Rituximab and Hyaluronidase injection, for subcutaneous use *(rituximab SC)*

BLA 761064

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Proposed Indications for Rituximab SC

a. Follicular Lymphoma (FL)

… indicated for the treatment of patients with:

- Relapsed or refractory, FL as a single agent.
- Previously untreated FL in combination with first line chemotherapy and, in patients achieving a complete or partial response to *TRADENAME™* for subcutaneous injection in combination with chemotherapy, as single-agent maintenance therapy.
- Non-progressing (including stable disease), FL as a single agent after first-line cyclophosphamide, vincristine, and prednisone (CVP) chemotherapy.

Proposed Indications for Rituximab SC

b. Diffuse Large B-Cell Lymphoma (DLBCL)

… indicated for the treatment of patients with previously untreated DLBCL in combination with cyclophosphamide, doxorubicin, vincristine, prednisolone (CHOP) or other anthracycline-based chemotherapy regimens.

c. Chronic Lymphocytic Leukemia (CLL)

… indicated, in combination with fludarabine and cyclophosphamide (FC), for the treatment of patients with previously untreated and previously treated CLL.

Comparison between rituximab intravenous (IV) and rituximab SC

Characteristics	Rituximab IV	Rituximab SC
Administration	IV infusion over 1.5 to 2.5 hours	SC injection over 5 minutes
Rituximab Concentration	10 mg/mL	120 mg/mL
Co-formulation	none	Hyaluronidase
Dosing regimen	Body surface area - based	Fixed
Doses	375 mg/m^2 → 1400 mg 500 mg/m^2 → 1600 mg	

Regulatory Considerations

Regular Approval as a 351(a) biologic

- Public Health Service Act
- Biologic must be shown to be “safe, pure, and potent” to be approved.
  - The concept of potency has long been interpreted to include effectiveness.
- Requires the conduct of adequate and well-controlled clinical trials

Regulatory Considerations

FDA Guidance on Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products (1998)

"In certain cases, effectiveness of an approved drug product for a new indication, or effectiveness of a new product, may be adequately demonstrated without additional adequate and well-controlled clinical efficacy trials. Ordinarily, this will be because other types of data provide a way to apply the known effectiveness to a new population or a different dose, regimen or dosage form."

Regulatory Considerations

FDA Guidance on Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products (1998)

"It may be possible to conclude that a new dose, regimen, or dosage form is effective on the basis of pharmacokinetic (PK) data without an additional clinical efficacy trial."

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- **PK-bridging approach**
  - targeted a trough concentration (C_{trough}) for the rituximab SC product that would be at least as high as that achieved with IV rituximab
- **Additional changes**
  - Use of fixed-dose regimen
  - Use of hyaluronidase to facilitate drug absorption

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ODAC Discussion Objectives:

- Provide feedback and insights on the development approach
- Assess whether the results of the clinical trials support the approval of the rituximab SC product for the proposed indications in FL, DLBCL, and CLL