FDA Executive Summary

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H130004
Pleximmune™

TABLE OF CONTENTS

I. INTRODUCTION **3**

II. INDICATIONS FOR USE **3**

III. BRIEF DEVICE DESCRIPTION **3**

IV. REGULATORY HISTORY **5**

V. PREMARKET DATA: CLINICAL INVESTIGATION **5**

VI. POSTMARKET DATA: ANNUAL DISTRIBUTION NUMBER **5**

VII. SYSTEMATIC LITERATURE REVIEW OF THE SAFETY OF THE DEVICE PLEXIMMUNE™ FOR THE PEDIATRIC POPULATION **6**

PURPOSE 6
METHODS 6
RESULTS 6
DISCUSSION 6
CONCLUSIONS 6

VIII. MEDICAL DEVICE REPORTS (MDRS) **6**

OVERVIEW OF MANUFACTURER AND USER FACILITY DEVICE EXPERIENCE DATABASE (MAUDE) 6
MDRS ASSOCIATED WITH THE PLEXIMMUNE 7

IX. SUMMARY **8**

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 the 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 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 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, CD 154 ($CD154^{+}TcM$), 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 lymphocyte (PBL) cells is performed in parallel (see design details below, describing the four cell culture reactions in the Pleximmune test). Third-party PBL cells obtained from normal human subjects is 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, the individual is at increased risk for rejection. If the response to third-party exceeds the donor-induced response, the individual is at decreased risk. This use of the response to third party mismatched PBL as a reference response makes 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 PBLs 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 negative control for the Flow Cytometry measurement.
2. Background - The recipient PBLs are cultured alone in culture medium which contains fluorochrome-labeled antibody to the inflammatory response marker, CD 154. This group of cells serves as background $CD154^{+}$TcM cells present in the unstimulated recipient blood at the time of testing.
3. Donor Reaction - The recipient PBLs are cultured with donor or surrogate donor PBL in culture medium which contains fluorochrome-labeled antibody to the inflammatory response marker, CD 154. 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, CD 154. 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 PBLs are isolated. Based on the HLA loci information of patient, surrogate donor PBL and third party PBL are selected. These PBLs are used in the four vitro cell culture reactions (as described above), incubated to elicit the immune reaction in the responder cells. The number of CD154+TcM cells is acquired by flow cytometry. These results are analyzed to calculate 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-CD45RO-APC, for labeling cytotoxic memory T (TcM) cells
- Anti-CD 154-PE, for labeling CD 154 expressing TcM cells
- 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 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 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 HDE application was approved by the Center for Devices and Radiological Health of the Food and Drug Administration.

V. POSTMARKET DATA: ANNUAL DISTRIBUTION NUMBER

Section 520(m)(6)(A)(ii) of The Food, Drug, and Cosmetic Act (FD&C) 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 tests total per year.

For the reporting period of June 01, 2017 until May 31, 2018, Plexision, Inc. performed a total of 510 Pleximmune™ tests for the total of 366 patients at Plexision's CLIA-approved laboratory. All specimens were post-transplant samples. No pre-transplant specimens were tested. Among the 366 patients, there are 187 males and 179 females. The average age of these patients is 8.54 years with an age range from 0.3 to 20.94 years old. The major organs transplanted are liver or intestine. The type of organ transplanted in these 366 patients is: liver (261), combined liver-kidney (1), combined liver-intestine (45), intestine alone (38), liver-intestine-other (14) and liver-other (7). The ethnicity of these patients is not available.

VI. SYSTEMATIC LITERATURE REVIEW OF THE SAFETY OF THE DEVICE Pleximmune™ FOR THE PEDIATRIC POPULATION

Purpose

In preparation for the FDA PAC 2018 fall meeting, a systematic literature review was conducted to address the following question: what adverse events are reported in the literature after treatment with the Pleximmune™, for any indication in the pediatric population (≤21 years old)?

Methods

A search on the internet was performed using the Web of Science, Embase, PubMed and Google Scholar sites for "Pleximmune™".

Results

A search on the internet for "Pleximmune™"using the Web of Science, Embase, PubMed and Google Scholar 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 over the period from June 01, 2017 to May 31, 2018.

Conclusion

The literature search raised no new safety concerns.

VII. MEDICAL DEVICE REPORTS (MDRs)

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

Each year, the FDA receives several hundred thousand medical device reports (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 is subjected to reporting bias, attributable to potential causes such as reporting practice, increased media attention, and/or other agency regulatory actions.

- MAUDE / PRIMO data does 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

MDR search for the procode '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 01, 2017 to May 31, 2018 (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.

VIII. SUMMARY

During the period between June 01, 2017 to May 31, 2018, 510 Pleximmune™ tests for the total of 366 patients had been 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.

FDA concludes that the Pleximmune for the aid in the evaluation of the risk of ACR intended to be used in patients less than 21 years old with liver or small bowel transplantation does not pose an unreasonable or increased risk of illness or injury, and that the probable benefit to health continues to outweigh the risk of injury or illness.

Therefore, FDA recommends continued surveillance and will report the following to the PAC in 2019:

- Annual distribution number
- Literature review
- MDR review