This request is for the Panel to consider the addition of nilotinib in section "CML-1" of the Chronic Myelogenous Leukemia and the associated "NCCN Drugs and Biologics Compendium™, as a category I recommendation. In several recent clinical trials summarized below, nilotinib has shown clinical efficacy and safety in treating newly diagnosed CML-CP patients with one Phase III study showing superior efficacy and safety compared to imatinib. Imatinib, the only currently approved first-line treatment, results in a complete cytogenetic response (CCyR) of 75% to 82% of cases at one and seven years of treatment, respectively, with a median time to response of 6 months, and a major molecular response (MMR) in 60-72% of cases at 12 and 24 months; and responses have been shown to be durable for up to 8 years.[1,2] However, 15% to 20% of patients exhibit resistance to imatinib over the course of treatment.[3,4]

In a Phase III, open-label multicenter study that compared nilotinib (300 mg or 400 mg BID) with imatinib (400 mg daily) in 846 newly diagnosed patients with Ph+ CML-CP (the largest randomized comparative study in this population), major molecular response (MMR) rates at 12 months (44% nilotinib 300mg BID vs. 22% imatinib, *P*<.0001; 43% 400 mg BID vs. 22% imatinib, *P*<.0001) and complete cytogenetic response (CCyR) rates by 12 months (80% nilotinib 300mg BID vs. 65% imatinib; *P*<.0001, 78% nilotinib 400 mg BID vs 65% imatinib, *P*<.0005) were significantly superior in both nilotinib arms compared with the imatinib arm.[5] In addition, at 13.8 months median follow-up, only two patients in the nilotinib 300mg BID group, one patient in the 400mg BID group and 11 patients in the imatinib group progressed to accelerated phase or blast crisis (AP/BC); the estimated rates of progression to AP/BC at 12 months were 0.7% in the nilotinib 300 mg BID group, and 0.4% in the 400 mg BID group, compared with 4% in the imatinib group (*P*=.0095 for nilotinib 300 mg BID, *P*=.0037 for nilotinib

400 mg BID). Nilotinib was superior to imatinib across all Sokal risk factor groups. At 18.5 months, the estimated rates of progression to AP/BC were 0.7%, 0.4% and 4.2%. [6] CML related deaths were two in the 300mg group (1 related to bone marrow transplant), 1 in the 400 mg group, and 8 in the imatinib group (2 related to BMT); and overall survival rates, respectively were 98.5%, 99.3% and 96.9%, (based on the intent to treat population. No patient in any arm who achieved an MMR progressed to AP/BC during the first year. At 12 months, agents were well-tolerated with no reports of QTcF interval >500msec and there were no reports of sudden death in any treatment arm. At 18 months, overall incidence of grade 3/4 adverse events were low, rates of grade 3/4 neutropenia and anemia were lower in both nilotinib arms (neutropenia 12% 300 mg BID, 10% 400 mg BID; anemia 3% both arms) compared to imatinib (neutropenia 20% and anemia 5%). In contrast, rates of grade 3/4 thrombocytopenia were similar across all arms (10% nilotinib 300mg BID arm, 12% nilotinib 400mg BID arm, 9% imatinib arm). Edema was reported more frequently in the imatinib arm compared to the nilotinib arms. The occurrence of pleural and pericardial effusion was minimal across all treatment arms (<1%). Grade 3/4 lab abnormalities were similar across all three arms. One patient in the imatinib arm and one in the nilotinib 400 mg BID arm discontinued the study due to acute pancreatitis. Based on the results, nilotinib 300mg BID had the fewest discontinuation rates due to AEs.

Additionally, single arm, Phase II ongoing trials in newly diagnosed CP-CML show results that support the results seen in the Phase III trial. A multicenter, Phase II, Italian study evaluated nilotinib 400 mg BID in 73 early chronic phase, previously untreated, Ph+ CML patients.[7, 8] The primary end-point of the trial was the CCyR rate after one year of treatment. At a median follow-up period of 24 months, the CCyR rate within one year was 100%, and the MMR rate was 85% at 12 months and 87% at 18 months. One patient with the T315I mutation progressed at 6 months to AP. The nilotinib dose intensity was high, the majority of patients received ≥ 600 mg daily. One patient progressed to blast crisis after achieving a CCyR at 3 months Grade 3/4 toxicities included: myelosupression (7%), skin rash (5%) and bone/muscle/joint pain (4%). Most adverse events were grade 1 and 2 and manageable with appropriate dose adaptations: the most frequent biochemical AEs were bilirubin increase (53% all grades, 16% grade 3), and lipase and amylase increase (29% and 18%, all grades, 8% and 4% grade 3+4, respectively); 2 patients went off treatment after 6 and 13 months due to recurrent episodes of amylase and/or lipase increase (no pancreatitis).

The use of nilotinib 400 mg BID was also studied in a second Phase II trial in 51 patients with previously untreated CML-CP. Results reported at a median follow-up of 17 months showed that responses occurred rapidly, with 96% of patients achieving a CCyR by 3 months.[9] An MMR was achieved in 39 (76%) of evaluable patients observed for at least 3 months; 12 (24%) achieved a complete molecular response by 12 months. Event free survival (EFS) (loss of CHR, loss of MCyR, AP/BP, death or treatment discontinuation due to toxicity) at 24 months was 90%. Grade 3/4 hematologic toxicities were transient and included thrombocytopenia (11%), neutropenia (12%), and anemia (5%). The most common grade 3/4 non-hematologic adverse events regardless of causality were: elevated bilirubin (7%), increased lipase (5%), hyperglycemia (5%), and non-neutropenic fever (5%). The median dose delivered was 800 mg daily; 37% (n=24) of patients had treatment interruptions. The most common causes for treatment interruption were increased liver enzyme (n=13), myelosuppression (n=8), and unrelated procedures or surgeries (n = 8).

Lastly, a Phase II, open label, non-randomized study evaluating the safety and efficacy of nilotinib 300 mg twice daily has reported initial results.[10] The primary endpoint is CCyR at 6 months. The CHR rate was 100% at 3 months. At 3 months, the MCyR rate and CCyR rate were 93% and 64%, respectively. Incidence of grade 3/4 toxicities was rare. The following Grade 3 toxicities were reported: musculoskeletal pain (n=1), elevation of serum lipase (n=4, 22%), neutropenia (n=1) and thrombocytopenia (n=1).

Specific changes recommended for the Guidelines & Compendium

Please add nilotinib as a Category I recommendation for the treatment of newly diagnosed patients with Ph+CML in Section CML-1.

FDA Status
Nilotinib is FDA-approved for the treatment of adult patients with chronic and accelerated phase Ph+CML resistant to or intolerant to prior therapy that included imatinib.

Rationale for recommended change
Efficacy and safety of nilotinib, and superiority over imatinib, the current standard of care, has been demonstrated in a large, multi-center phase III trial in patients with newly diagnosed Ph+CML.

Literature support

1. Gleevec [package insert]. East Hanover, NJ: Novartis Pharmaceuticals Corporation.
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3. de Lavallade H, Apperley JF, Khorashad JS, et al. Imatinib for newly diagnosed patients with chronic myeloid leukemia: incidence of sustained responses in an intention-to-treat analysis. *J Clin Oncol*. 2008; 26(20):3358-3363.
4. Apperley JF. Part I: Mechanisms of resistance to imatinib in chronic myeloid leukemia. *Lancet Oncol*. 2007; 8(11):1018-29.
5. Saglio G, Kim DW, Issaragrisil S, et al. Nilotinib Versus Imatinib for Newly Diagnosed Chronic Myeloid Leukemia. *N Engl J Med.* 2010; e-published June 5, 2010. 10.1056/NEJMoa912614.
6. Larson R, Le Coutre P, Reiffers J., et al. Nilotinib is Superior to Imatinib in Patients (pts) with Newly Diagnosed Chronic Myeloid Leukemia in Chronic Phase (CML-CP): ENESTnd Beyond 1 Year. Presented at the 46th Annual meeting of the American Society of Clinical Oncology, Chicago, IL. Oral Presentation CRA 6501.
7. Rosti G, Palandri F, Castagnetti F, et al. Nilotinib for the frontline treatment of Ph+ chronic myeloid leukemia. *Blood*. 2009;114:4933-4938.
8. Rosti G, Castagnetti F, Palandri F, et al. Efficacy and safety of nilotinib 800 mg daily in early chronic phase, ph+ chronic myeloid leukemia: Results of a phase II trial at 2 years. Presented at the 46th Annual meeting of the American Society of Clinical Oncology, Chicago, IL. Poster 6515.
9. Cortes JE, Jones D, O'Brien S, et al. Niltoinib as front-line treatment for patients with chronic myeloid leukemia in early chronic phase. *J Clin Oncol*. 2010;28(3):392-397.
10. O'Dwyer MD, Kent E, Parker M, et al. Nilotinib 300 mg twice daily is effective and well tolerated as first line treatment of ph-positive chronic myeloid leukemia in chronic phase: preliminary results of the ICORG 0802 phase 2 study. *Blood*. 2009;14(11):Abstract 3294.

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We appreciate the opportunity to provide this additional information for consideration by the NCCN Chronic Myelogenous Leukemia 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
Director, Medical Information Oncology
Novartis Pharmaceuticals Corporation

Enclosures: Copies of referenced primary literature