

Risk Evaluation and Mitigation Strategy (REMS) Document

Kymriah (tisagenlecleucel) REMS Program

I. Administrative Information

Application Number: BLA 125646

Application Holder: Novartis Pharmaceuticals Corporation

Initial REMS Approval: 8/2017

Most Recent REMS Update: XX/2019

II. REMS Goals

The goals of the Kymriah® REMS Program are to mitigate the risks of cytokine release syndrome (CRS) and neurological toxicities by:

- Ensuring that hospitals and their associated clinics that dispense Kymriah are specially certified and have on-site, immediate access to tocilizumab.
- Ensuring those who prescribe, dispense, or administer Kymriah are aware of how to manage the risks of cytokine release syndrome and neurological toxicities.

III. REMS Requirements

Novartis must ensure that hospitals and their associated clinics, and patients comply with the following requirements:

1. Hospitals and their associated clinics that dispense Kymriah must:

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| To become certified to dispense | <ol style="list-style-type: none">1. Have a minimum of two doses of tocilizumab available on-site for each patient for immediate administration (within 2 hours).2. Designate an authorized representative to carry out the certification process and oversee implementation and compliance with the REMS Program on behalf of the hospital and their associated clinics.3. Have the authorized representative take the Live Training Program provided by the REMS Program.4. Have the authorized representative successfully complete the Knowledge Assessment and submit it to the REMS Program.5. Have the authorized representative enroll in the REMS Program by completing the Hospital Enrollment Form and submitting it to the REMS program.6. Train all relevant staff involved in prescribing, dispensing, or administering of Kymriah on the REMS Program requirements using the Live Training Program.7. Have all relevant staff involved in prescribing, dispensing, or administering successfully complete the Knowledge Assessment. |
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8. Establish processes and procedures to ensure new staff involved in the prescribing, dispensing, or administration of Kymriah are trained and complete the [Knowledge Assessment](#).
9. Establish processes and procedures to verify that a minimum of two doses of tocilizumab are available on-site for each patient and are ready for immediate administration (within 2 hours).
10. Establish processes and procedures to provide patients with the [Patient Wallet Card](#).

Before infusion	<ol style="list-style-type: none"> 11. Provide the patient with the Patient Wallet Card. 12. Verify that a minimum of two doses of tocilizumab are available on-site for each patient and are ready for immediate administration (within 2 hours) through the processes and procedures established as a requirement of the REMS Program.
To maintain certification to dispense	<ol style="list-style-type: none"> 13. Have the new authorized representative enroll in the REMS Program by completing the Hospital Enrollment Form.
To maintain certification to dispense, if Kymriah has not been dispensed at least once annually from the date of certification in the REMS Program	<ol style="list-style-type: none"> 14. Train all relevant staff involved in prescribing, dispensing, or administering of Kymriah on the REMS Program requirements using the Live Training Program. 15. Have all relevant staff involved in prescribing, dispensing, or administering successfully complete the Knowledge Assessment.
At all times	<ol style="list-style-type: none"> 16. Report any adverse events suggestive of cytokine release syndrome or neurological toxicities to the REMS Program. 17. Maintain records of staff training. 18. Maintain records that all processes and procedures are in place and are being followed. 19. Comply with audits carried out by Novartis or a third party acting on behalf of Novartis to ensure that all processes and procedures are in place and are being followed.

2. Patients who are prescribed Kymriah:

Before infusion	<ol style="list-style-type: none"> 1. Receive the Patient Wallet Card.
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Novartis must provide training to hospital staff who prescribe, dispense, or administer Kymriah.

The training includes the following educational materials: [Live Training Program](#) and [Knowledge Assessment](#). The training must be provided in-person or live webcast.

To support REMS Program operations, Novartis must:

1. Ensure Kymriah is only distributed to certified hospitals and their associated clinics.
2. Establish and maintain a [REMS Program website](http://www.Kymriah-REMS.com), www.Kymriah-REMS.com. The REMS Program website must include the option to print the PI, Medication Guide, and REMS materials. All product websites for consumers and healthcare providers must include prominent REMS-specific links to the REMS Program website.
3. Make the REMS Program website fully operational and all REMS materials available through website or call center.
4. Establish and maintain a REMS Program call center for REMS participants at 1-844-459-6742.
5. Establish and maintain a validated, secure database of all REMS participants who are enrolled and/or certified in the REMS Program.
6. Ensure hospitals and their associated clinics are able to enroll in the REMS Program in person, online, fax, and phone.
7. Notify hospitals and their associated clinics after they become certified in the REMS Program.

To ensure REMS participants' compliance with the REMS Program, Novartis must:

8. Verify annually that the designated authorized representative for certified hospitals and associated clinics remains the same. If different, the hospital and their associated clinics must re-certify with a new authorized representative.
9. Maintain adequate records to demonstrate that REMS requirements have been met, including, but not limited to records of: Kymriah distribution and dispensing; certification of hospitals and their associated clinics, and audits of REMS participants. These records must be readily available for FDA inspections.
10. Monitor hospitals and their associated clinics on an ongoing basis to ensure the requirements of the REMS are being met. Take corrective action if non-compliance is identified, including de-certification.
11. Maintain an ongoing annual audit plan of hospitals and their associated clinics.
12. Audit all hospitals and their associated clinics no later than 180 calendar days after the hospital places its first order of Kymriah to ensure that all REMS processes and procedures are in place, functioning, and support the REMS Program requirements. Certified hospitals and their associated clinics must also be included in Novartis' ongoing annual audit plan.
13. Take reasonable steps to improve implementation of and compliance with the requirements in the Kymriah REMS Program based on monitoring and evaluation of the Kymriah REMS Program.

IV. REMS Assessment Timetable

Novartis must submit REMS Assessments to the FDA at 6 months, 12 months, and annually thereafter from the date of the initial approval of the REMS (8/30/2017). To facilitate inclusion of as much information as possible while allowing reasonable time to prepare the submission, the reporting interval covered by each assessment should conclude no earlier than 60 calendar days before the submission date for that assessment. Novartis must submit each assessment so that it will be received by the FDA on or before the due date.

V. REMS Materials

The following materials are part of the Kymriah REMS:

Enrollment Forms:

Health Care Setting:

1. [Hospital Enrollment Form](#)

Training and Educational Materials

Patient:

2. [Patient Wallet Card](#)

Health Care Setting:

3. [Live Training Program](#)
4. [Knowledge Assessment](#)

Other Materials

5. [REMS Program website](#)