NOVARTIS

Direct shipment process is confirmed by Israeli HA.

Pharmacy/Cell Lab/Infusion Center Training Material - IL

This material can help you follow the steps for reception, storage, handling, thawing, administration and preparation for infusion of a CD19-directed genetically modified autologous T cell immunotherapy, delivered in its final packaging of 1-3 infusion bags for a specific patient ("Kymriah") to mitigate a decrease in cell viability.

Kymriah is indicated for the treatment of:

- Paediatric and young adult patients up to and including 25 years of age with CD19+ B-cell acute lymphoblastic leukaemia (ALL) that is refractory, in relapse post-transplant or in second or later relapse.
- Adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL) after two or more lines of systemic therapy.

  Limitation of Use: Kymriah is not indicated for treatment of patients with primary or secondary central nervous system lymphoma.
- Adult patients with relapsed or refractory follicular lymphoma (FL) after two or more lines of systemic therapy.

Good receipt process done by the medical site described in this document is part of the medical site training and will be included in the supply agreement between Novartis and the medical site.

Kymriah product shipments due to unique product nature (ATMP) and strict transport requirements is delivered directly to the medical site from abroad, and exempt from retention duty of batch retained samples in Israel. Kymriah batch shipments are exempt from any official batch testing by HA (usually requires for medicinal products), after arrival to Israel including exemption of first batch submission. This set-up was confirmed by the Israeli HA on 26-12-2018.

Process Overview

Arrival, Receipt and Storage of Kymriah

- Kymriah is supplied as a cell dispersion in 1-3 infusion bags ("Dose") labelled for the specific patient. Kymriah is shipped directly to the cryostorage facility associated with the infusion centre in a dry vapour shipper in the vapour phase of liquid nitrogen.
- Verify the number of bag(s) received for the dose of Kymriah with the Manufacturer Batch Certificate/Batch Documents
- Confirm that there were no temperature excursions during transport
- Unload Kymriah from the dry vapour shipper.
- Open the secondary packaging, inspect the product and note the Donation Identification Number (DIN) or apheresis ID and all additional identification parameters (in accordance with your institutional procedures)
- Store the Kymriah infusion bag(s) below -120°C, e.g., in a container for cryogenic storage in the vapour phase of liquid nitrogen. Ensure that Kymriah is stored in a protective packaging that has been validated in the cryostorage tank, following institutional procedures to avoid a bag integrity risk
- The site will fill out good receipt form and forward a sign form by cell lab and site pharmacy, to the QP in Novartis Israel LTD for final batch approval.
- Site will receive the Israeli approval from Novartis Israel QP ASAP. Only after receiving the Israeli QP written approval the batch can be used.

Handling Kymriah

- Kymriah is prepared from autologous blood of the patient collected by leukapheresis and contains genetically modified human blood cells. Patient leukapheresis material and Kymriah may carry a risk of transmitting infectious viruses to healthcare professionals handling the product.
- Healthcare professionals should employ appropriate precautions (wearing gloves and glasses) when handling leukapheresis material or Kymriah to avoid potential transmission of infectious diseases when handling the product.
- Kymriah should be transported within the facility in closed, break-proof, leak-proof containers. Do not irradiate.
- All material that has been in contact with Kymriah (solid and liquid waste) should be handled and disposed of as potentially infectious waste in accordance with local guidelines on handling of biological waste.

Kymriah is recommended to be infused 2 to 14 days after completion of the lymphodepleting chemotherapy for B-cell ALL and DLBCL indications. Kymriah is recommended to be infused 2 to 6 days after completion of the lymphodepleting chemotherapy for FL indication.

1. Preparation for Infusion

The timing of thaw of Kymriah and infusion should be coordinated. The infusion start time should be confirmed in advance and adjusted for thaw so that Kymriah is available for infusion when the recipient is ready.

Once Kymriah infusion bag has been thawed and is at room temperature (20°C - 25°C), it should be infused within 30 minutes to maintain maximum product viability, including any interruption during the infusion.

- One dose of tocilizumab and emergency equipment must be available per patient prior to infusion and during the recovery period. The treatment centre must have access to additional doses of tocilizumab within 8 hours to manage cytokine-release syndrome (CRS) according to the CRS management algorithm per local prescribing information.
- In the exceptional case where tocilizumab is not available due to a shortage that is listed in the Ministry of Health website, suitable alternative measures to treat CRS instead of tocilizumab must be available prior to infusion.
- Confirm patient identity: Prior to Kymriah preparation, match the patient's identity with the patient identifiers on the Kymriah infusion bag(s). Kymriah is for autologous use only

2. Thawing Kymriah

One Dose comprises 1-3 infusion bags. If more than one infusion bag has been received for the Dose, the next bag should only be thawed after the contents of the preceding bag have been infused.

Do not thaw Kymriah until it is ready to use.

- Examine the Kymriah infusion bag for any breaks or cracks prior to thawing. Place the Kymriah infusion bag inside a second sterile bag during thawing to protect ports from contamination and avoid spills in the unlikely event of the bag leaking
- If the Kymriah infusion bag appears to have been damaged or to be leaking, it should not be infused and should be disposed of according to local procedures on handling of biological waste.
  Call the **Novartis Customer Service Centre at +800 100 10 100** in parallel inform Novartis Country Quality Organization to notify them of the product issue

- Thaw Kymriah at 37°C using either a water bath or dry thaw method until there is no visible ice in the infusion bag
  - Remove infusion bag from the thawing device immediately and keep at room temperature (20°C - 25°C) until infusion
  - Once an infusion bag has been thawed and is at room temperature (20°C - 25°C), it should be infused within 30 minutes, including any interruption during the infusion, to maintain maximum product viability.
  - Kymriah should not be manipulated. Do not wash, spin down, and/or resuspend Kymriah in new media prior to infusion
  - There may be a decrease in cell viability of Kymriah due to inappropriate handling of the manufactured product, including transport and storage, in addition to thawing and standing time prior to infusion. This may impact the efficacy and safety profile of Kymriah

3. Administration of Kymriah

- The patient's identity must be confirmed with the patient identifiers on the Kymriah infusion bag
- Kymriah is infused by intravenous infusion through latex-free intravenous tubing without a leukocyte depleting filter at approximately 10-20 mL per minute by gravity flow.
- If the volume of Kymriah to be administered is ≤20 mL, intravenous push may be used as an alternative method of administration
- Sterile sodium chloride 9 mg/mL (0.9%) solution for injection should be used to prime the tubing prior to infusion and to rinse it after infusion
- Infuse all contents of the Kymriah infusion bag. The Kymriah infusion bag should be rinsed with 10 to 30 mL sodium chloride 9 mg/ mL (0.9%) solution for injection by back priming to ensure as many cells as possible are infused into the patient.

Repeat sections 2-3 above, sequentially, for any additional Kymriah infusion bag (s) received.

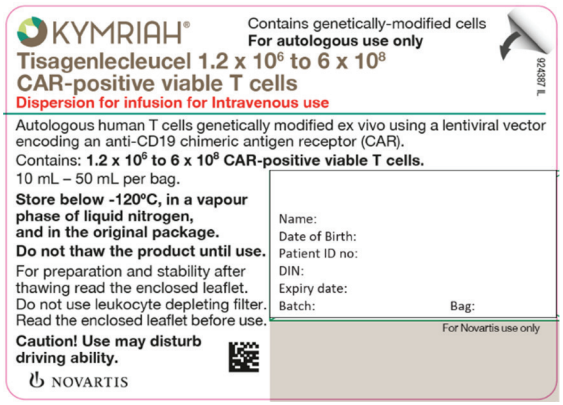
Supplemental Information

Kymriah Packaging and Shipment

Kymriah is supplied as a frozen dispersion of genetically modified autologous T cells in up to 3 infusion bags labeled for the specific recipient

- Kymriah Infusion bag(s) have an affixed product label containing unique patient identifiers, including patient name, patient social ID no., patient date of birth (DOB), and either patient Donation Identification Number (DIN) or apheresis ID (Figure 1)

Figure 1:
Example of KYMRIAH Product Label



- Kymriah is shipped from Novartis to the cryostorage facility associated with the infusion center in a dry vapour shipper in the vapour phase of liquid nitrogen
  - During transport, Kymriah is maintained below -120°C
  - Temperature is continuously monitored and recorded using an online data log viewer
- A shipping notification e-mail containing a tracking link is sent to all registered Novartis ordering platform users when Kymriah is shipped from the Novartis manufacturing facility
  - A shipment tracking link can also be found within the Novartis ordering platform

Arrival, receipt and storage of Kymriah

After delivery of the dry vapour shipper, the cryostorage facility associated with the infusion centre must:

- Confirm that there were no temperature excursions during transport by viewing temperature data in the online data log viewer
- Retrieve the Manufacturer Batch Certificate/Batch Documents (will be available in the Novartis ordering platform system) and the Shipment Documents. These documents need to be compared with the actual label on the received product, any discrepancies need to be reported on the Goods receipt form.
- Unload Kymriah from the dry vapour shipper
- Perform visual check of the product and take a quick photo (without flash), right after, the product should be stored back at the needed conditions immediately. The photo will enable review and documentation of the product label attributes confirming all product details are accurate and align with the drug order & batch documents (e.g. batch no., patient name, etc.)
- Confirm patient identity and receipt of Kymriah in the Novartis ordering platform.
- Transfer Kymriah to on-site storage below -120°C, e.g., in a container for cryogenic storage in the vapour phase of liquid nitrogen
- Store the Kymriah infusion bag(s) in a protective packaging that has been validated in the cryostorage tank, following institutional procedures to avoid a bag integrity risk
- Fill out Novartis good receipt form and provide all needed documents to Novartis Israel QP in accordance to the quality terms in the supply agreement.

- Wait for Novartis Israel QP final approval for the batch (written approval will be available in the dedicated system and/or via email), before any use of the product.

The following steps provide details on how to complete these requirements:

While performing these steps, follow institutional standard operating procedures to ensure that Kymriah is kept below -120°C. Follow local guidelines on handling of biological waste and employ appropriate precautions (wearing gloves and glasses) when handling Kymriah to avoid potential transmission of infectious diseases.

Use closed, break-proof, leak-proof containers when transporting Kymriah within the facility.

1. Access the temperature recordings for the shipment through the online data log viewer

- Access the online data log viewer via the tracking link in either the shipping notification e-mail or the link found within the Novartis ordering platform
- To ensure the most updated temperature recordings are displayed, refresh in the online data log viewer

2. Check the temperature recordings to ensure there were no temperature excursions during transport

- Note: A temperature reading above -120°C represents a temperature excursion; however, a brief spike above -120°C is normal and acceptable at the time Kymriah was loaded into the dry vapour shipper
- Report any temperature excursions by calling the **Novartis Customer Service Centre at +800 100 10 100** and contacting the Novartis Country Quality Organisation (please copy the QP/QA team at Novartis Israel on any communication in this regards by the following email: QA.Israel@Novartis.com).
- An exported PDF version of the temperature profile should be kept with the patient's medical records

3. Unload Kymriah and accompanying documentation from the dry vapour shipper

- Upon delivery, ensure that the dry vapour shipper is sealed with an intact uniquely identifiable tamper-proof zip tie. If the zip tie is not intact, call the **Novartis Customer Service Centre at +800 100 10 100** and contact the Novartis Country Quality Organization
- Follow institutional standard operating procedures for liquid nitrogen handling when unloading the dry vapour shipper
- Verify the number of bags received for the Dose of Kymriah with the Manufacturer Batch Certificate/Batch Documents.

4. Carefully examine the Kymriah infusion bag(s) and ensure that the bag(s) is/are intact and free from any damage, including cracks, leaks, etc. Confirm that the patient identifiers on the Kymriah infusion bag label(s) match those in institutional records. If damage is noted, or patient identifiers do not match, call the **Novartis Customer Service Centre at +800 100 10 100** and contact the Novartis Country Quality Organization. Please copy the QP/QA team at Novartis Israel on any communication in this regards by the following email: QA.Israel@Novartis.com.

- Take a quick photo without flash (the product should be stored back at the needed conditions immediately). The photo will enable review of the product label attributes confirming all product and patient details are accurate.
- Follow institutional standard operating procedures to ensure that Kymriah is kept below-120°C

5. Log in to the Novartis ordering platform and document the receipt of Kymriah

- Retrieve the Manufacturer Batch Certificate/Batch Documents (will be available in the Novartis ordering platform system) and the Shipment Documents. These documents need to be compared with the actual label on the received product, any discrepancies need to be reported and should be mentioned on the Goods receipt form.
- Fill out Novartis good receipt form and provide all needed documents including product Photos to Novartis Israel QP in accordance to the supply agreement.
- Wait for Novartis Israel QP final approval for the batch, before any use of the product. Final Israel QP written approval will be uploaded in to the dedicated system.

6. Transfer Kymriah to on-site storage

- Store and transport frozen product below -120°C, e.g., in a container for cryogenic storage in the vapour phase of liquid nitrogen. Store the Kymriah infusion bag(s) in a protective packaging that has been validated in the cryostorage tank, following institutional procedures to avoid a bag integrity risk

7. The empty dry vapour shipper will be picked up the next business day. If you need a different pickup arrangement, please call the **Novartis Customer Operations Service Centre at +800 100 10 100**

For questions, please contact your Novartis Cell Therapy Operations Manager or call the Novartis Customer Service Centre at +800 100 10 100.

Please see the full product labelling for Kymriah.

Reporting Adverse Reactions

Adverse reactions may be reported to the Ministry of Health by means of the online form for reporting adverse reactions located at: https://sideeffects.health.gov.il

You may also report to the Registration Holder Novartis Israel LTD. at: safetydesk.israel@novartis.com

For further information, please refer to the Prescribing information.

This document has been determined by the Ministry of Health and the content therefore has been checked and approved on November 2022.

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