FDA Executive Summary

Prepared for the
September 16, 2015 meeting of 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 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. 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 donor. 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 donor response is exceeded by the response to third-party, 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.

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. PREMARKET DATA: CLINICAL INVESTIGATION

Summary of Clinical Studies:

A clinical study was performed to determine the safety and probable benefit, sensitivity, specificity, and positive and negative predictive values (PPV, NPV) of Pleximmune™ for predicting rejection in the intended use population.

A total of 122 specimens from 87 individual pediatric transplant patients were enrolled in the clinical validation study. Of these, 97 samples consisting of 33 pediatric pre-transplant (IRO) subjects and 64 post-transplant (30 IRl and 34 IRx) samples from 72 pediatric subjects were analyzable because 16 specimens failed to generate signal and 9 specimens had inadequate cell count.

Results**:**
Using the post-transplant rejection-risk cutoff threshold of 1.10, the sensitivity, specificity, PPV and NPV were 84%, 80%, 64% and 92%, respectively (AUC 0.791) when applied to 64 post-transplant samples in the validation study. Using the pre-transplant rejection-risk cutoff threshold of 1.23, the sensitivity, specificity, PPV and NPV were 57%, 89%, 80%, 74%, respectively (AUC 0.842), when applied to 33 IRO samples in the validation study.

Cohort	**AUC**	**Sensitivity [n] (95% CI)**	**Specificity [n] (95% CI)**	**PPV [n] (95% CI)**	**NPV [n] (95% CI)**
IRO set (n=33)	0.842	**57%** [8/14] (30%-81%)	**89%** [17/19] (65% - 98%)	**80%** [8/10] (44% - 96%)	**74%** [17/23] (51%-89%)
IRl+IRx set (n=64)	0.791	**84%** [16/19] (60% - 96%)	**80%** [36/45] (65% - 90%)	**64%** [16/25] (43%-81%)	**92%** [36/39] (78% - 98%)

Conclusions:
A summary of the results obtained for pre-transplant samples:

1) The test predicted correctly the risk of ACR 80% of times (8/10 samples analyzed), and gave 20% false positive results (2/10 samples analyzed).
2) The test predicted correctly no risk of ACR 74% of times (17/23 samples analyzed), and gave 26% false negative results (6/23 samples analyzed).

A summary of the results obtained for post-transplant samples (IR1+IRx combined):

1) The test predicted correctly the risk of ACR 64% of times (16/25 samples analyzed), and gave 36% false positive results (9/25 samples analyzed).
2) The test predicted correctly no risk of ACR 92% of times (36/39 samples analyzed), and gave 8% false negative results (3/39 samples analyzed).

Summary of Preclinical Studies:

Non-clinical laboratory studies were performed to evaluate the analytical performance of Pleximmune™. For these studies, normal human samples were used since clinical samples were difficult to get from the intended population of children with liver and small bowel transplant. A single antigenically dissimilar stimulator was used to stimulate PBL from normal human subjects. The studies performed included an assessment of specificity of individual antibodies in the reagent cocktail of six different fluorophores and dyes with overlapping emission spectra, the effect of lot-to-lot variation of reagents, the estimation of device imprecision (e.g., the impact on testing one sample over time when different operators, instruments, runs, days, etc., are involved). Sample storage stability was evaluated to show that the Pleximmune™ test performance is not impacted when fresh or frozen PBL samples are used.

VI. POSTMARKET DATA: ANNUAL DISTRIBUTION NUMBER

The Food and Drug Administration Safety and Innovation Act (FDASIA) amended section 520(m) of the Federal Food, Drug, and Cosmetic Act (FD&C) and allowed 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). The ADN was defined to be the number of devices "reasonably needed to treat, diagnose, or cure a population of 4,000 individuals in the United States." FDA has interpreted that to imply that the calculation of the ADN should be 4,000 multiplied by the number of devices reasonably necessary to treat an individual. The approved ADN for Pleximmune™ is 4000 tests total per year.

Since the approval of Pleximmune™ on August 26, 2014 until May 31, 2015, Plexision, Inc. performed a total of 97 Pleximmune™ tests for a total of 75 patients at Plexision's CLIA-approved laboratory. All specimens were post-transplant samples. No pre-transplant specimens were tested. Among the 75 patients, there are 39 males and 36 females. The average age of these patients is 6 years with an age range from 7 months to 21 years old. 56 had liver transplants, 14 had intestine transplants, and 5 had both liver and intestine transplants.

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

Purpose

In preparation for the FDA PAC 2015 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, ECRI and Google Scholar sites for "Pleximmune™".

Results

A search on the internet for "Pleximmune™"using the Web of Science, Embase, PubMed, ECRI 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 August 26, 2014 to May 31, 2015.

Conclusion

The literature search raised no new safety concerns.

VIII. MEDICAL DEVICE REPORTS (MDRs)

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

Each year, the FDA receives several hundred thousand medical device reports (MDRs) of suspected device-associated deaths, serious injuries and malfunctions. The MAUDE 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 data is subjected to reporting bias, attributable to potential causes such as reporting practice, increased media attention, and/or other agency regulatory actions.

- MAUDE 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' (the product code for the Pleximmune™ device), for 'Pleximmune™' and 'Plexision' over the period from August 26, 2014 to May 31, 2015 in the MAUDE database revealed that no MDRs were submitted for the device in this time period.

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 August 26, 2014 to May 31, 2015 (the test was approved on August 26, 2014). The sponsor stated that there were no MDRs, adverse events, or complaints received by the sponsor during this period.

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

IX. SUMMARY

As of June 1, 2015, 97 Pleximmune™ tests for the total of 75 patients had been performed. Our review of the published literature and MDR database 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™, when used as an aid in the evaluation of the risk of ACR 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 2016:

- Annual distribution number
- PAS follow-up results
- Literature review
- MDR review