INSTRUCTIONS FOR USE

Version: March 2020

KYSLECEL® (MINIMALLY MANIPULATED AUTOLOGOUS PANCREATIC ISLETS)

DESCRIPTION

KYSLECEL® is a suspension comprising minimally manipulated autologous pancreatic islets for intraportal or intraperitoneal infusion.

REGULATORY CLASSIFICATION

KYSLECEL is processed and distributed in accordance with US FDA requirements for Human Cellular and Tissue-based Products (HCT/P) under 21 CFR Part 1271 regulations and US State regulations. KYSLECEL is to be dispensed only by or on the order of a licensed physician.

INDICATIONS FOR USE

KYSLECEL is intended to preserve beta-cell mass and insulin secretory capacity in chronic or recurrent acute pancreatitis patients after pancreatectomy, a procedure referred to as Total Pancreatectomy and Islet Autotransplantation (TPIAT).

CONTRAINDICATIONS

KYSLECEL is contraindicated for use in any patient for whom TPIAT is contraindicated. This includes patients with C-peptide negative diabetes, type 1 diabetes, portal vein thrombosis, portal hypertension, significant liver disease, high-risk cardiopulmonary disease, or known pancreatic cancer.

WARNINGS AND PRECAUTIONS

- KYSLECEL is for autologous use only.
- Do not use a filter in the infusion line.
- Inherent uncertainty exists in the number and function of each patient's pancreatic islets as well as the ability of islets to engraft after infusion. Despite the risk of developing diabetes due to preexisting pancreatitis, patients are at greater risk of experiencing compromised insulin secretory capacity and developing type 3c diabetes as a result of TPIAT.
- KYSLECEL is not routinely tested for transmissible infectious diseases. Patient organ material and KYSLECEL may carry the risk of transmitting infectious diseases to health care professionals handling the organ material or product. **Employ universal precautions**.
- KYSLECEL is distributed prior to obtaining results of sterility testing. Expedited gram stain results will be communicated to the prescribing physician as soon as practicable; however, the expedited results may not be available prior to infusion. Final sterility tests are unavailable by the time of product infusion. If sterility results are positive after the product has been distributed, Koligo will notify the prescribing physician. Koligo will attempt to identify the microorganism, perform antibiotic sensitivity testing on recovered microorganisms, and communicate the results to the prescribing physician.

- Do not use KYSLECEL after the labeled expiration time, if stored outside of 2-8 °C, if the bag leaks, or if packaging integrity has been violated, opened, or damaged.
- KYSLECEL is routinely formulated with human serum albumin, heparin, and ciprofloxacin. The prescribing physician should inform Koligo if the patient is sensitive to any of these additives. Alternative manufacturing additives may be utilized upon request.

ADVERSE EVENTS

The following adverse events are anticipated and may potentially occur during or as a result of TPIAT.

- Diabetes
- Portal hypertension
- Acute Inflammation-related Infusion Reactions
- Bleeding due to heparin

Recommended premedication and concomitant medication may mitigate anticipated adverse events.

Inherent risks of any surgical procedure include infection, blood loss, pain, and anesthesia associated complications. Complications specific to pancreatic surgery include weight loss, pancreatic enzyme insufficiency, and delayed gastric emptying.

Immediately report any adverse reaction involving a communicable disease related to KYSLECEL to Koligo Therapeutics, Inc. Also report other unexpected adverse events, errors, accidents, and product complaints to Koligo Therapeutics, Inc.

SCHEDULING, RESECTION, TRANSPORT OF PANCREAS

The date and time of pancreas resection must be confirmed between the infusion site and Koligo Therapeutics, Inc. in a written **KYSLECEL Product Authorization Form**. This form will identify certain patient information for product tracking and safety, including any known sensitivities to KYSLECEL additives. Koligo will provide pancreas packaging materials prior to the resection.

Resection should be a pancreatectomy (total, partial, or completion) with the following modifications:

- Minimize warm ischemia time. Maintain arterial perfusion and unimpeded venous outflow from the pancreas as long as possible prior to resection. Delay ligation of the splenic and gastroduodenal arteries until final steps.
- Division of the pancreas at the neck to remove the body and tail separately from the head is acceptable if this facilitates removal.

Using **sterile technique**, remove pancreas from the operating table and prepare as follows:

- Do not trim the pancreas. Do not remove the duodenum or spleen from the specimen.
- Flush the splenic and gastroduodenal arteries with cold UW or HTK solution; do not use saline.
- Place pancreas in UW or HTK solution in one sterile plastic bag and tie securely.
- Insert the bagged pancreas into a sterile rigid (cylinder) container.
- Fill container with UW or HTK solution to eliminate air in the container.
- Cover the container with a second sterile bag and tie securely.
- Securely affix a mustard color polyplastic “pancreas” tag.
- Affix a patient sticker with medical record number (MRN) on the mustard pancreas tag.

- Promptly place organ package within a lined insulated container filled with wet ice and close the insulated container.
- Place a copy of the KYSLECEL Product Authorization Form and 6 patient stickers with MRN inside of a plastic bag and place on top of the closed insulated container.
- Seal the outer corrugated box. Sign the **Chain of Custody** form and attach to the outside of the outer box. Hand over to the representative or assigned courier of Koligo Therapeutics, Inc.

Ensure blood glucose of 80 – 120 mg/dL from the time of pancreatectomy, through the infusion period, and the post-operative period.

The planned method of portal infusion may dictate the placement of catheter at the time of resection.

Koligo Therapeutics, Inc. will confirm receipt of the pancreas and confirm KYSLECEL delivery time (usually early morning the day after resection).

KYSLECEL INSTRUCTIONS FOR USE

1. Prepare necessary infusion materials prior to the planned infusion time:
   a. Infusion line with no filter
   b. Extension tubing
   c. Three-way stopcocks
   d. Water monometer
   e. Heparinized saline to flush infusion tubing
2. Premedication and concomitant medication to mitigate possible anticipated side effects:
   a. Insulin – maintain continuous insulin during the postoperative period and during KYSLECEL infusion. It is recommended to eventually transition to subcutaneous insulin injections to maintain blood glucose of 80 – 120 mg/dL. It is recommended to continue insulin therapy for at least 3 months to protect the transplanted islets from toxic hyperglycemia. Monitor blood glucose carefully and immediately wean insulin therapy if signs of hypoglycemia occur.
   b. Heparin - administer IV heparin bolus (35 units / kg) immediately prior to islet infusion. Heparin is added to KYSLECEL (as an additional 35 units / kg) unless otherwise requested by the prescribing physician. Units of heparin added is clearly noted on KYSLECEL label.
   c. Antimicrobial – it is recommended to administer broad spectrum antimicrobial prophylaxis for 72 hours. Koligo will provide interim and final microbiology reports as available. If microbiology reports are positive, treat for 14 days. KYSLECEL is **not** routinely tested for transmissible infectious diseases. Ciprofloxacin is added to KYSLECEL unless otherwise requested by the physician. Units of ciprofloxacin added is clearly noted on KYSLECEL label.
   d. Anti-inflammatory - consider premedication and continued postoperative treatment with anti-inflammatory agents blocking TNF-alpha and IL-1 (e.g. etanercept and anakinra) to mitigate the rare risk of severe inflammatory response.
3. Place appropriately sized catheter for islet infusion and portal vein pressure measurements to access portal vein or tributary (if not done previously).
4. Do not use a filter in the infusion line to assure islets can flow freely.
5. Immediately prior to KYSLECEL infusion, open the insulated container and match the patient's identity with the patient identifiers on the product **Infusion Summary** form and KYSLECEL label(s).
6. Verify temperature information and record temperature data from the temperature data logger on product Infusion Summary form.

7. Inspect the infusion bag(s). Do not administer if a bag has leaked. Contents of the bag(s) will be slightly cloudy, with an off-white to yellow color. The islet tissue may form visible, small clumps and settle in the bag(s).
8. Gently manipulate the bag(s) prior to infusion to prevent islets from clumping and settling. Small clumps of cellular material should disperse with gentle manual mixing. Do not administer if a bag leaks during handling.
9. Administer KYSLECEL slowly via gravity drainage.
    a. Administer bag #1 first, then bag #2 (if applicable).
    b. Unclamp and administer bag #2 (if applicable) through bag #1.
    c. Unclamp and administer small rinse bag through bag #2 (if applicable) and/or through bag #1.
10. During infusion, each bag should be gently and continuously manipulated to prevent islets from clumping or settling. Infuse entire volume of each bag.
11. Regularly monitor portal venous pressure – maintain less than 25 cm H_2O above baseline.
12. Monitor vital signs, blood glucose, and for potential infusion reactions.
13. Slow infusion, or stop and restart infusions, as necessary.
14. If portal pressure remains unacceptably high, stop intraportal infusion and complete the infusion intraperitoneally.
15. Administer appropriate medical therapy in the event of infusion reactions.
16. Observe the patient for at least 30 minutes following infusion.
17. Consider continued systemic anti-coagulation for significant elevations in portal venous pressure or if the patient has a history of hypercoagulable state.
18. Complete Infusion Summary document and fax to Koligo Therapeutics, Inc. at 502-265-4839.

HOW SUPPLIED

KYSLECEL is a suspension containing the maximum number of autologous islets able to be harvested from the patient's resected pancreas in HEPES buffer solution and human serum albumin with heparin and ciprofloxacin added (unless otherwise requested by the prescribing physician). Depending on the number of islets obtained from the patient's pancreas, KYSLECEL is supplied in one or two 200 mL infusion bags, labeled for the specific recipient.

TRANSPORT AND STORAGE

KYSLECEL is shipped directly to the infusing provider in an insulated container at 2-8 °C. The insulated container should remain closed until shortly before infusion. Infusion of KYSELCEL is recommended as soon as practicable. The expiration time for KYSLECEL is 24 hours after loading the islets into the infusion bag(s). The expiration date and time is recorded on the KYSLECEL label. Use of KYSLECEL after the expiration time could result in a lack of efficacy due to poor islet viability or an increased risk of bacterial, endotoxin, or fungal growth.

DISPOSAL

Dispose of unused product and disposable materials in accordance with accepted medical practice and applicable local, state and federal laws and regulations.

The outer box, the insulated panels, and the temperature data logger are reusable. Contact Koligo Therapeutics, Inc. to arrange for return of these materials.

INQUIRIES

For more information, patient scheduling, or to report product complaints or adverse reactions, contact Koligo Therapeutics, Inc.:

Phone: 502-265-4830
Fax: 502-265-4839
Email: info@koligo.net

KYSLECEL is distributed and manufactured by:

Koligo Therapeutics, Inc.
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