

Summary Basis for Regulatory Action

Date: April 21, 2017

From: Winson Tang, MD FACP

BLA/ STN#: STN 103869/5365

Applicant Name: Genzyme Corporation

Date of Original Submission: December 23, 2015
Class 1 Re-Submission: February 21, 2017

PDUFA Goal Date, Resubmission: April 21, 2017

Proprietary Name/ Established Name: Thymoglobulin/Anti-thymocyte globulin (Rabbit)

Reason for Submission: Addition of the indication of prophylaxis of acute rejection in patients receiving a kidney transplant

Indication: THYMOGLOBULIN is an immunoglobulin G indicated for the prophylaxis and treatment of acute rejection in patients receiving a kidney transplant. Use in conjunction with concomitant immunosuppression.

Recommended Action: Approval

Signatory Authorities Action: Approval

Offices Signatory Authority: Tejashri Purohit-Sheth, M.D.

I concur with the summary review.
 I concur with the summary review and include a separate review to add further analysis.
 I do not concur with the summary review and include a separate review.

Material Reviewed/ Consulted	Specific documentation used in developing the SBRA
Reviewer Name – Document(s)	Date
Clinical Review	Winson Tang, MD FACP review - April 5, 2017
Clinical Consultation (DTOP)	Marc Cavaille-Coll, MD PhD review – October 20, 2016
Clinical Review	Charles Maplethorpe, MD PhD review – October 19, 2016
Clinical Pharmacology Review	N/A
Statistical Review	N/A
CMC Review	N/A
Pharmacology/ Toxicology Review	N/A
Bioresearch Monitoring Review	N/A
Establishment Inspection Report	N/A
Advisory Committee Transcript	N/A
Epidemiology	N/A

1. Introduction

Genzyme submitted an Efficacy Supplement to BLA 103869 on Dec 23, 2015 to expand the indication of Thymoglobulin for use in prophylaxis of kidney transplant allograft rejection in patients at high risk of rejection. The FDA issued a Complete Response Letter on October 20, 2016 to the Applicant, in which FDA communicated to Genzyme that there were no deficiencies identified other than the labeling changes necessary to comply with the Physician Labeling Rule (PLR). Therefore, Genzyme sent a Class 1 submission in response to the Complete Response Letter, with a PLR-formatted label that included the new prophylaxis indication.

2. Background:

Thymoglobulin was approved for the treatment of acute rejection in renal transplantation in conjunction with concomitant immunosuppression by the Food and Drug Administration in December 1998. Genzyme submitted a supplemental BLA (sBLA) to expand the use of Thymoglobulin for prophylaxis of acute rejection following kidney transplantation. The safety and efficacy of THYMOGLOBULIN for the prophylaxis of acute rejection in patients receiving a kidney transplant were evaluated in 2 randomized, open-label, active comparator, international, multicenter trials in patients receiving solitary kidney transplants.

1. SMC-101-1010 (a.k.a study 1010) was an open label, 1:1 randomized, active-controlled, 2-arm parallel group, 12-month, multi-center and multi-country, phase 2 IND study. The study was conducted in the USA, France, Spain, Germany, and UK, and compared Thymoglobulin vs. Simulect (anti-IL-2R monoclonal antibody) induction in 278 high risk kidney transplant recipients. Subjects also received cyclosporine A, mycophenolate and corticosteroids.
2. TAXI-2009 was a non-IND, randomized (1:1), open-label, multi-center study comparing Thymoglobulin vs. Zenapax (anti-IL-2R monoclonal antibody) induction in 230 high risk kidney transplant recipients undergoing repeat transplantation. Subjects also received tacrolimus, mycophenolate and corticosteroids. This study was conducted in France and Belgium.

3. Chemistry Manufacturing and Controls (CMC): No new information

4. Nonclinical Pharmacology/Toxicology: No new information

5. Clinical Pharmacology: No new information

6. Clinical/Statistical:

The sBLA approval is recommended based upon the following data obtained from two non-inferiority studies designed to assess the safety and effectiveness of the prophylactic use of Thymoglobulin for acute rejection following renal transplantation:

1. SMC-101-1010: the treatment failure rate within 12 months post-transplantation in Thymoglobulin group was 24.8% compared with 38.0% in the Simulect group, with an estimated treatment group difference (Thymoglobulin - Simulect) of -13.1% (95% CI: -23.9% to -2.3%). The p-value was 0.0202 based on a 2-sided Fisher's exact test.
2. TAXI-2009, the treatment failure rate in Thymoglobulin group was 25.4% compared with 33.6% in the Zenapax group, with an estimated treatment group difference (Thymoglobulin- Zenapax) of -8.2% (95% CI: -19.9% to 3.6%).

In the pooled analysis, the treatment failure rate in Thymoglobulin group was 25.1% compared with 36% in the control group, the estimated between-treatment group difference

(Thymoglobulin - Control) was -10.9% (95% CI: -18.8% to -2.9%). Therefore, the pre-specified non-inferiority margin of 10% was satisfied.

7. Safety:

Primary safety data to support the prophylaxis indication were gathered from the two randomized, open-label, active comparator controlled studies discussed above.

1. SMC-101-1010: There were 3 subjects (2201002, 2201006, and 2204003) with lymphomas in the Thymoglobulin arm, and none in the Simulect arm.
2. TAXI-2009: There were 5 subjects (731288, 831998, 861254, 901342, and 941154) in the Thymoglobulin arm reported to have experienced serum sickness, and none in the Zenapax arm. Another Thymoglobulin subject (661138) developed a donor-originated metastatic melanoma, leading to death.

Overall, the safety profile of thymoglobulin was supported by the studies and no new safety signals were identified.

8. Advisory Committee Meeting:

There were no issues pertaining to this supplement that required input from an Advisory Committee.

9. Other Relevant Regulatory Issues:

Compliance of the Package Insert with the Physician Labeling Rule

10. Labeling

The existing label was revised to include the following:

1. The indication for THYMOGLOBULIN was expanded to add prophylaxis of acute rejection in patients receiving a kidney transplant.
2. New dosing information for the prophylaxis of acute rejection.
3. Addition of a summary of the new clinical studies that supports the prophylaxis indication to Section 14.1.
4. Addition of a summary of Adverse Reactions noted in the studies supporting the prophylaxis indication to Section 6.1.
5. Revision of the previous label to
 - a. Conform to the new labeling guidelines (PLR)
 - b. Grammatical changes to improve clarity
 - c. Change the name of the reference agent to “Active Comparator” in Tables 1-9
 - d. Rounding of percentages to the nearest integer
 - e. Addition of layperson terms to MEDRA terms such as tachycardia (fast heart rate) to the Adverse Reaction Tables and within the text.

The package insert (PI) was reviewed by the review committee, including the reviewer from the Advertising and Promotional Labeling Branch. All issues were acceptably resolved after exchange of information and discussions with the Applicant.

11. Recommendations and Risk/ Benefit Assessment:

a. Recommended Regulatory Action

The Committee recommends approval of the Applicant’s BLA supplement, which includes data supporting a labeling change to add prophylaxis of acute rejection in patients receiving a kidney transplant as an additional indication.

b. Risk/Benefit Assessment

Data submitted supported that the product has a favorable benefit / risk profile for the additional use of Thymoglobulin as prophylaxis against acute rejection of kidney allografts.

c. Recommendation for Postmarketing Activities

None required for this efficacy supplement.