December 22, 2014

Joan McClure, MS
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Dear Ms. McClure,

On behalf of Lilly Oncology, please see the attached updated prescribing information for CYRAMZA® (ramucirumab) injection, for intravenous infusion, for review by the NCCN Guidelines panel for Non-Small Cell Lung Cancer.

CYRAMZA® was initially approved by the Food and Drug Administration (FDA) on April 21, 2014 as a single-agent treatment for patients with advanced or metastatic gastric cancer or gastroesophageal junction (GEJ) adenocarcinoma that has progressed on or after prior fluoropyrimidine- or platinum-containing therapy[1]. On November 5, 2014, the FDA approved Cyramza as a single agent or in combination with paclitaxel as a treatment for people with advanced gastric or gastro-esophageal junction (GEJ) adenocarcinoma whose cancer has progressed after prior fluoropyrimidine- or platinum-containing chemotherapy[1]. On December 12, 2014, the FDA approved Cyramza in combination with docetaxel for the treatment of metastatic nonsmall cell lung cancer (NSCLC) with disease progression on or after platinum-based chemotherapy[1].

We request that the NCCN Guidelines panel for Non-Small Cell Lung Cancer review the data that supports the most recent FDA-approved indication for ramucirumab: Cyramza, in combination with docetaxel, is indicated for treatment of metastatic nonsmall cell lung cancer with disease progression on or after platinum-based chemotherapy. Patients with EGFR or ALK genomic tumor aberrations should have disease progression on FDA-approved therapy for these aberrations prior to receiving Cyramza[2].

We request the panel to consider an evidence category of 1 (high-level evidence)[3] based on the following rationale:

1. FDA approval for this indication[2] following a priority review[1];
2. The REVEL trial is a large (more than 1200 patients) randomized, controlled trial[4] and the first registration trial in approximately a decade to demonstrate a survival benefit over an active comparator in the second-line setting for NSCLC[5,6];
3. This is the first and only FDA approval of a combination treatment regimen shown to improve overall survival versus docetaxel alone (category 2A)[3] in the second line setting for NSCLC;
4. The trial demonstrated robust and consistent improvements across relevant efficacy endpoints including OS, PFS, and ORR[4]; independent of histology[7];
5. The safety profile of the combination is manageable[4] and does not have a negative impact on global quality-of-life scores[7];
6. Despite currently available therapies, there continues to be a need for new second-line treatment options for patients with NSCLC[4].

Approval status: Cyramza has FDA approval for this use (please see approval letter attached, dated December 12, 2014).

See important safety information, including the Boxed Warning for hemorrhage, in the accompanying full prescribing information.

WARNING: HEMORRHAGE

See full prescribing information for complete boxed warning.

CYRAMZA increased the risk of hemorrhage, including severe and sometimes fatal hemorrhagic events. Permanently discontinue CYRAMZA in patients who experience severe bleeding *[see Dosage and Administration (2.3), Warnings and Precautions (5.1)]*.

Please see the following attachments:

- Prescribing Information
- FDA approval letter

For medical inquiries, please contact me directly.

Sincerely,

Carolyn Moore, RN, MSM
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References

1. FDA News Release: FDA expands approved use of Cyramza to treat aggressive non-small cell lung cancer. 12 December, 2014. Accessed 18 December 2014. http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm426720.htm
2. Cyramza® [package insert]. Indianapolis, IN: Eli Lilly and Company; 2014.
3. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology Non-Small Cell Lung Cancer (version 2.2015, 10Dec2014). http://www.nccn.org/professionals/physician_gls/pdf/nscl.pdf. Accessed 18Dec2014.
4. Garon EB, Ciuleanu TE, Arrieta O, et al. Ramucirumab plus docetaxel versus placebo plus docetaxel for second-line treatment of stage IV non-small-cell lung cancer after disease progression on platinum-based therapy (REVEL): a multicentre, double-blind, randomised phase 3 trial. *Lancet.* 2014;384(9944):665-673.
5. Alimta® [package insert]. Indianapolis, IN: Eli Lilly and Company; 2013.
6. Tarceva® [package insert]. South San Francisco, CA: Genentech; 2014.
7. Supplement to: Garon EB, Ciuleanu T-E, Arrieta O, et al. Ramucirumab plus docetaxel versus placebo plus docetaxel for second-line treatment of stage IV non-small-cell lung cancer after disease progression on platinum-based therapy (REVEL): a multicentre, double-blind, randomised phase 3 trial. *Lancet* 2014; published online June 2. http://dx.doi.org/10.1016/S0140-6736(14)60845-X.