Package leaflet: Information for the patient or carer

Kymriah 1.2 x 10^6 – 6 x 10^8 cells dispersion for infusion
tisagenlecleucel (CAR+ viable T cells)

▼This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before you (or your child) are given this medicine because it contains important information.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor.
- If you get any side effects, talk to your doctor. This includes any possible side effects not listed in this leaflet. See section 4.
- Your doctor will give you a Patient Alert Card. Read it carefully and follow the instructions on it.
- Always show the Patient Alert Card to the doctor or nurse when you see them or if you go to hospital.
- The information in this leaflet is for you or your child – but in the leaflet it will just say "you".

What is in this leaflet

1. What Kymriah is and what it is used for

What Kymriah is
Kymriah, also known as tisagenlecleucel, is made from some of your own white blood cells called T cells. T cells are important for your immune system (the body's defences) to work properly.

How does Kymriah work?
The T cells are taken from your blood and a new gene is put into the T cells so that they can target the cancer cells in your body. When Kymriah is infused into your blood, the modified T cells will find and kill the cancer cells.

What Kymriah is used for
Kymriah is used to treat:
- **B-cell acute lymphoblastic leukaemia (B-cell ALL)** - a form of cancer that affects some other types of white blood cells. The medicine can be used in children and young adults up to and including 25 years of age with this cancer.
- **Diffuse large B-cell lymphoma (DLBCL)** - a form of cancer that affects some types of white blood cells, mostly in the lymph nodes. The medicine can be used in adults (18 years of age or older) with this cancer.
- **Follicular lymphoma (FL)** - a form of cancer that affects some types of white blood cells, called lymphocytes, mostly in the lymph nodes. The medicine can be used in adults (18 years of age or older) with this cancer.

If you have any questions about how Kymriah works or why this medicine has been prescribed for you, ask your doctor.

2. What you need to know before you are given Kymriah

You should not be given Kymriah:
- if you are allergic to any of the ingredients of this medicine (listed in section 6). If you think you may be allergic, ask your doctor for advice.

Warnings and precautions
Kymriah is made from your own white blood cells and should only be given to you.

Before you are given Kymriah you should tell your doctor if:
- You have had a stem cell transplant in the last 4 months. Your doctor will check if you have signs or symptoms of graft-versus-host disease. This happens when transplanted cells attack your body, causing symptoms such as rash, nausea, vomiting, diarrhoea and bloody stools.
- You have any lung, heart or blood pressure (low or raised) problems.
- You notice the symptoms of your cancer are getting worse. If you have leukaemia this might include fever, feeling weak, bleeding gums, bruising. If you have lymphoma, this might include unexplained fever, feeling weak, night sweats, sudden weight loss.
- You have an infection. The infection will be treated before the Kymriah infusion.
- You have had hepatitis B, hepatitis C or human immunodeficiency virus (HIV) infection.
- You are pregnant, think you may be pregnant, or plan to become pregnant (see sections "Pregnancy and breast-feeding" and "Contraception for women and men" below).
- You had a vaccination in the previous 6 weeks or are planning to have one in the next few months.

If any of the above apply to you (or you are not sure), talk to your doctor before being given Kymriah.

Test and checks
Before you are given Kymriah your doctor will:
- Check your lungs, heart and blood pressure.
- Look for signs of infection; any infection will be treated before you are given Kymriah.
- Check if your lymphoma or leukaemia is getting worse.
- Look for signs of graft-versus-host disease that can happen after a transplant.
- Check your blood for uric acid and for how many cancer cells there are in your blood. This will show if you are likely to develop a condition called tumour lysis syndrome. You may be given medicines to help prevent the condition.
- Check for hepatitis B, hepatitis C or HIV infection.

After you have been given Kymriah
Tell your doctor or nurse immediately if you have any of the following:
- Fever, which may be a symptom of an infection. Your doctor will regularly check your blood counts as the number of blood cells and other blood components may decrease.
- Take your temperature twice a day for 3-4 weeks after treatment with Kymriah. If your temperature is high, see your doctor immediately.
- Extreme tiredness, weakness and shortness of breath, which may be symptoms of a lack of red blood cells.
- Bleeding or bruising more easily, which may be symptoms of low levels of cells in the blood known as platelets.

There may be an effect on the results of some types of HIV test – ask your doctor about this.

Your doctor will regularly monitor your blood counts after you receive Kymriah as you may experience a reduction in the number of blood cells and other blood components.

Do not donate blood, organs, tissues or cells.

Children and adolescents
- There is limited experience with Kymriah in paediatric patients below the age of 3 years.

- Kymriah is not recommended to be used in children and adolescents below 18 years of age to treat DLBCL. This is because there is limited experience in the treatment of non-Hodgkin lymphoma in this age group.
- Kymriah should not be used in children and adolescents below 18 years of age to treat FL. This is because Kymriah has not been studied in this age group.

Other medicines and Kymriah
Tell your doctor if you are taking, have recently taken or might take any other medicines, including medicines obtained without a prescription. This is because other medicines can affect the way Kymriah works.

In particular, you must not be given certain vaccines called live vaccines:
- in the 6 weeks before you are given the short course of chemotherapy (called lymphodepleting chemotherapy) to prepare your body for the Kymriah cells.
- during Kymriah treatment.
- after treatment while the immune system is recovering.

Talk to your doctor if you need to have any vaccinations.

Before you are given Kymriah tell your doctor or nurse if you are taking any medicines that weaken your immune system such as corticosteroids, since these medicines may interfere with the effect of Kymriah.

Pregnancy and breast-feeding
If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor for advice before being given this medicine. This is because the effects of Kymriah in pregnant or breast-feeding women are not known, and it may harm your unborn baby or your newborn/infant.
- If you become pregnant or think you may be pregnant after treatment with Kymriah, talk your doctor immediately.
- You will be given a pregnancy test before treatment starts. Kymriah should only be given if the result shows you are not pregnant.

Contraception for women and men
Discuss pregnancy with your doctor if you have received Kymriah.

Driving and using machines
Do not drive, use machines, or take part in activities that need you to be alert for. Kymriah can cause problems such as altered or decreased consciousness, confusion and seizures (fits) in the 8 weeks following infusion.

Kymriah contains sodium, dimethylsulfoxide (DMSO) and dextran 40.
This medicine contains 24.3 to 121.5 mg sodium per dose. This is equivalent to 1 to 6% of the recommended maximum daily dietary intake of 2 g sodium for an adult. You should be observed closely during the infusion period.

3. How Kymriah is given

Kymriah will always be given to you by a doctor in a qualified treatment centre.

Kymriah contains human blood cells. Your doctor handling Kymriah will therefore take appropriate precautions (wearing gloves and glasses) to avoid potential transmission of infectious diseases.

Giving blood to make Kymriah
Kymriah is made from your own white blood cells.
- Your doctor will take some of your blood using a catheter placed in your vein (a procedure called leukapheresis). Some of your white blood cells are separated from your blood and the rest

of your blood is returned to your vein. This can take 3 to 6 hours and may need to be repeated.
- Your white blood cells are frozen and sent away to make Kymriah. It usually takes about 3 to 4 weeks to make Kymriah but the time may vary.
- Kymriah is a treatment that is manufactured specifically for you. There are situations where Kymriah cannot be successfully manufactured and be given to you. In some cases, a second manufacturing of Kymriah may be attempted.

Before you are given Kymriah, your doctor may give you a type of treatment called lymphodepleting chemotherapy for a few days to prepare your body.

Cancer treatment while Kymriah is being made
During the period while Kymriah is being made, your lymphoma or leukaemia may get worse and your doctor may decide to use an additional treatment (known as "bridging therapy") to stabilise your cancer by stopping new cancer cells from developing. This treatment may lead to side effects and these may be severe or life-threatening. Your doctor will inform you of the potential side effects of this treatment.

Medicines given immediately before Kymriah treatment
During the 30 to 60 minutes before you are given Kymriah you may be given other medicines. This is to help prevent infusion reactions and fever. These other medicines may include:
- Paracetamol
- An antihistamine such as diphenhydramine.

How you are given Kymriah
- Your doctor will check that the individual patient identifiers on the Kymriah infusion bag match up to you.
- Your doctor will give you Kymriah by infusion, which means it will be given as a drip through a tube in your vein. This usually takes less than 1 hour. During the infusion your doctor will check if you have difficulty breathing or dizziness (possible symptoms of an allergic reaction).
- Kymriah is a one-time treatment.

After you are given Kymriah
- Plan to stay within 2 hours' travel from the hospital where you were treated for at least 4 weeks after you have been given Kymriah. Your doctor will recommend that you return to the hospital daily for at least 10 days and will consider whether you need to stay at the hospital as an in-patient for the first 10 days after infusion. This is so your doctor can check if your treatment is working and help you if you have any side effects.

If you miss an appointment, call your doctor or the hospital as soon as possible to reschedule.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Tell your doctor immediately if you get any of the following side effects after the Kymriah infusion. They usually happen in the first 8 weeks after the infusion, but can also develop later:

Very common: may affect more than 1 in 10 people
- high fever and chills. These may be symptoms of a serious condition called cytokine release syndrome which may be life-threatening or fatal. Other symptoms of cytokine release syndrome are difficulty breathing, nausea, vomiting, diarrhoea, loss of appetite, fatigue, muscle pain, joint pain, swelling, low blood pressure, fast heartbeat, headache, heart, lung and kidney failure and liver injury. These symptoms almost always occur within the first 14 days after infusion.
- problems such as altered thinking or decreased consciousness, loss of contact with reality, confusion, agitation, seizures, difficulty speaking and understanding speech, difficulty walking. These may be symptoms of a condition called immune effector cell-associated neurotoxicity

syndrome (ICANS).
- feeling warm, fever, chills or shivering, sore throat or mouth ulcers may be signs of an infection. Some infections may be life-threatening or fatal.

Common: may affect up to 1 in 10 people
- Rapid breakdown of tumour cells causing release of their contents into the bloodstream. This can interfere with the workings of various body organs, especially the kidneys, heart and nervous system (tumour lysis syndrome).

Other possible side effects
Other side effects are listed below. If these side effects become severe or serious, tell your doctor immediately.

Very common: *may affect more than 1 in 10 people*
- Pale skin, weakness, breathlessness due to low number of red blood cells or low haemoglobin
- Excessive or prolonged bleeding or bruising due to low number of platelets
- Fever with dangerously low white blood cell count
- Increased risk of infection due to abnormally low number of white blood cells
- Frequent and persistent infections due to decreased antibodies in your blood
- Weakness, abnormal heart rhythms, due to abnormally low level of blood salts including phosphorus, potassium
- High levels of liver enzymes or creatinine in the blood that show that your liver or kidneys are not working normally
- Fast or irregular heart beat
- Raised blood pressure
- Shortness of breath, laboured breathing, rapid breathing, fluid in the lungs
- Cough
- Abdominal pain, constipation
- Bone and back pain
- Skin rash
- Swollen ankles, limbs and face

Common: *may affect up to 1 in 10 people*
- Fever, malaise, enlarged liver, yellow colour of your skin and eyes, low blood cell counts due to severe immune activation
- Dizziness or fainting, flushing, rash, itching, fever, shortness of breath or vomiting, abdominal pain, diarrhoea due to infusion related reaction
- Rash, nausea, vomiting, diarrhoea including bloody stools (possible symptoms of graft-versus-host disease which is when transplanted cells attack your cells)
- Pain in the joints due to high level of uric acid
- Abnormal blood test results (high level of: phosphorus, potassium, calcium and sodium, an enzyme called alkaline phosphatase to help detect liver disease, fibrin d-dimer, serum ferritin; low level of: blood protein called albumin, sodium, magnesium)
- Convulsion, fits (seizures)
- Muscle spasms/cramping due to abnormally low level of blood salts including calcium
- Involuntary or uncontrollable movements
- Involuntary shaking of the body, difficulty writing, difficulty expressing thoughts verbally, impaired attention, sleepiness
- Tingling or numbness, difficulty moving because of nerve damage
- Decreased vision
- Thirst
- Weight loss
- Nerve pain
- Anxiety, irritability
- Severe state of confusion

- Difficulty sleeping
- Breathlessness, difficulty breathing when lying down, swelling of the feet or legs (possible symptoms of heart failure), stopped heart beat
- Swelling and pain due to blood clots
- Swelling due to fluids leaking from blood vessels into the surrounding tissue
- Bloating and discomfort (abdominal distension),due to an accumulation of fluid in the abdomen
- Dry mouth, sore mouth, bleeding in the mouth, inflammation in the gums
- Yellow skin and eyes due to abnormally high levels of bilirubin in the blood
- Itching
- Excessive sweating, night sweats
- Flu-like illness
- Failure of multiple organs

Uncommon: *may affect up to 1 in 100 people*
- Abnormal blood test results (high level of magnesium)
- Weakness or paralysis of limbs or face, difficulty speaking (possible symptoms of stroke as a result of reduced blood supply)
- Warm or rapidly reddening skin
- Cough that produces phlegm or sometimes blood, fever, shortness of breath or difficulty breathing
- Difficulty in controlling movement

Not known: *frequency cannot be estimated from the available data*
- Difficulty breathing or dizziness (possible symptoms of an allergic reaction)
- Weakness or numbness in the arms or legs, worsening of or loss of vision, having fixed and irrational thoughts that are not shared by others, headache, impaired memory or thinking, unusual behaviour

Reporting of side effects
If you get any side effects, talk to your doctor. This includes any possible side effects not listed in this leaflet. You can also report side effects directly (see below details). By reporting side effects, you can help provide more information on the safety of this medicine.

United Kingdom	Yellow Card Scheme Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store

5. How to store Kymriah

The following information is intended for doctors only.

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the infusion bag label after EXP.

Store and transport below -120°C. Do not thaw the product until it is ready to be used.

Do not use this medicine if the infusion bag is damaged or leaking.

This medicine contains genetically-modified blood cells. Local guidelines on handling of biological waste should be followed for unused medicine or waste material.

6. Contents of the pack and other information

What Kymriah contains

- The active substance of Kymriah is called tisagenlecleucel. Each infusion bag of Kmyriah contains tisagenlecleucel cell dispersion at a batch-dependent concentration of autologous T cells genetically modified to express an anti-CD19 chimeric antigen receptor (CAR-positive viable T cells). 1 or more bags contain a total of $1.2 \times 10^6 – 6 \times 10^8$ CAR+ viable T cells.
- The other ingredients are glucose, sodium chloride, human albumin solution, dextran 40 for injection, dimethylsulfoxide, sodium gluconate, sodium acetate, potassium chloride, magnesium chloride, sodium-N-acetyltryptophanate, sodium caprylate, aluminium, and water for injections. See section 2, “Kymriah contains sodium, dimethylsulfoxide (DMSO) and dextran 40”.

What Kymriah looks like and contents of the pack
Kymriah is a cell dispersion for infusion. It is supplied as an infusion bag containing a cloudy to clear, colourless to slightly yellow dispersion of cells. Each bag contains 10 mL to 50 mL of dispersion.

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Novartis Pharmaceuticals UK Limited
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Manufacturers
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For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

United Kingdom
Novartis Pharmaceuticals UK Ltd.
Tel: +44 1276 698370

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The following information is intended for healthcare professionals only:

Preparation of the infusion bag
The timing of thaw of Kymriah and of infusion should be coordinated. Confirm the infusion time in advance and adjust the start time for thaw so that Kymriah is available for infusion when the recipient is ready. Once Kymriah 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.

The infusion bag should be placed inside a second, sterile bag during thawing to protect ports from contamination and avoid spills in the unlikely event of the bag leaking. Kymriah should be thawed at 37°C using either a water bath or dry thaw method until there is no visible ice in the infusion bag. The bag should be removed immediately from the thawing device and kept at room temperature (20°C-25°C) until infusion. If more than one infusion bag has been received for the treatment dose (refer to the batch certificate for number of bags constituting one dose), the next bag should only be thawed after the contents of the preceding bag have been infused.

Kymriah should not be manipulated. For example, Kymriah should not be washed (spun down and resuspended in new media) prior to infusion.

The infusion bag(s) should be examined for any breaks or cracks prior to thawing. If the infusion bag appears to have been damaged or to be leaking, it should not be infused and should be disposed of according to local guidelines on handling of biological waste.

Administration
Kymriah intravenous infusion should be administered by a healthcare professional experienced with immunosuppressed patients and prepared to manage anaphylaxis. Ensure that one dose of tocilizumab per patient and emergency equipment are available prior to infusion and during the recovery period. Hospitals should have access to additional doses of tocilizumab within 8 hours.

The patient's identity should be matched with the patient identifiers on the infusion bag. Kymriah is for autologous use only. Kymriah should be administered as an intravenous infusion using latex-free intravenous tubing without a leukocyte depleting filter, at approximately 10 to 20 mL per minute by gravity flow. All contents of the infusion bags should be infused. Sterile sodium chloride 9 mg/mL (0.9%) solution for injection should be used to prime the tubing prior to infusion as well as rinse it afterwards. When the full volume of Kymriah has been infused, the 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.

Precautions to be taken before handling or administering Kymriah
Kymriah contains genetically-modified human blood cells. Local guidelines on handling of biological waste should be followed for disposal.

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 should be transported within the facility in closed, break-proof, leak-proof containers.

Kymriah is prepared from autologous blood of the patient collected by leukapheresis. Patient leukapheresis material and Kymriah may carry a risk of transmitting infectious viruses to healthcare professionals handling the product. Accordingly, healthcare professionals should employ appropriate precautions (wearing gloves and glasses) when handling leukapheresis material or Kymriah to avoid potential transmission of infectious diseases.