CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761064Orig1s000

RISK ASSESSMENT and RISK MITIGATION REVIEW(S)

Division of Risk Management (DRISK)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Application Type	BLA
Application Number	761064
PDUFA Goal Date	June 26, 2017
OSE RCM #	2016-1981
Reviewer Name(s)	Elizabeth Everhart, MSN, RN, ACNP
Team Leader	Doris Auth, PharmD
Division Director	Cynthia LaCivita, PharmD
Review Completion Date	April 4, 2017
Subject	Evaluation of Need for a REMS
Established Name	Rituximab subcutaneous and Hyaluronidase
Trade Name	Rituxan Hycela
Name of Applicant	Genentech, Inc.
Therapeutic Class	Anti-CD 20 monoclonal antibody
Formulation(s)	Subcutaneous injection; co-formulation of rituximab and recombinant human hyaluronidase
Dosing Regimen	1400 mg rituximab and 23,400 USP units hyaluronidase per 11.7 mL solution in a single-dose vial and 1600 mg rituximab and 26,800 USP units hyaluronidase per 13.4 mL solution in a single dose vial for subcutaneous injection after patient receives one full dose of intravenous rituximab – dosing regimen based on indication.

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EXECUTIVE SUMMARY

This review by the Division of Risk Management (DRISK) evaluates whether a risk evaluation and mitigation strategy (REMS) for the new co-formulation of rituximab subcutaneous and recombinant human hyaluronidase (rituximab SC) is necessary to ensure the benefits of this product outweigh its risks. Genentech submitted a Biologic Licensing Application (BLA) #761064 for rituximab SC with the proposed indications of use in adults for the treatment of follicular lymphoma (FL), diffuse large B-Cell lymphoma (DLBCL) and chronic lymphocytic leukemia (CLL); these are the same oncology-related indications as intravenous rituximab (rituximab IV). Similar to rituximab IV, the risks associated with rituximab SC include severe mucocutaneous reactions, Hepatitis B virus (HBV) reactivation, and Progressive Multifocal Leukoencephalopathy (PML), administration-related reactions, Tumor Lysis Syndrome (TLS), infections, cardiac arrhythmias, renal toxicity, bowel obstruction and perforation, and immunization with live vaccines. The applicant did not submit a proposed REMS or risk management plan with this application, but did submit a Medication Guide as part of labeling.

DRISK and the Division of Hematology Products agree that a REMS is not needed to ensure the benefits of rituximab SC outweigh its risks. Rituximab SC has similar efficacy and safety profiles as that of rituximab IV and will have the same Boxed Warning in its prescribing information to communicate the risks of severe mucocutaneous reactions, Hepatitis B virus (HBV) reactivation, and Progressive Multifocal Leukoencephalopathy (PML), as well as the same Warnings and Precautions statements to communicate the risks of administration-related reactions, Tumor Lysis Syndrome (TLS), infections, cardiac arrhythmias, renal toxicity, bowel obstruction and perforation, immunization with live vaccines, and the importance of laboratory monitoring; labeling will also include a Medication Guide.

1 Introduction

This review by the Division of Risk Management (DRISK) evaluates whether a risk evaluation and mitigation strategy (REMS) for the new formulation of rituximab subcutaneous (SC) and recombinant human hyaluronidase (rHuPH20) (rituximab SC) is necessary to ensure the benefits of this product outweigh its risks. Genentech submitted a Biologic Licensing Application (BLA 761064) for rituximab SC injection with the proposed indication of use in adults for the treatment of follicular lymphoma (FL), diffuse large B-Cell lymphoma (DLBCL) and chronic lymphocytic leukemia (CLL); these are the same oncology-related indications as rituximab IV. This application is under review in the Division of Hematology Products (DHP). The applicant did not submit a proposed REMS or risk management plan with this application, but did submit a Medication Guide as part of product labeling.

2 Background

2.1 Product Information

Rituximab SC is a subcutaneous co-formulation of rituximab and rHuPh20. Rituximab is a monoclonal antibody that binds CD20 and induces B-cell lysis. It is not a new molecular entity[a] (NME). The intravenous formulation of rituximab (rituximab IV) has been approved and marketed for oncology

[a] FDAAA factor (F): Whether the drug is a new molecular entity.

indications, including Non-Hodgkin's Lymphoma (NHL). All patients must receive at least one full dose of rituximab IV before receiving rituximab SC. Treatment length is dependent upon indication, with rituximab SC given in cycles with or without chemotherapy weekly for 6 months for as long as 16 cycles for non-progressing FL. [b]

The applicant proposes the same labeling as that of rituximab IV, with Boxed Warnings to communicate the risks of severe mucocutaneous reactions, Hepatitis B virus (HBV) reactivation, and Progressive Multifocal Leukoencephalopathy (PML), as well as the same Warnings and Precautions statements to communicate the risks of administration-related reactions, Tumor Lysis Syndrome (TLS), infections, cardiovascular adverse reactions, renal adverse reactions, bowel obstruction and perforation, immunization, and laboratory monitoring.

Hyaluronidase recombinant is a purified preparation of the enzyme recombinant human hyaluronidase. Hyaluronidase facilitates absorption and dispersion of subcutaneously injected drugs. Hyaluronidase has been approved as an adjuvant in subcutaneous fluid administration for achieving hydration, to increase the dispersion and absorption of other injected drugs, and in subcutaneous urography for improving resorption of radiopaque agents. According to the Applicant, rHuPh20 has no activity or effect beyond serving to enhance permeation.

Rituximab SC in the 1400 mg dose was first approved for the treatment of NHL in the European Union (EU) in March, 2014, and has subsequently received approval in an additional 42 countries worldwide, based upon data from the same studies submitted to this BLA.[1] Additionally, in May, 2016, the 1600 mg dose of rituximab SC was approved for the treatment of CLL in the EU, and in June, 2016 in South Korea. Regulatory reviews for that dose are currently ongoing in other countries. Of note, rHuPH20 is classified by many regulatory authorities outside of the U.S. (EMA, Health Canada, for example) as an excipient, rather than as a co-formulated drug.[2]

2.2 REGULATORY HISTORY

The following is a summary of the regulatory history for BLA 761064 relevant to this review:

- 08/26/2016: BLA 761064 submission for Follicular Lymphoma, Diffuse Large B-cell Lymphoma, Chronic Lymphocytic Leukemia indications received.
- 01/18/2017: An internal Mid-cycle meeting was held and, based on current data, there are no safety issues that require a REMS for Rituximab SC.
- 03/29/2017: Oncology Drug Advisory Committee (ODAC) Meeting was convened to discuss the clinical development program of rituximab SC, which is a PK-based bridging program. The ODAC voted 11 Yes /0 No that the benefit-risk is favorable for rituximab SC for the proposed indications in follicular lymphoma (FL), diffuse large B-cell lymphoma (DLBCL), and chronic lymphocytic leukemia (CLL).

[b] FDAAA factor (D): The expected or actual duration of treatment with the drug.

3 Therapeutic Context and Treatment Options

3.1 Description of the Medical Condition

Non-Hodgkin Lymphoma (NHL) is cancer of the lymphatic system; there are many types of NHL, divided into two cell lines, T-cells and B-cells. B-cell lymphomas include CLL, DLBCL, and FL, among others. In the U.S. in 2016, there were an estimated 72,580 cases, with 20,150 deaths, translating to 4.3% and 3.4% of all new cancer cases and all cancer deaths, respectively.[3,c,d]

3.2 Description of Current Treatment Options

Treatment of NHL depends upon histology and stage of disease. In patients who have indolent, asymptomatic disease, a watchful waiting approach may be used. In progressive and/or aggressive disease, treatment can include radiation, anti-CD20 monoclonal antibodies Rituximab or Obinutuzumab with or without chemotherapy (usually CHOP – cyclophosphamide, doxorubicin, vincristine, and prednisone), as well as other agents such as idelalisib, fludarabine, bendamustine, as well as other chemotherapy combinations such as FC (fludarabine and cyclophosphamide), CVP (cyclophosphamide, vincristine, and prednisone), and C-MOPP (cyclophosphamide, vincristine, procarbazine, and prednisone).[4]

4 Benefit Assessment

Rituximab SC was developed to decrease the time patients must spend at the oncology clinic to receive treatment with rituximab; compared with intravenous infusions that typically range from 1.5 to 6 hours in clinical practice, the administration time with rituximab SC injections is approximately 5−7 minutes. The development program of rituximab SC was based on the premise that the anti-CD 20 monoclonal antibody in rituximab SC is the same as the one in rituximab IV. Therefore, the clinical development was based on PK-bridging; in other words, demonstrating non-inferior serum C_{trough} levels at the established doses and dosing intervals most commonly used for rituximab IV[5]. The development program for rituximab SC focused on investigating the effect of the change in the route of administration on the overall benefit/risk profile of rituximab for the treatment of B cell malignancies and was, therefore, not designed to re-establish the benefit/risk profile of rituximab in each approved indication. FDA verified that rituximab SC demonstrated equal or higher C_{trough} as compared to rituximab IV in patients studied for the oncology indications of FL, CLL, and DLBCL. Adding hyaluronidase increased absorption of rituximab and the fixed-dose strategy of rituximab SC led to C_{trough} considered reasonably consistent with body surface area-based dosing of rituximab IV.[6] [e]

In Pivotal study BO22334, a phase III two-stage, randomized study of rituximab SC 1400 mg vs rituximab IV 375 mg/m^2 in previously untreated NHL, induction followed by maintenance, patients with FL

[c] Section 505-1 (a) of the FD&C Act: FDAAA factor (B): *The seriousness of the disease or condition that is to be treated with the drug.*

[d] Section 505-1 (a) of the FD&C Act: *FDAAA factor (A): The estimated size of the population likely to use the drug involved.*

[e] Section 505-1 (a) of the FD&C Act*: FDAAA factor (C): The expected benefit of the drug with respect to such disease or condition.*

received a full dose of rituximab IV, followed by rituximab SC (1400 mg rituximab and 23,400 U hyaluronidase) given as a single agent weekly for up to 8 doses, in combination with chemotherapy for up to 8 doses, or following chemotherapy for up to 16 doses. A total of 410 patients were enrolled, 205 in the rituximab SC arm and 205 in the rituximab IV arm, 3 patients discontinued prior to beginning treatment, and a total of 407 patients received at least one dose of rituximab (204 IV and 203 SC). The primary endpoint of stage 1 was non-inferior rituximab C_{trough} of SC vs IV; the primary endpoint of stage 2 was overall response rate (ORR). Of the 410 patients included in the analysis of ORR, 347 (84.6%) achieved a complete (CR) or partial (PR) response at the end of induction treatment; 174 patients (84.9%) in the rituximab IV arm and 173 (84.4%) in the rituximab SC arm.

In Pivotal study MO28107, a phase III b randomized study investigating the efficacy of rituximab SC 1400 mg vs rituximab IV 375 mg/m^2, patients with DLBCL received a full dose of intravenous rituximab, followed by rituximab SC (1400 mg rituximab and 23,400 U hyaluronidase), given in combination with chemotherapy for up to 7 doses, or following chemotherapy for up to 20 doses. The primary endpoint was CR/CRu (complete response rate, complete response unconfirmed). There were 576 patients enrolled in the study and randomized in a 2:1 ratio; 381 patients were randomized to receive rituximab SC and 195 patients were randomized to receive rituximab IV, with a total of 572 patients treated with at least one dose of rituximab (SC=378 IV-194). At the end of the induction phase, the CR/Cru as assessed by the investigator was 42.1% in the rituximab IV arm vs 47% in the rituximab SC arm.

In supportive study BO25341, a phase Ib two-part randomized study (part 1 was dose finding of a single injection of rituximab SC at 1400/1600/1870 mg; part 2 was 2-6 cycles of 1600 mg), patients with CLL received a full dose of intravenous rituximab, followed by rituximab SC (1600 mg rituximab and 26,800 U hyaluronidase) in combination with fludarabine and cyclophosphamide.[7] The primary endpoint was non-inferior rituximab C_{trough} of rituximab SC vs IV. Rituximab SC 1600 mg demonstrated non-inferior exposure (C_{trough}) compared with the established rituximab IV BSA-adjusted dose (500 mg/m2) at the 4-weekly dosing interval established in CLL.[8]

Supportive study M028457 was a phase 3b, prospective, multi-center, multinational, open-label, randomized study in 743 adult patients with previously untreated DLBCL or FL. Patients were evaluated for their preference of treatment between rituximab IV and rituximab SC. The patient preference was evaluated by a Patient Preference Questionnaire (PPQ); at the end of treatment cycle 8, 80% of patients preferred rituximab SC as demonstrated by the PPQ.[9]

5 Risk Assessment & Safe-Use Conditions

Overall, there were no new safety signals observed with rituximab SC for FL and DLBCL or rituximab SC for CLL, and the safety profile of rituximab SC for subcutaneous injection was comparable to that of rituximab IV.[f]

[f] Section 505-1 (a) of the FD&C Act: *FDAAA factor (E): The seriousness of any known or potential adverse events that may be related to the drug and the background incidence of such events in the population likely to use the drug.*

In the clinical trials of rituximab SC in patients with FL and DLBCL, the most common adverse events (≥25%) observed were nausea, neutropenia and constipation; in the clinical trials in patients with CLL, the most common adverse events (≥25%) observed were infections, nausea, neutropenia, pyrexia, and injection site erythema.

5.1 Serious Adverse Reactions

Serious risks associated with Rituximab SC are severe mucocutaneous reactions, the risk of Hepatitis B HBV) reactivation, and the risk of Progressive Multifocal Leukoencephalopathy (PML); these risks will be communicated in a Boxed Warning in label. Rituximab IV has the same serious risks also communicated in a Boxed Warning in label.

6 Expected Postmarket Use

Rituximab SC will be given in the outpatient clinic setting by healthcare providers, typically medical oncologists, who should be familiar with the risks associated with rituximab IV and rituximab SC.

7 Risk Management Activities Proposed by the Applicant

The Applicant did not propose any risk management activities for rituximab SC beyond routine pharmacovigilance and labeling.

8 Discussion of Need for a REMS

When considering whether a REMS is necessary to ensure that the benefits outweigh the risks of a particular drug, DRISK considers factors such as the size of the patient population, the seriousness of the disease, the expected benefit of the drug, the seriousness of the known or potential adverse events, and the likely prescribers. DRISK and the Division of Hematology Products agree that a REMS is not necessary to ensure the benefits of rituximab SC outweigh its risks. Rituximab SC has a similar safety profile as that of rituximab IV and will have the same Boxed Warning s and Warnings and Precautions in its label. Healthcare providers who treat patients with CLL, DLBCL, and FL should be familiar with managing the risks associated with rituximab IV and regular visits to receive treatment with rituximab SC will allow monitoring for toxicities.

The Applicant proposes communicating the risks associated with rituximab SC through labeling with the same with Boxed Warnings concerning the risks of severe mucocutaneous reactions, Hepatitis B virus (HBV) reactivation, and Progressive Multifocal Leukoencephalopathy (PML), as well as the same Warnings and Precautions statements concerning the risks of administration-related reactions, Tumor Lysis Syndrome (TLS), infections, cardiac arrhythmias, renal toxicity, bowel obstruction and perforation, immunization with live vaccines, and the importance of laboratory monitoring.

To mitigate the risk of severe mucocutaneous reactions, the label recommends discontinuation of rituximab SC in patients who experience such a reaction.

To mitigate the risk of HBV reactivation, the label recommends monitoring patients for evidence of current or prior HBV infection for laboratory and clinical signs of HBV reactivation during and for several months following treatment with rituximab SC. In addition, the label recommends discontinuation of rituximab SC should a patient develop HBV reactivation.

To mitigate the risk of PML, the label recommends discontinuing rituximab SC in patients who develop PML. The label also recommends that the diagnosis of PML be considered in any patients who presents with new-onset neurologic manifestations. [10]

A Medication Guide will also be included as part of labeling, as does the label of rituximab IV.

9 Conclusion & Recommendations

Based on the clinical review, the benefit-risk profile is favorable therefore, with the efficacy and safety profiles for rituximab SC similar to that of rituximab IV, a REMS is not necessary for rituximab SC to ensure the benefits outweigh the risks. At the time of this review, evaluation of safety information and labeling was ongoing. Please notify DRISK if new safety information becomes available that changes the benefit-risk profile; this recommendation can be reevaluated.

10 Materials Reviewed

The following is a list of materials informing this review:

1. Genentech. Proposed Prescribing Information for Rituxan SC, February, 2017.
2. Genentech. Clinical Overview for Rituximab SC, August, 2016.
3. Genentech. Summary of Clinical Safety for Rituximab SC, August, 2016.
4. Schwarsin, Alexandria. Division of Hematology Products. Mid-cycle Clinical Review slides for Rituximab SC, BLA 761064, January 18, 2017.
5. FDA Briefing Document for BLA 761064. Oncologic Drugs Advisory Committee, dated March 6, 2017.

11 References

[1] Clinical Overview for BLA 761064. Genentech. Pg. 19

[2] Clinical Overview for BLA 761064. Genentech. Pg. 7

[3] Cancer Stat Facts: Non-Hodgkin Lymphoma, Surveillance, Epidemiology, and End Results (SEER) Program, NCI, accessed 2/9/17, https://seer.cancer.gov/statfacts/html/nhl.html .

[4] Adult Non-Hodgkin Lymphoma Treatment (PDQ®)–Health Professional Version, National Cancer Institute, accessed 2/14/17, https://www.cancer.gov/types/lymphoma/hp/adult-nhl-treatment-pdq#link/_338 .

[5] Summary of Clinical Efficacy. Genentech. Pp 26-60.

[6] FDA Briefing Document for Oncologic Drugs Advisory Committee, pg. 53.

[7] Draft Prescribing Information for BLA 761064. February, 2017.

[8] Clinical Overview for BLA 761064. Genentech. Pg. 40.

[9] FDA Briefing Document for Oncologic Drugs Advisory Committee, pg. 53.

[10] Draft Prescribing Information for BLA 761064. February, 2017.

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/s/

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