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Submitted by:
Krupa Parekh, Pharm.D.
Managed Care Medical Communications, Medical Affairs
Genentech, Inc.
1 DNA Way
South San Francisco, CA 94080
Phone: (973)-216-2891
Email: genentechmedinfo-d@gene.com
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NCCN Guidelines Panel: B-Cell Lymphomas

On behalf of Genentech, Inc., I respectfully request the NCCN Non-Hodgkin's Lymphomas (NHL) B-Cell Lymphomas Guideline Panel to consider the following key enclosed data for:

- **Rituxan Hycela™ (rituximab and hyaluronidase human) injection, for subcutaneous use:** Follicular Lymphoma (FL) and Diffuse Large B-Cell Lymphoma (DLBCL)

  - Davies A, Merli F, Mihaljevic B, et al. Efficacy and safety of subcutaneous rituximab versus intravenous rituximab for first-line treatment of follicular lymphoma (SABRINA): a randomised, open-label, phase 3 trial. *Lancet Haematol*. May 2, 2017.
  - Davies A, Merli F, Mihaljevic B, et al. Pharmacokinetics and safety of subcutaneous rituximab in follicular lymphoma (SABRINA): stage 1 analysis of a randomised Phase 3 study. *Lancet Oncol* 2014;15:343-352.
  - Lugtenburg P, Rueda A, Avivi I, et al. Rituximab SC and IV plus CHOP show similar efficacy and safety in the randomized MabEase study in first-line DLBCL. Presented at International Conference on Malignant Lymphoma, Lugano, Switzerland 14–17 June, 2017. ICML Poster P186.
  - Rummel M, Kim TM, Plenteda C, et al. Preference for subcutaneous or intravenous administration of rituximab among patients with untreated CD20þ diffuse large B-cell lymphoma or follicular lymphoma: results from a prospective, randomized, open-label, crossover study (PrefMab). *Annals of Oncology* 2017 28: 836–842.

Specific Changes:

- For your updating purposes, please consider the following trials:
  - SABRINA: Efficacy and Safety in FL patients
  - MabEase: Efficacy, Safety, and Patient Preference in DLBCL patients
  - PrefMab: Patient Preference in FL and DLBCL patients

FDA Clearance:

- On **June 22, 2017** the FDA approved Rituxan Hycela for the following:
  - Treatment of adult patients with:
    - Relapsed or refractory, follicular lymphoma as a single agent.
    - Previously untreated follicular lymphoma in combination with first line chemotherapy and, in patients achieving a complete or partial response to rituximab in combination with chemotherapy, as single-agent maintenance therapy.
    - Non-progressing (including stable disease), follicular lymphoma as a single agent after first-line cyclophosphamide, vincristine, and prednisone (CVP) chemotherapy.
  - Treatment of adult patients with previously untreated DLBCL in combination with cyclophosphamide, doxorubicin, vincristine, prednisone (CHOP) or other anthracycline-based chemotherapy regimens.
- Please refer to the prescribing information for a full listing of FDA-approved indications and safety information.
  - Full Rituxan Hycela prescribing information available at:
    - https://www.gene.com/download/pdf/rituxan_hycela_prescribing.pdf

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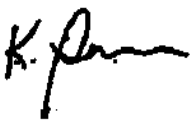
Rationale:

- SABRINA was a Phase III, two-stage, randomized, multicenter study designed to demonstrate noninferiority of fixed-dose Rituxan Hycela 1,400 mg to rituximab IV 375 mg/m^2 in patients with previously untreated Grade 1 to 3a, CD20+ FL also receiving chemotherapy.
    - Stage 1: The first stage of the study demonstrated PK noninferiority of Rituxan Hycela with a C_{trough}, SC:C_{trough}, IV ratio of 1.62 (90% confidence interval [CI]: 1.36 to 1.94).
    - Stage 2: In Stage 2, an additional 283 patients were randomized to assess the efficacy and safety of Rituxan Hycela.
    - Pooled Analysis: In the pooled population of the two stages (N=410) the investigator-assessed overall response rates (ORRs) were 84.4% with Rituxan Hycela and 84.9% with rituximab IV at the end of induction therapy.
    - The rates of adverse events (AE) was similar in both groups; 95% in rituximab IV vs 96% in the Rituxan Hycela.
        - The frequency of grade ≥3 AEs or higher was also similar; 55% in rituximab IV vs 56% in Rituxan Hycela.
        - The incidence of administration-related events (ARRs) was higher in the Rituxan Hycela group; 35% in rituximab IV and 48% in the Rituxan Hycela group.
- MabEase was a Phase IIIb study designed to evaluate the efficacy, safety, and patient satisfaction of Rituxan Hycela compared with rituximab IV, in combination with CHOP in patients with previously untreated DLBCL.
    - The primary endpoint of investigator-assessed complete response/unconfirmed complete response (CR/CRu) at the end of induction was 50.6% for the Rituxan Hycela group vs 42.4% for rituximab IV (p=0.076).
    - The rates of grade ≥3 AEs and ARRs were similar in both groups
        - Grade ≥3 AEs: 58.3% Rituxan Hycela and 54.3% rituximab IV
        - ARRs: 20.9% Rituxan Hycela and 21.3% rituximab IV
    - The Rituxan Hycela arm had a higher number of injection site reactions compared to rituximab IV, 5.7% and 0% respectively (p<0.001).
    - Mean Rituximab Administration Satisfaction Questionnaire (RASQ) scores at Cycle 7 were higher with Rituxan Hycela compared to rituximab IV.
    - 90.8% of patients expressed a preference for Rituxan Hycela over rituximab IV
- The PrefMab study was a Phase III, multicenter, open-label, randomized, cross-over study evaluating patient preference for Rituxan Hycela vs rituximab IV when given with chemotherapy in 743 patients with previously untreated FL or DLBCL. In Arm A, patients received 1 cycle of rituximab IV, 3 cycles of Rituxan Hycela, and 4 cycles of rituximab IV, while patients in Arm B received 4 cycles of rituximab IV then 4 cycles of Rituxan Hycela.
    - At Cycle 8, 81% of patients completing the Patient Preference Questionnaire (PPQ) (the primary endpoint) preferred Rituxan Hycela to rituximab IV.
    - The most commonly identified reasons for the preference for Rituxan Hycela included: ‘requires less time in the clinic’, ‘feels more comfortable during administration’, and ‘feels less emotionally distressing’.

Respectfully submitted,



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