FDA Executive Summary

Prepared for the
Fall 2022 review by the
FDA's Pediatric Advisory Committee

H130004
Pleximmune™

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I. INTRODUCTION

In accordance with the Pediatric Medical Device Safety and Improvement Act this review provides a safety update based on the postmarket experience with the use of Pleximmune™, a prognostic test for liver and small bowel transplant rejection in pediatric patients.

Pleximmune™ is an *in vitro* diagnostic test that measures the risk of acute cellular rejection (ACR) of transplanted liver and/or small bowel (small intestine) organs in children who are less than 21 years of age. Pleximmune™ measures recipient inflammatory immune response toward the donor organ in children with liver or small bowel transplantation. The test system includes an *in vitro* lymphocyte co-culture to elicit the inflammatory response of the recipient to the donor. This inflammatory response to the donor is measured as a rejection-risk signal by quantitatively measuring CD154 positive T-cytotoxic memory cells from the recipient using flow cytometry.

The purpose of this review is to provide the Pediatric Advisory Committee with postmarket safety data, so the committee can advise the Food and Drug Administration (FDA) on potential safety concerns associated with the use of this device in children. This executive summary will include summaries of the premarket clinical study, postmarket follow-up of the clinical study, the peer-reviewed literature associated with the device, and postmarket medical device reporting (MDR) for adverse events.

II. INDICATIONS FOR USE

The Pleximmune™ is intended to be performed at a single laboratory to measure the CD154 expression on T-cytotoxic memory cells (TcM) in patient's peripheral blood lymphocytes (PBL) isolated from heparinized whole blood (anticoagulant – sodium heparin). The Pleximmune™ is a qualitative prognostic test intended to be used in patients less than 21 years old with liver or small bowel transplantation. The Pleximmune™ test is an aid in the evaluation of the risk of acute cellular rejection (ACR) and must be used in conjunction with biopsy, standard clinical assessment and other laboratory information.

The Pleximmune™ test is intended for use at the following time periods:

- Pre-transplantation period: For blood samples collected before transplantation, the test predicts the risk of transplant rejection within 60 days after transplantation.
- Early and late post-transplantation period: For blood samples collected within 60 days (early) after transplantation and for blood samples collected at 200 or more days (late) after transplantation, the test predicts the risk of transplant rejection within 60 days after sampling.

III. BRIEF DEVICE DESCRIPTION

Pleximmune™ is an adjunctive blood test which is intended as an aid in the evaluation of the risk of ACR of a transplant by measuring recipient inflammatory immune response towards the donor organ in children with liver or small bowel transplantation. The Pleximmune™ test system uses *in vitro* lymphocyte co-culture to elicit the inflammatory response of the recipient to the donor. This inflammatory response to the donor is measured as a rejection-risk signal by quantitatively measuring the T-cytotoxic memory cells (TcM) from the recipient, which express the inflammatory marker, CD154 ($CD154_+$TcM), using flow cytometry.

To determine if the donor specific inflammatory response is increased or decreased, a reference inflammatory response of the recipient toward "third-party" peripheral blood lymphocytes (PBL) is performed in parallel (see design details below, describing the four cell culture reactions in the Pleximmune™ test). Third-party PBL obtained from normal human subjects are dissimilar to the recipient and donor at the Human Leukocyte Antigen (HLA) loci. To determine similarity and dissimilarity, the HLA-A, -B, and -DR loci are compared between recipient and donors. This information is generated at the time of transplantation as a component of routine care. Additionally, because donor cells are not easily obtained from cadaveric donors, which are the major sources of liver and small bowel transplants in children, cells from normal human subjects which are antigenically similar to the donor are used. These cells are termed "surrogate donor" cells.

To characterize rejection-risk in the individual recipient, the recipient's inflammatory response to donor cells is expressed as a fraction of his/her inflammatory response to the third-party cells. This fraction or ratio is termed the immunoreactivity index (IR). If the donor-induced response exceeds the response to third-party cells, the individual may be at increased risk for rejection. If the response to third-party cells exceeds the donor-induced response, the individual may be at decreased risk. This use of the response to third party mismatched PBL as a reference response is intended to make test results specific for the transplant recipient and comparable between recipients. Thus, the IR value of the recipient PBL sampled prior and after the small bowel and/or liver transplantation correlates with the risk of acute cellular rejection of the transplant. The IR is intended to be used by physicians as a tool, in conjunction with all other clinical and laboratory data and biopsy, to predict the transplant patient's rejection risk level.

Pleximmune™ Design - The Pleximmune™ test system uses four cell culture reactions as follows:

1. Negative Control - The recipient PBL are cultured alone in culture medium which does not contain fluorochrome-labeled antibody to the inflammatory response marker, CD154. This group of cells serves as the negative control for the Flow Cytometry measurement.
2. Background - The recipient PBL are cultured alone in culture medium which contains fluorochrome-labeled antibody to the inflammatory response marker, CD154. This group of cells serves as the background for $CD154_{+}$TcM present in the unstimulated recipient blood at the time of testing.
3. Donor Reaction - The recipient PBL are cultured with donor or surrogate donor PBL in culture medium which contains fluorochrome-labeled antibody to the inflammatory response marker, CD154. This group of cells represents the immune reaction of the recipient to the donor.
4. Third-party Reaction - The recipient PBL are cultured with mismatched PBL in culture medium which contains fluorochrome-labeled antibody to the inflammatory response marker, CD154. This group of cells represents the immune reaction of the recipient to mismatched PBL. As stated above, this reaction is used as a reference reaction, in ratio to the donor reaction, when calculating the IR of the recipient.

Method of Operation - Transplant patient blood or blood from normal human subjects is collected and PBL are isolated. Based on the HLA loci information of the patient, surrogate donor PBL and third party PBL are selected. These PBL are used in the four cell culture reactions (as described above) and incubated to elicit the immune reaction in the responder cells. The number of CD154+TcM is acquired by flow cytometry. These results are analyzed to calculate the IR, which is used to assign the risk of rejection for the transplant patient sample.

The fluorochrome labeled antibodies used in the Pleximmune™ test to identify subsets of T lymphocytes in the recipient, donor and third party PBL are:

- Anti-CD3-FITC, for labeling CD3 expressing T lymphocytes
- Anti-CD8-APC-H7, for labeling recipient CD8 expressing cytotoxic T cells
- Anti-CD8-PE-Cy7, for labeling donor/surrogate donor/third party CD8 expressing cytotoxic T cells
- Anti-CD45-RO-APC, for labeling TcM
- Anti-CD154-PE, for labeling CD154 expressing TcM
- Viability dye 7-aminoactinomycin-D (7-AAD), stains dead cells

Interpretation of Pleximmune™ Results:
The number of $CD154_+$TcM per TcM in the donor and third-party reactions are each compared with those present in the background reaction using the statistical Poisson test, (the Poisson test is recognized for a comparison of proportions between two samples). For the Pleximmune™ results to be valid for generating an IR and assigning a rejection risk category (i.e., decreased or increased risk of rejection), at least one reaction must pass the Poisson test ($p < 0.05$). If both reactions fail the Poisson test, the Pleximmune™ test is considered invalid, and the IR is not reported. The IR is calculated by dividing the frequency of $CD154_+$TcM induced in the donor reaction by those induced in the third-party reaction. For post- transplant blood samples, an IR ≥ 1.1 indicates increased risk of transplant rejection, and an IR < 1.1 indicates decreased risk of transplant rejection. For pretransplant samples, an IR ≥ 1.23 indicates increased risk of transplant rejection, and an IR < 1.23 indicates decreased risk of transplant rejection.

IV. REGULATORY HISTORY

On June 12, 2009, Pleximmune™ received designation as a Humanitarian Use Device (HUD). On August 26, 2014, the Humanitarian Device Exemption (HDE) application was approved by the Center for Devices and Radiological Health of the Food and Drug Administration.

V. PREMARKET DATA: CLINICAL INVESTIGATION

Summary of Clinical Studies:
A clinical study with a total of 122 specimens from 87 individual pediatric transplant patients was performed to determine the safety and probable benefit of the Pleximmune™ test for predicting rejection in the intended use population. Using the post-transplant rejection-risk cutoff threshold of 1.10, the sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) were 84%, 80%, 64% and 92%, respectively. Using the pre-transplant rejection-risk cutoff threshold of 1.23, the sensitivity, specificity, PPV and NPV were 57%, 89%, 80%, 74%, respectively. For pre-transplant samples, the test correctly predicted the risk of ACR 80% of the time and the risk of no ACR 74% of the time. For post-transplant samples, the test correctly predicted the risk of ACR 64% of the time and the risk of no ACR 92% of the time.

Summary of Safety and Probable Benefit:
The Pleximmune™ test is a prognostic tool which may provide additional information to the clinician about the patient's immunologic risk level and could be valuable in the management of transplant patients. As per the device label, the transplant physicians who are already familiar with the care of transplant recipients will not be likely to solely rely on the Pleximmune™ test results for clinical decision making but will use it as an adjunctive tool and primarily rely on other diagnostic tools such as biopsy, liver function tests and other laboratory or clinical data in addition to the assay results for managing transplant patients.

VI. POSTMARKET DATA: ANNUAL DISTRIBUTION NUMBER

Section 520(m)(6)(A)(ii) of the Food, Drug, and Cosmetic Act (FD&C Act) allows HDEs indicated for pediatric use to be sold for profit as long as the number of devices distributed in any calendar year does not exceed the annual distribution number (ADN). On December 13, 2016, the 21st Century Cures Act (Pub. L. No. 114-255) updated the definition of ADN to be the number of devices "reasonably needed to treat, diagnose, or cure a population of 8,000 individuals in the United States." Based on this definition, FDA calculates the ADN to be 8,000 multiplied by the number of devices reasonably necessary to treat an individual. However, it is to be noted that unless the sponsor requests to update their ADN based on the 21st Century Cures Act, the ADN will still be based on the previously approved ADN of 4,000. The approved ADN for Pleximmune™ is 4000 total tests per year.

For the reporting period of June 1, 2021 until May 25, 2022, Plexision, Inc. performed a total of 625 Pleximmune™ tests on a total of 402 patients at Plexision's CLIA-approved laboratory. All specimens were post-transplant samples. No pre-transplant specimens were tested. Among the 402 patients, there were 218 males and 184 females. The average age of these patients was 10.37 years with a range from 0.56 to 20.98 years. The major organs transplanted were liver or intestine. The type of organ transplanted in these 402 patients was: liver (273), combined liver-kidney (5), combined liver-intestine (64), intestine alone (40), liver-intestine-other (10) and liver-other (10). The ethnicity of these patients is not available.

VII. SYSTEMATIC LITERATURE REVIEW OF THE SAFETY OF THE Pleximmune™ TEST IN THE PEDIATRIC POPULATION

Purpose

In preparation for the FDA PAC 2022 fall meeting, a literature review was conducted to address the following question: what adverse events are reported in the literature associated with the use of the Pleximmune™ test, for any indication in the pediatric population (≤21 years old)?

Methods

A search on the internet was performed using the Web of Science Core Collection, Embase, PubMed, UpToDate and EBSCOhost database sites for "Pleximmune".

Results

A search on the internet for "Pleximmune" using the Web of Science Core Collection, Embase, PubMed, UpToDate and EBSCOhost database sites did not reveal any articles with safety data (including adverse events) associated with the use of the Pleximmune™ test.

Discussion

A literature search yielded no articles with safety data for the Pleximmune™ test over the period from June 1, 2021 to May 25, 2022. The sponsor was also asked to provide any information

describing adverse events associated the use of the Pleximmune test from the literature and they indicated that they were not aware of any such reports.

Conclusion

The literature search raised no new safety concerns.

VIII. MEDICAL DEVICE REPORTS (MDRs)

Overview of Manufacturer and User Facility Device Experience Database (MAUDE / PRIMO)

Each year, the FDA receives several hundred thousand MDRs of suspected device-associated deaths, serious injuries and malfunctions. The MAUDE / PRIMO database houses MDRs submitted to the FDA by mandatory reporters (manufacturers, importers, and device user facilities) and voluntary reporters such as health care professionals, patients and consumers. The FDA uses MDRs to monitor device performance, detect potential device-related safety issues, and contribute to benefit-risk assessments of these products. MDR reports can be used effectively to:

- Establish a qualitative snapshot of adverse events for a specific device or device type
- Detect actual or potential device problems used in a "real world" setting/ environment, including:
    - rare, serious, or unexpected adverse events
    - adverse events that occur during long-term device use
    - adverse events associated with vulnerable populations
    - off-label use
    - use error

Although MDRs are a valuable source of information, this passive surveillance system has limitations, including the potential submission of incomplete, inaccurate, untimely, unverified, or biased data. In addition, the incidence or prevalence of an event cannot be determined from this reporting system alone due to potential under-reporting of events and lack of information about frequency of device use. Because of this, MDRs comprise only one of the FDA's several important postmarket surveillance data sources. Other limitations of MDRs include, but are not necessarily limited to:

- MDR data alone cannot be used to establish rates of events, evaluate a change in event rates over time, or compare event rates between devices. The number of reports cannot be interpreted or used in isolation to reach conclusions about the existence, severity, or frequency of problems associated with devices.
- Confirming whether a device actually caused a specific event can be difficult based solely on information provided in a given report. Establishing a cause-and-effect relationship is especially difficult if circumstances surrounding the event have not been verified or if the device in question has not been directly evaluated.
- MAUDE / PRIMO data are subject to reporting bias, attributable to potential causes such as reporting practice, increased media attention, and/or other agency regulatory actions.

- MAUDE / PRIMO data do not represent all known safety information for a reported medical device and should be interpreted in the context of other available information when making device-related or treatment decisions.

MDRs Associated with the Pleximmune™ test:
MDR search for the product code 'PHK' (associated with the Pleximmune), for 'Pleximmune' and 'Plexision' in the PRIMO database did not find any MDRs for the device, Pleximmune™.

The sponsor was contacted for information on any adverse events and complaints they may have received from ordering physicians or patients during the period from June 1, 2021 to May 25, 2022 (the test was approved on August 26, 2014). As per the sponsor, there were no MDRs, adverse events or complaints received by the sponsor from ordering physicians or patients during this period.

MDR Summary:
The MDR search and information from the sponsor raised no new safety concerns.

IX. SUMMARY

During the period between June 1, 2021 to May 25, 2022, 625 Pleximmune™ tests on a total of 402 patients were performed. Our review of the published literature and received MDRs since the time of approval has not identified any new or unexpected risks for the pediatric population when compared to the premarket data. Based on the available data, and considering the probable benefits and risks, FDA believes that the HDE remains appropriately approved for pediatric use. Therefore, FDA recommends continued surveillance and will report the following to the PAC in 2023:

- Annual distribution number
- Literature review
- MDR review