Cyramza® (ramucirumab) – New indication and boxed warning removal

- On May 13, 2019, Eli Lilly announced the FDA approval of Cyramza (ramucirumab), as a single agent, for the treatment of hepatocellular carcinoma (HCC) in patients who have an alpha fetoprotein (AFP) of ≥ 400 ng/mL and have been treated with Nexavar® (sorafenib).

- Cyramza is also indicated for the treatment of patients with advanced or metastatic, gastric or gastro-esophageal junction adenocarcinoma, metastatic non-small cell lung cancer, and metastatic colorectal cancer.

- HCC is the most common form of liver cancer, comprising up to 90% of all cases. It is estimated that approximately 40% of all people with advanced HCC are AFP-High (AFP ≥ 400 ng/mL) and these patients are known to have a poorer prognosis relative to the general HCC patient population. Once patients who are AFP-High enter the second-line treatment setting, the expected survival is 3 to 5 months if untreated.

- The approval of Cyramza for the new indication was based on the placebo-controlled REACH-2 study of 292 patients with advanced HCC with AFP ≥ 400 ng/mL who had disease progression on or after prior Nexavar therapy or who were intolerant to Nexavar. Patients received Cyramza or placebo every 2 weeks until disease progression or unacceptable toxicity. The major efficacy outcome measure was overall survival (OS).

    - The median OS was 8.5 months in the Cyramza-treated patients vs. 7.3 months in the placebo group (hazard ratio [HR] = 0.71; 95% CI: 0.53, 0.95; p = 0.020).
    - The median progression-free survival was 2.8 months in the Cyramza-treated patients vs. 1.6 months in the placebo-group (HR = 0.45; 95% CI: 0.34, 0.60; p < 0.0001).
    - The overall response rate for the Cyramza-treated patients was 4.6% (95% CI: 1.7, 7.5) vs. 1.1% (95% CI: 0, 3.1) for the placebo group.

- In addition, the *Boxed Warning* for hemorrhage, gastrointestinal perforation, and impaired wound healing was removed from the Cyramza drug label.

    - The updated Cyramza labeling continues to provide important information on these specific risks in the *Warnings and Precautions* section of the drug label.

- The most common adverse reactions (≥ 15% and ≥ 2% higher than placebo) with Cyramza use in HCC treated patients were fatigue, peripheral edema, hypertension, abdominal pain, decreased appetite, proteinuria, nausea, and ascites.

- The most common laboratory abnormalities (≥ 30% and a ≥ 2% difference in incidence between arms) with Cyramza use in HCC treated patients were thrombocytopenia, hypoalbuminemia, and hyponatremia.

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- The recommended dose of Cyramza for HCC is 8 mg/kg every 2 weeks administered by intravenous infusion over 60 minutes. Cyramza should be continued until disease progression or unacceptable toxicity.
    - Consult the Cyramza drug label for dosing recommendations for all other indications.