Novartis Oncology

Pharmacy/Cell Lab/Infusion Centre Training Material

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.

Kymriah▼ is indicated for the treatment of:

- Paediatric and young adult patients up to and including 25 years of age with 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.
- Adult patients with relapsed or refractory follicular lymphoma (FL) after two or more lines of systemic therapy

Process Overview

Arrival, Receipt and Storage of KYMRIAH

- Kymriah is supplied as a cell dispersion in one or more 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 QP Batch Certificate or Certificate of Conformance
- 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 (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 the institutional procedures to avoid a bag integrity risk.

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

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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 a 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 European Medicines Agency shortage catalogue, prior to infusion the treatment centre must have access to suitable alternative measures instead of tocilizumab to treat CRS
- 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 one or more 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 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 (00 800 100 10 100)** and contact Novartis Country Quality Organisation 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

- **Administration of KYMRIAH**

- The patient's identity must be confirmed with the patient identifiers on the Kymriah infusion bag

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- Kymriah is infused by intravenous infusion through latex-free intravenous tubing without a leukocyte depleting filter at approximately 10-20mL 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 mL 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.

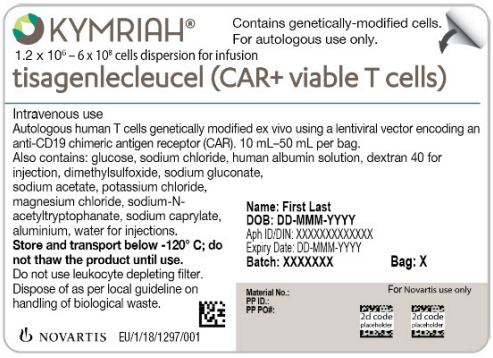
This guide can help you prepare for the arrival and receipt of Kymriah.

Supplemental Information

KYMRIAH Packaging and Shipment

- Kymriah is supplied as a frozen dispersion of genetically modified autologous T cells in one or more infusion bags labelled for the specific recipient
  - Kymriah infusion bags have an affixed product label containing unique patient identifiers, including patient name, 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 centre 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
- Unload Kymriah from the dry vapour shipper
- 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

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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 (00 800 100 10 100)** and contacting the Novartis Country Quality Organisation
   - 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 (00 800 100 10 100)** and contact the Novartis Country Quality Organisation
   - 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 QP Batch Certificate or Certificate of Conformance
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 (00 800 100 10 100)** and contact the Novartis Country Quality Organisation
   - 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
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 pick-up arrangement, please call the **Novartis Customer Service Centre at (00 800 100 10 100)**

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For questions, please contact your Novartis Cell Therapy Operations Manager or call the Novartis Customer Service Centre at (00 800 100 10 100).

Please see the full product labelling (SmPC) for Kymriah.

▼*This medicinal product is subject to additional monitoring. Reporting suspected adverse reactions of the medicinal product is important to Novartis and the HPRA. It allows continued monitoring of the benefit/risk profile of the medicinal product. All suspected adverse reactions along with the batch ID of the medicinal product should be reported via HPRA Pharmacovigilance on www.hpra.ie. Adverse events could also be reported to Novartis preferably via www.report.novartis.com or by email: drugsafety.dublin@novartis.com or by calling 01 2080 612.*

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