Genentech
A Member of the Roche Group
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IMPORTANT DRUG WARNING

February 2014

Subject: **Information for Healthcare Providers on higher incidence of thrombocytopenia and hemorrhage during the first cycle of treatment with GAZYVA™ (obinutuzumab) plus chlorambucil as compared to rituximab plus chlorambucil or chlorambucil alone in patients with CLL in the pivotal study BO21004/CLL11.**

Dear Healthcare Provider,

Genentech, a member of the Roche group, would like to inform you about the following safety information regarding Gazyva:

Summary:

During the first cycle, a higher incidence of thrombocytopenia and hemorrhagic events was observed in patients with CLL treated with obinutuzumab plus chlorambucil as compared to patients treated with rituximab plus chlorambucil or chlorambucil alone, in the phase 3 pivotal study BO21004/CLL11 (*An open-label, multi-center, three arm randomized, phase III study to compare the efficacy and safety of obinutuzumab plus chlorambucil (GClb), rituximab plus chlorambucil (RClb) or chlorambucil (Clb) alone in previously untreated CLL patients with comorbidities*).

Gazyva, in combination with chlorambucil, is indicated for the treatment of patients with previously untreated chronic lymphocytic leukemia (CLL). The risk of thrombocytopenia is included in the current USPI. The observations described below highlight the importance of monitoring in the first cycle. Based on these findings, Genentech is working closely with the FDA to update the product label.

Further Information on the Safety Concern:

The incidence of all grade and fatal hemorrhagic events was similar across the study arms (GClb 4 deaths (n=336), RClb 3 deaths (n=321), Clb 2 deaths (n=116)). However, all four (4) fatal hemorrhagic events in GClb patients occurred in Cycle 1, compared to none in RClb patients and one (1) in Clb patients.

Due to the small number of patients with fatal hemorrhagic events, limitations of the existing laboratory data and presence of confounding factors in all cases (pre-existing thrombocytopenia due to CLL, concomitant medical conditions, and concomitant treatments such as platelet inhibitors, and anticoagulants), no clear relationship could be established between thrombocytopenia and the fatal hemorrhagic events.

Recommendations to Healthcare Provider:

- Closely monitor patients for thrombocytopenia and risk factors for hemorrhage, especially during the first cycle. If thrombocytopenia occurs, perform regular laboratory tests until the event resolves and consider dose delay in case of severe (Grade 3) or life-threatening (Grade 4) thrombocytopenia. Consider transfusion of blood products (i.e. platelet transfusion) according to institutional practice.
- Use of selected concomitant therapies (including platelet inhibitors and anticoagulants) could worsen hemorrhagic related events, especially during the first cycle. Consider withholding these therapies for appropriate patients.
- Patients with thrombocytopenia prior to the treatment and history of bleeding may be at increased risk for thrombocytopenia or hemorrhagic events and should be closely monitored.
- Discuss the risks that may be associated with Gazyva therapy, including those observed during the first cycle, with patients and their caregivers.

Call for Reporting:

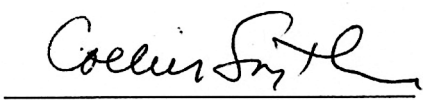
Healthcare professionals should report any serious adverse events suspected to be associated with the use of Gazyva to: Genentech at 1-888-835-2555. Alternatively, this information may be reported to FDA's MedWatch reporting system by phone (1-800-FDA-1088), by facsimile (1-800-FDA-0178), online (https://www.accessdata.fda.gov/scripts/medwatch/) or mailed, using the MedWatch form FDA 3500, to the FDA Medical Products Reporting Program, 5600 Fishers Lane, Rockville, MD 20852-9787.

Company Contact Point:

Should you have any questions regarding the use of Gazyva, please feel free to contact us at: Genentech Medical Information/Communications Department at 1-800-821-8590. The important safety information in this letter is not comprehensive. Please refer to the full Prescribing Information.

Sincerely,

Genentech, a Member of the Roche Group



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