Review Memo, November 10, 2011 - Hemacord

MEMORANDUM

Wilson W. Bryan, MD
Director
FDA/CBER/OCTGT/DCEPT

BLA#125397/1	
Submission date	January 1, 2011
Review date	November 10, 2011

Product Reviewers	Mercy Quagraine, PhD; Steven Bauer, PhD Joydeep Ghosh, PhD; Bharat Joshi, PhD Safa Karandish, BS, MT; Brenton McCright, PhD
Nonclinical Reviewer	ATM Shamsul Hoque, PhD
Clinical Reviewers	John Hyde, PhD, MD Maura O'Leary, MD Donna Przepiorka, MD, PhD
Clinical Team Leaders	Peter Bross, MD Bindu George, MD
Biostatistician	Renee Rees, PhD
Office Director	Celia M. Witten, PhD, MD
Pharmacovigilance	Damon Green, MD Craig Zinderman, MD
DMPQ Review	Mohammad Heidaran, PhD Gang Wang, PhD
Advertising and Promotional Labeling Review	Loan Nguyen, PharmD Lisa Stockbridge, PhD
RPM	Terrolyn Thomas, MS, MBA

Sponsor	New York Blood Center
Product	Hematopoietic Progenitor Cells-Cord Blood (Hemacord)
Proposed Use	Use in unrelated donor hematopoietic progenitor cell transplantation procedures in conjunction with an appropriate preparative regimen for hematopoietic and immunologic reconstitution in patients with disorders affecting the hematopoietic system that are inherited, acquired, or result from myeloablative treatment
Recommendation	Approval

New York Blood Center (NYBC) has submitted biologics license application (BLA) 125397 for hematopoietic progenitor cells-cord blood (Hemacord) for hematopoietic and immunologic reconstitution in patients with disorders affecting the hematopoietic system that are inherited, acquired, or result from myeloablative treatment.

The regulatory history of hematopoietic progenitor cells-cord blood (HPC-C; umbilical cord blood) is well documented in the reviews of this BLA. This is the first BLA for marketing approval of an HPC-C.

In the original BLA submission, NYBC proposed the following indication statement: Hemacord is intended for use for allogeneic HPC transplantation for the treatment of patients with hematologic malignancies, Hurler Syndrome (MPS I), Krabbe Disease (Globoid Leukodystrophy), X-linked Adrenoleukodystrophy, primary immunodeficiency diseases, bone marrow failure, and beta thalassemia. The clinical review of the BLA focused on these seven specific proposed indications.

Sources of data for the clinical review included published literature, the docket (i.e., Docket FDA-1997-N-0100 (Legacy Docket number 97N-0010) and Docket FDA-2006-D-0157 (Legacy Docket number 06D-0514)), and the COBLT study. The data from these sources were based on HPC-C manufactured by various blood banks. In addition, the applicant provided data from experience with their product.

Following consideration of recommendations from an FDA Advisory Committee, NYBC replaced the original proposed indication statement with the following:

Hemacord is an allogeneic cord blood hematopoietic progenitor cell therapy indicated for use in unrelated donor hematopoietic progenitor cell transplantation procedures in conjunction with an appropriate preparative regimen for hematopoietic and immunologic reconstitution in patients with disorders affecting the hematopoietic system that are inherited, acquired, or result from myeloablative treatment.

The risk benefit assessment for an individual patient depends on the patient characteristics, including disease, stage, risk factors, and specific manifestations of the

disease, on characteristics of the graft, and on other available treatments or types of hematopoietic progenitor cells.

The purpose of this memo is primarily to discuss the evidence of effectiveness of Hemacord for the proposed indication, and secondarily to address other selected BLA review issues.

Effectiveness

Survival is more clinically meaningful than other efficacy or safety outcome measures. The clinical reviews conducted to support this BLA document that HPC-C has the ability to improve survival, but that HPC-C is also associated with an early mortality rate of 25%. Whether the overall effect on survival is favorable or unfavorable depends on the specific disorder and specific clinical situation.

In specific disorders and situations where short-term survival is consistently poor (e.g., hematologic malignancies and severe combined immunodeficiencies), the clinical reviews by Drs. O'Leary, Hyde, and Przepiorka describe compelling evidence that HPC-C provides an overall benefit in survival. In contrast, Dr. Hyde's review of the docket data and published literature illustrates the potential for HPC-C to increase short-term mortality in disorders where the short-term survival is variable (e.g., Hurler syndrome) or high (e.g., in beta thalassemia). Since Hemacord has the potential to either markedly improve or markedly worsen survival in different clinical situations, a decision on marketing approval should be based on reliable evidence of the overall effect of Hemacord on survival in specific clinical situations.

All of the clinical reviews discuss problems with the quality of the available datasets. Dr. Hyde's review notes problems with data integrity in the docket dataset. Dr. Przepiorka's reviews note that most of the statistical analyses of efficacy data are exploratory, so that the meaningfulness of the p-values presented is unclear. Many of the statistical analyses presented in the clinical reviews include comparisons of HPC-C results to historical controls, but without sufficient data to assess whether the two groups being compared are well-matched for prognostic factors. All of the clinical reviews considered published literature; however, FDA did not have access to the relevant raw data and therefore could not confirm the statistical analyses presented in these publications. The BLA review did not include site inspection to verify the validity of the data in the docket or in the COBLT dataset. Because of the numerous weaknesses in these datasets, the BLA does not provide reliable evidence of the overall effect of Hemacord on survival in most clinical situations.

The FDA requires substantial evidence of effectiveness to support approval of a BLA. The evidence of effectiveness of Hemacord for improving survival in hematological malignancies and SCID meets this standard. Due to the poor quality of the data and the variability in the natural history of the disorders, there is not substantial evidence of effectiveness of Hemacord for improving survival in the other originally specified indications (i.e., Hurler syndrome, Krabbe disease, X-linked adrenoleukodystrophy,

primary immunodeficiencies, bone marrow failure, and beta thalassemia). In the absence of reliable data on the effect of Hemacord on survival, reliance on outcome measures other than survival entails a risk of marketing approval when the product may have a negative effect on survival and an unacceptable overall risk-benefit profile.

In accordance with the revised indication statement, the safe and effective post-marketing administration of Hemacord will depend on careful patient selection.

Manufacturers of HPC-C products should be encouraged to conduct additional well-designed, prospective studies of the effect of HPC-C on survival in specific indications.

Other BLA review issues

Pediatrics

The clinical and statistical joint review for the BLA describes requests for partial waivers of the PREA requirements for Hemacord for specific indications. That review also notes that the data were sufficient to assess engraftment across all pediatric age groups. Therefore, the subsequent change in the proposed indication from specific disorders to hematopoietic and immunologic reconstitution resulted in a change in the pediatric assessment. A revised pediatric assessment was submitted to the FDA Pediatric Review Committee (PeRC) on October 26, 2011. The PeRC agreed with the review team assessment that the application included sufficient data to fulfill PREA (Pediatric Research Equity Act) requirements for all pediatric age groups.

Boxed Warning

HPC-C is associated with Day-100 mortality of 25%. Causes of Day-100 mortality include graft failure, graft versus host disease (GVHD), engraftment syndrome, and infusion reactions. The nature and frequency of these events warrant the boxed warning to advise healthcare professionals of the risks associated with Hemacord administration.

Donor Cell Leukemia and Transmission of Serious Infection

The clinical safety review documents reports of nine cases of donor cell leukemia and one report of transmission of serious infection. In the absence of systematic collection and reporting of adverse events in a defined group of patients who underwent HPC-C transplantation, the currently available reports are not sufficient to support reliable estimates of the incidences of these adverse events.

Dextran 40

The clinical and CMC review teams agreed that Dextran 40 in the final product may be the cause of some infusion reactions associated with HPC-C. The clinical / statistical joint review recommends a post-marketing commitment for NYBC to conduct an in vitro

study to determine the lowest concentration of Dextran 40 that can be used without impairing the product function. The CMC review favored a broader initiative for a collaborative study by multiple stakeholders to provide data relevant to all potential BLAs for HPC-C. Both approaches are reasonable and each has advantages. However, since the Dextran 40 issue is a problem that faces multiple HPC-C manufacturers, the best solution would be a collaborative study, rather than a post-marketing commitment that places the responsibility on a single manufacturer.

DMSO Overdosage

HPC-C has been associated with infusion reactions, including allergic reactions. Some of these reactions may be caused by dimethyl sulfoxide (DMSO) in the final HPC-C product. The applicant and the FDA review team have agreed on labeling that is informative with regard to the risks of DMSO, including the risk of DMSO overdosage. With regard to the management of DMSO overdosage, the references provided for the clinical safety review include one case report of a patient with DMSO overdosage who was treated with dialysis, and one case report of a patient with DMSO overdosage who was treated with plasmapheresis. These single case reports do not contain sufficient information to determine the role of either dialysis or plasmapheresis in the treatment of DMSO overdosage.

Recommendation:

1. Approval of Hemacord for the treatment of hematological malignancies and severe combined immunodeficiency (SCID).
2. Manufacturers of HPC-C products should be encouraged to conduct additional well-designed, prospective studies of the effect of HPC-C on survival in specific indications.