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APPLICATION NUMBER:

761064Orig1s000

SUMMARY REVIEW

Summary Review for Regulatory Action

Date	(electronic stamp)
From	Ann. T. Farrell, M.D., Division Director
Subject	Division Director Summary Review
NDA/BLA # **Supplement #**	761064
Applicant Name	Genentech Roche
Date of Submission	August 26, 2016
PDUFA Goal Date	June 26, 2017
Proprietary Name / Established (USAN) Name	Rituxan HYCELA
Dosage Forms / Strength	1400 mg rituximab/23,400 Units hyaluronidase per vial (120 mg/mL rituximab and 2000 U/mL hyaluronidase) 1600 mg rituximab/26,800 Units hyaluronidase per vial (120 mg/mL rituximab and 2000 U/mL hyaluronidase)
Proposed Indication(s) – same as Rituxan	Follicular Lymphoma (FL) • 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 Diffuse Large B-cell Lymphoma (DLBCL) • Previously untreated diffuse large B-cell lymphoma in combination with cyclophosphamide, doxorubicin, vincristine, prednisone (CHOP) or other anthracycline-based chemotherapy regimens Chronic Lymphocytic Leukemia (CLL) • Previously untreated and previously treated CLL in combination with fludarabine and cyclophosphamide (FC)
Action/Recommended Action for NME:	Approval

Material Reviewed/Consulted OND Action Package, including:	
Regulatory Project Health Manager	Laura Wall, RN

Associate Director for Labeling	Virginia Kwitkowski, RN, MS, ACNP-BC
Medical Officer Review	Alexandria Schwarsin, M.D./Vishal Bhatnagar, M.D.
Statistical Review	Chia-Wen Ko, Ph.D./Lei Nie, Ph.D./Raji Sridhara, Ph.D.
Pharmacology Toxicology Review	Natalie Simpson, Ph.D./Christopher Sheth, Ph.D./John Leighton, Ph.D.
OPQ Review	Marjorie Shapiro/Shen Luo/Thuy Nguyen/Candace Gomez-Broughton/Natalia Pripuzova/Jibril Abdus-Samad/Melinda Bauerlien/Serge Beaucage/Reyes Candau-Chacon/Peter Qiu/Marjorie Shapiro/Kathleen Clouse Strebel
Microbiology Review	See list above
Clinical Pharmacology Review	Olanrewaju Okusanya, PharmD, MS/Justin Earp, PhD/Bahru Habtemariam, PharmD/Nam Atiqur Rahman, PhD/Issam Zineh, PharmD, MPH
OPDP	L. Shenee Toombs/Elaine Cunningham/Olga Salis/ Michael Wade/Kathleen Davis
OSI	Anthony Orencia M.D., F.A.C.P./Janice Pohlman M.D., M.P.H./Kassa Ayalew, M.D., M.P.H.
CDTL Review	Angelo DeClaro, M.D.
Clinical Outcomes Assessment	Nikunj B. Patel, PharmD/Selena Daniels, PharmD, MS/Elektra J. Papadopoulos, MD, MPH
DMPP	LaShawn Griffiths, MSHS-PH, BSN, RN/Barbara Fuller, RN, MSN, CWOCN/Sharon R. Mills, BSN, RN, CCRP/L. Shenee' Toombs, Pharm. D.
OSE/DMEPA	Sue Kang/Todd Bridges, RPh./Neil Vora/Leeza Rahimi, Pharm.D./Hina Mehta, Pharm.D./Lubna Merchant, M.S, Pharm.D. Nicole Garrison, PharmD, BCPS/QuynhNhu Nguyen, MS
OSE/DRISK	Elizabeth Everhart, MSN, RN, ACNP/Doris Auth, PharmD/Cynthia LaCivita, PharmD
Labeling Review	Virginia Kwitkowski, MS, ACNP-BC
IRT	Dhananjay Marathe/Xiaofeng Wang/Janelle Chen/Qianyu Dang/Michael Y Li/Christine Garnett

OND=Office of New Drugs
DDMAC=Division of Drug Marketing, Advertising and Communication
OSE= Office of Surveillance and Epidemiology

Signatory Authority Review Template

1. Introduction

Genentech has submitted this application for RITUXAN HYCELA, a fixed combination product consisting of two active ingredients which is supplied as rituximab/hyaluronidase Injection at either 1400 mg rituximab and 23,400 units (U) hyaluronidase or 1600 mg rituximab and 26,800 U hyaluronidase. Rituxan HYCELA is intended to be used to deliver rituximab subcutaneously after the patient receives the first dose of rituximab intravenously.

Genentech's Rituxan (rituximab) has been approved and marketed for hematologic indications such as non-Hodgkins Lymphoma (NHL) and chronic lymphocytic leukemia (CLL) since 1997.

Hyaluronidase is a purified preparation of the enzyme recombinant human hyaluronidase. Hyaluronidase facilitates absorption and dispersion of subcutaneously injected drugs by cleaving glycosidic bonds of hyaluronic acid and other acid mucopolysaccharides of the connective tissue. Recombinant hyaluronidase as Hylenex has been approved as a tissue permeability modifier indicated 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.

RITUXAN HYCELA is considered a fixed combination with two active ingredients, rituximab as the API with activity against B cell malignancies, and rHuPH20, recombinant human hyaluronidase, to increase the dispersion and absorption of rituximab when administered subcutaneously.

This development strategy allows more convenient dosing of rituximab for patients.

The Applicant is seeking all hematologic indications which are in the Rituxan (rituximab) labeling and presents data supporting a new dose regimen.
The submitted data are from 4 trials: SABRINA in patients with follicular lymphoma (FL), MabEase in patients with diffuse large B cell lymphoma (DLBCL), SAWYER in patients with chronic lymphocytic leukemia (CLL) and PrefMab, a patient preference study in patients with FL and DLBCL. Objective response rates (ORR) were the primary efficacy endpoint in two main clinical studies: SABRINA and MabEase. Secondary endpoints included time-to-event endpoints of progression-free survival (PFS) and overall survival (OS). None of the studies had pre-specified hypotheses on the clinical efficacy, nor were multiple endpoints adjusted for multiplicity.

2. Background

See text above.

3. CMC/Device

The following text is taken from the CMC review:

The Office of Pharmaceutical Quality, CDER, recommends approval of STN 761064 for Rituxan HYCELA, manufactured by Genentech pending acceptable compliance checks. The data submitted in this application are adequate to support the conclusion that the manufacture of Rituxan HYCELA is well controlled and leads to a product that is pure and potent. We recommend that Rituxan HYCELA be approved for human use under the conditions specified in the package insert.

Fill size and dosage form
1400 mg rituximab/23,400 Units hyaluronidase per vial
1600 mg rituximab/26,800 Units hyaluronidase per vial

Dating period:
Drug product – 30 months; 2-8oC
Drug substance (rituximab) – (b) (4)
Drug substance (hyaluronidase - (b) (4)

Excipients
L-Histidine and L-Histidine hydrochloride monohydrate – (b) (4)
α,α Trehalose dihydrate – (b) (4)
L-Methionine – (b) (4)
Polysorbate 80 – 0.06% (w/v)

The amount of each excipient per vial is dependent whether it is a 1400 mg or 1600 mg vial.

The shelf life for drug product in both strengths is 30 months at 2-8oC.

All facilities are acceptable at this time.

4. Nonclinical Pharmacology/Toxicology

The following text is taken from the Pharmacology/Toxicology Team Leader review:

Pharmacology studies in Mantle Cell Lymphoma (MCL) xenograft mice and a monkey B-cell depletion model were submitted comparing IV and subcutaneous (SC) rituximab formulations. Despite exposure differences, there were no major differences

in pharmacodynamic (PD) effects of tumor growth inhibition or B-cell depletion in mice or monkeys, respectively. Also, several rHuPH20 pharmacology studies were submitted (which were previously reviewed under NDA 21859 (HYLENEX)), to emphasize the transient, locally acting effects of rHuPH20 in animals at concentrations (and doses) within the range proposed for humans, 2000 U/mL rHuPH20 (390 to 447 U/kg, assuming a 60 kg adult). In mice, 100 to 500 U/mL rHuPH20 (87 to 435 U/kg, assuming a 0.023 kg mouse), increased dye dispersion approximately 40-66% compared to controls within 5 minutes, which is a time frame relevant for SC injections. In mice, dispersion of dye following intradermal administration of 100 U/mL rHuPH20 (174 U/kg) was complete within 6 to 18 hours and up to 30,000 U/mL rHuPH20 (52,000 U/kg) did not act distally. The Applicant characterized the tissue protein and RNA expression of hyaluronidase in human adult and fetal tissues and mouse and rabbit tissues. It is primarily expressed in male reproductive organs (protein and mRNA), with some mRNA detection in the bone/cartilage, kidney, placenta, skeletal muscle, and synoviocytes in adult human samples and the gastrointestinal tract (colon, small intestine, and stomach), ovary, and pancreas in fetal human samples.

Dedicated safety pharmacology studies were not performed for rituximab SC; however, cardiovascular endpoints were included as part of the 8-week general toxicology study with rituximab SC described below.

The following pharmacokinetic (PK) studies with SC administration of rituximab were reviewed: an SC bioavailability study in female Göttingen Minipigs with rituximab (with 2000, 4000, or 6000 U rHuPH20 or 230, 460, and 690 U/kg rHuPH20, respectively); a comparative PK study between rituximab administered intravenously, or subcutaneously with 6000 U/mL rHuPH20 (30,000 U/kg), in severe combined immunodeficiency (SCID) beige mice; and, a PK/PD study with subcutaneously administered rituximab with 6000 U/mL rHuPH20 (1000 U/kg) in cynomolgus monkeys. The minipig study provides evidence to support that the addition of rHuPH20 to rituximab formulations administered subcutaneously improved the absorption rate of rituximab in minipigs (compared to a SC formulation without rHuPH20), reducing Tmax from 48 to 24 hours. There were no major differences in systemic exposure in minipigs administered 10 mg/kg rituximab intravenously or 14 mg/kg (120 mg/mL rituximab with 2000 U/mL rHuPH20) rituximab SC. However, maximum plasma levels following IV administration of 10 mg/kg rituximab could not be achieved with rituximab SC in minipigs (or in mice administered 30 mg/kg rituximab with 6000 U/mL rHuPH20 subcutaneously, compared to 30 mg/kg IV rituximab). The minipig study also demonstrated that the addition of more concentrated rHuPH20 to the formulation did not increase Cmax. However, in monkeys administered 20 mg/kg rituximab with 6000 U/mL rHuPH20 (1000 U/kg) subcutaneously, maximum plasma concentrations were achieved at 24 hours and they were comparable to levels observed in studies reviewed with the BLA for rituximab IV. Overall, the animal pharmacology and PK data supports that there is a need for rHuPH20 to improve the absorption rate of rituximab administered

subcutaneously, that rHuPH20 is locally acting, and rHuPH20 does not appear to affect the activity of rituximab.

Single dose toxicology studies were not performed for rituximab SC. A GLP-compliant 8-week repeat dose general toxicology, with a 13-week recovery phase, study with rituximab SC in cynomolgus monkeys was submitted. Monkeys were administered vehicle control (containing 2000 U/mL rHuPH20 (340 U/kg)) or 20 mg/kg rituximab SC (containing 120 mg/mL rituximab and 2000 U/mL rHuPH20 (340 U/kg)). Toxicities with SC administration are overall consistent with what is known historically with rituximab IV administration. Decreases in neutrophils, cardiac arrhythmias (increases in QRS complex R and S waves in recovery animals only), and liver toxicity (liver enzyme elevations, hepatomegaly, and marked multifocal hepatocellular necrosis) were observed in this study that were not observed in nonclinical studies submitted to support the rituximab IV BLA; but, neutropenia, cardiac arrhythmias, and liver toxicity have been observed in patients administered rituximab IV. There were some injection site findings that could be related to SC administration (inflammation, with only minimal necrosis in the draining axillary lymph nodes); however, they were not adverse. The 20 mg/kg rituximab SC dose resulted in exposure levels in monkeys that were comparable to those achieved at the highest doses in the corresponding nonclinical IV safety program.

No genetic toxicology or carcinogenicity studies were submitted or are required since rituximab SC is a biologic [ICH Guidance S6(R1)]. No new reproductive and developmental toxicology studies were reviewed since there were no changes to the reproductive and developmental toxicology data from the RITUXAN and HYLENEX labels except for updating of language and animal:human exposure margins for rHuPH20 in order to comply with the Pregnancy and Lactation Labeling Final Rule (PLLR) (see Table 19).

In a local tolerance study in male New Zealand White Rabbits, there were no adverse injection site findings related to rituximab SC treatment (120 mg/mL rituximab and 2000 U/mL rHuPH20 (~300 U/kg, assuming a 3 kg rabbit)), but there was edema and mixed cell infiltrates at a higher incidence/severity at the rituximab SC injection sites compared to controls.

Overall, the pharmacodynamic, pharmacokinetic and toxicity profile of SC administered rituximab is consistent with IV administered rituximab. Cardiac arrhythmias, liver toxicity, and decreases in neutrophils observed with rituximab SC that were not observed in toxicity studies submitted with the rituximab IV BLA have been observed as adverse events in patients treated with rituximab IV. Injection site reactions are clinically relevant, but based on the nonclinical data, are not expected to be adverse.

No issues arose during the review which precluded approval.

5. Clinical Pharmacology/Biopharmaceutics

No issues arose during the review which precluded approval. No post approval commitments are recommended.

From the primary clinical pharmacology review:

The Applicant used primarily a PK-bridging approach to establish the safety and effectiveness of a rituximab and hyaluronidase product intended for subcutaneous route of administration. A notable feature of the Applicant's approach was the targeting of a trough concentration (Ctrough) for the rituximab SC product that would be at least as high as that achieved with the rituximab IV product. Additional changes include the use of a fixed-dose regimen instead of BSA-based dosing, and the addition of hyaluronidase to facilitate absorption and administration. Note that hyaluronidase has been approved as an adjuvant and one of its indications is to increase the dispersion and absorption of other injected medicines…

The clinical development of rituximab SC was based on a comparative pharmacokinetic (PK) noninferiority paradigm in which the PK of rituximab SC was compared to the PK of rituximab IV in patients with follicular lymphoma (FL) and CLL. The objective of the comparative PK program was to select rituximab SC doses that achieve similar or higher rituximab plasma Ctrough compared to rituximab IV doses. The PK data showed that the proposed fixed rituximab SC doses of 1400 mg and 1600 mg achieved equal or higher rituximab Ctrough relative to the approved 375 and 500 mg/m2 rituximab IV doses for NHL and CLL, respectively. Exposure-safety analysis did not show a significant relationship between rituximab Ctrough and Grade 3+ adverse events, which is consistent with published data that showed rituximab IV tolerated up to a dose of 2250 mg/m2 (PMID 11226005). This exposure-safety evaluation provided sufficient evidence to conclude that the higher average rituximab plasma concentrations with the SC formulation would not result in higher rates of systemic adverse events compared to what would be expected with IV administration. No significant difference in immunogenicity rates was observed between the two formulations…

We conclude that the data from the studies support the applicant's claim. Although the clinical trials were not designed for efficacy hypothesis testing, the data tend to show that the rituximab SC and Rituximab IV arms are comparable and efficacy results are similar across studies.

I concur.

6. Clinical Microbiology

Not applicable

7. Clinical/Statistical-Efficacy

This application was based on a PK bridging study and several randomized trials with descriptive statistics for efficacy (response rate) and safety.

From the CDTL review:
Efficacy and safety of Rituxan Hycela was established for the above recommended indications based on the results from multiple randomized clinical trials, including SABRINA, MabEase, and SAWYER, which demonstrated: (a) non-inferior rituximab trough concentrations (Ctrough) levels for Rituxan Hycela 1,400 mg/23,400 Units compared to a rituximab product 375 mg/m2 administered intravenously, (b) non-inferior rituximab Ctrough levels for Rituxan Hycela 1,600 mg/26,800 Units compared to a rituximab product 500 mg/m2 administered intravenously, and
(c) comparable efficacy and safety results. Postmarketing ex-US experience with Rituximab (MabThera) for SC injection provides for supportive evidence of safety.

The Applicant submitted the results of a patient preference study which showed that patients preferred the rituximab and hyaluronidase SC administration compared with the rituximab IV administration.

I concur with the conclusions of the clinical and statistical review teams regarding the demonstrations of efficacy for the hematologic indications.

8. Safety

There were no new safety issues identified during the review. There were minor differences in injection site reactions, neutropenia and infections.

I concur with the conclusions of the clinical and statistical review teams.

9. Advisory Committee Meeting

This product was discussed at an Oncologic Drugs Committee meeting on March 29, 2017. FDA requested discussion at the Oncologic Drugs Advisory Committee (ODAC) to obtain feedback and insights on the acceptability of the development approach to support the approval of Rituxan Hycela for the same hematologic indications (extrapolation) as intravenous rituximab (Rituxan).

The ODAC meeting voted on the following question:
Is the benefit-risk favorable for the above drug product for the proposed indications in follicular lymphoma (FL), diffuse large B cell lymphoma (DLBCL), and chronic lymphocytic leukemia (CLL).

YES: 11 NO: 0 ABSTAIN: 0

The committee unanimously voted in favor of the benefit-risk for biologics license application (BLA) 761064, rituximab and hyaluronidase human injection for

subcutaneous use for the proposed indications in follicular lymphoma (FL), diffuse large B-cell lymphoma (DLBCL), and chronic lymphocytic leukemia (CLL).

10. Pediatrics

From the CDTL review:

FDA granted Orphan Drug Designation for rituximab and hyaluronidase for the following indications (designation date): follicular lymphoma (22 August 2016), diffuse large B cell lymphoma (7 September 2016), and chronic lymphocytic leukemia (22 August 2016).

11. Other Relevant Regulatory Issues

No applicant integrity issues exist.

Financial Disclosure was provided and reviewed.

Office of Surveillance and Epidemiology was consulted including DMEPA who provided labeling input.

Division of Scientific Investigation (DSI) noted that the study data derived from these clinical sites are considered reliable in support of the requested indication.

There are no other unresolved relevant regulatory issues.

12. Labeling

The labeling was reviewed by all disciplines and consultant staff and revisions made to Applicant's proposed labeling.

13. Decision/Action/Risk Benefit Assessment

- Recommended regulatory action

Regular Approval for the oncologic indications

- Risk Benefit Assessment

The Applicant's strategy of combining fixed doses of rituximab with fixed doses of human hyaluronidase and then selecting rituximab and hyaluronidase doses for subcutaneous (SC) injection that achieve similar or higher rituximab plasma C_{trough} compared to rituximab given intravenously (IV) was successful. Rituxan is one of the most widely used products for the treatment of non-Hodgkins lymphoma and chronic lymphocytic leukemia. This strategy allows more convenient dosing for patients. The efficacy results demonstrated that the fixed

combination of rituximab and hyaluronidase given SC and rituximab IV are comparable. In addition, there were no major differences in safety findings between rituximab SC and rituximab IV, with the exception of a slight increase in administration site-related local reactions with rituximab SC.

- Recommendation for Post marketing Risk Management Activities

Routine post-marketing surveillance

- Recommendation for other Post marketing Study Requirements (PMR)/ Commitments (PMC) -None

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/s/

ANN T FARRELL
06/19/2017