

KYMRIAH[®]

tisagenlecleucel

Consumer Medicine Information

WARNING: CYTOKINE RELEASE SYNDROME

Cytokine Release Syndrome (CRS), including fatal or life threatening reactions, occurred in patients receiving KYMRIAH. Do not administer KYMRIAH to patients with active infection or inflammatory disorders. Treat severe or life threatening CRS with tocilizumab as per the CRS management algorithm.

What is in this leaflet

This leaflet answers some common questions about KYMRIAH[®]. It does not contain all the available information. It does not take the place of talking to your doctor.

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 your (or your child's) doctor or nurse when you see them or if you go to hospital.

All medicines have risks and benefits. Your doctor has weighed the risks of you taking KYMRIAH[®] against the benefits they expect it will have for you.

If you have any concerns about taking this medicine, ask your doctor.

Keep this leaflet.

You may need to read it again.

What KYMRIAH[®] is used for

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

Kymriah is used to treat:

- B-cell precursor acute lymphoblastic leukaemia (B-cell ALL) that is refractory, in relapse

post-transplant, or in second or later relapse - a form of cancer that affects some types of white blood cells. It can be used in children and young adults up to 25 years of age with this cancer

- Relapsed or refractory diffuse large B-cell lymphoma (DLBCL) after two or more lines of systemic therapy - a form of cancer that affects some types of white blood cells, mostly in the lymph nodes. It can be used in adults (18 years of age or older) with this cancer. Kymriah is not indicated for patients with primary central nervous system lymphoma

How Kymriah works:

The T-cells are taken from your blood and are genetically modified so that they can find the cells causing your cancer. When Kymriah is infused into your blood, the modified T-cells will find the cancer cells and destroy them.

Ask your doctor if you have any questions about how Kymriah works or why this medicine has been prescribed for you.

Before you are given Kymriah

Follow all the doctor's instructions carefully. They may differ from the

general information contained in this leaflet.

When you must not take it

You should not receive Kymriah if you have an allergy to:

- tisagenlecleucel
- any of the ingredients listed at the end of this leaflet including dimethyl sulfoxide (DMSO) and dextran 40

If you think you may be allergic, ask your doctor for advice.

If you have not been previously exposed to dextran 40 or DMSO you should be observed closely during the first minutes of the infusion period.

Some of the symptoms of an allergic reaction may include:

- shortness of breath
- wheezing or difficulty breathing
- swelling of the face, lips, tongue or other parts of the body
- rash, itching or hives on the skin

Before receiving Kymriah

If any of these apply to you, tell your doctor before receiving Kymriah:

- 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, diarrhoea and bloody stools

- If you have/had any lung, heart or blood pressure (low or raised) problems, kidney problems or active central nervous system disorder
- If you notice the symptoms of your leukaemia worsening, such as fever, weakness, bleeding at the gums, bruising
- If you notice the symptoms of your lymphoma worsening, such as unexplained fever, weakness, night sweats, sudden weight loss
- If you have any infections. Your infection will be treated before the Kymriah infusion
- If you have ever had viral hepatitis B or C or HIV
- If you had a vaccination in the previous 6 weeks or are planning to have one in the next few months

Pregnancy

Kymriah is not recommended during pregnancy and in women of child-bearing potential who are not using contraception.

The effects of Kymriah in pregnant women are not known, but it may harm your unborn baby.

If you are pregnant, think you might be pregnant or are planning to have a baby, ask your doctor for advice before you receive this medicine.

Your doctor will discuss with you the potential risk(s) of receiving Kymriah during pregnancy.

The pregnancy status of women who may become pregnant should be verified before starting treatment and Kymriah should only be used if the result is negative.

Women of child-bearing potential should use highly effective (methods that result in less than 1% pregnancy rates) birth control after being given Kymriah. Ask your doctor about options of effective birth control.

If you become pregnant or think you are pregnant after treatment with Kymriah, tell your doctor right away.

If you are breastfeeding, ask your doctor for advice before receiving Kymriah.

Sexually active males treated with Kymriah should use a condom for intercourse.

Monitoring before your treatment with Kymriah:

Before you receive Kymriah infusion, your doctor will:

- Check your lungs, heart and blood pressure
- Look for signs of infection. Any active infection will be treated before administration of Kymriah
- Check if your cancer is getting worse
- Look for signs of a medical complication called “Graft versus Host Disease” that may occur after a transplant
- Check your blood for uric acid and for how many cancer cells there are in your blood. This will indicate 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 or C or HIV infection

Taking other medicines

Before you are administered Kymriah, tell your doctor if you are taking or have recently taken, or might take any other medicines, including medicines obtained without a prescription, because they can affect the way Kymriah works.

In particular, do not receive ‘live’ vaccines:

- in the 6 weeks before being given a short course of chemotherapy to prepare your body for the Kymriah cells (called “lymphodepleting” chemotherapy)
- during Kymriah treatment

- after treatment while the immune system is recovering

How you will receive Kymriah

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 manufacture Kymriah. It takes about 3 to 4 weeks to make Kymriah, but the time may vary. It is possible the manufacture of Kymriah may fail and cannot be used for your treatment

Medicines given before Kymriah administration

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.

Additional chemotherapy (not the lymphodepletion) may be necessary.

During the 30 to 60 minutes before being given Kymriah you may receive other medicines to help to reduce infusion reactions and/or fever. These may include paracetamol and an antihistamine.

How you are given Kymriah

- Prior to Kymriah infusion, your doctor will check that your identity matches with the patient identifiers on the Kymriah

infusion bag(s). Kymriah is made from your own white blood cells **and should only be given 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

Kymriah is given to you only once.

After you receive Kymriah

Plan to stay within 2 hours distance of where you were given your treatment for at least 4 weeks after you have been given Kymriah. Your doctor will check to see if your treatment is working and help you with any side effects.

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

Monitoring after your treatment with Kymriah

- 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 blood components
- Your doctor will regularly check for signs of cytokine release syndrome (CRS) or neurological problems

Things you must do

Tell your doctor immediately if you get any of these symptoms after administration of Kymriah:

- High fever and chills. These maybe symptoms of a serious condition called Cytokine Release Syndrome (CRS). Other symptoms of CRS include difficulty breathing, muscle pain, joint pain, nausea, vomiting, diarrhoea, low blood pressure, or dizziness/light-headedness. When occurring, these

symptoms are almost always noticed within the first 10 days after infusion, but can occur later

- If you experience neurological problems like altered or decreased consciousness, delirium, confusion, agitation, seizures, difficulty speaking and understanding speech or loss of balance. This is usually in the first 8 weeks after the infusion, but it can occur later as well
- If you experience feeling warm, fever, chills or shivering, sore throat or mouth ulcers. These can be symptoms of an infection

If you are about to be started on any new medicine, remind your doctor and pharmacist that you have received Kymriah.

Tell any other doctors, dentists, and pharmacists who treat you that you have received Kymriah.

If you are going to have surgery, tell the surgeon or anaesthetist that you have received this medicine.

It may affect other medicines used during surgery.

If you are about to have any blood tests, tell your doctor that you have received this medicine.

It may interfere with the results of some types of HIV tests.

Keep all of your doctor's appointments so that your progress can be checked.

Things you must not do

Do not drive, operate heavy machinery, or engage in activities that you need to be alert for. Kymriah can cause neurological problems such as altered or decreased consciousness, confusion and seizures in the 8 weeks following the Kymriah infusion.

Do not donate blood, organs, tissues and cells for transplants.

Side effects - acute lymphoblastic leukaemia (ALL)

This medicine helps most people with ALL, but it may have unwanted side effects in a few people. All medicines can have side effects. Sometimes they are serious, most of the time they are not. You may need medical attention if you get some of the side effects.

Do not be alarmed by the following lists of side effects. You may not experience any of them.

Some side effects could be serious.

If you experience any serious side effects, **tell your doctor immediately.**

Very common: *may affect more than 1 in 10 people*

- Feeling warm, fever, chills or shivering (possible symptoms of a viral, fungal, bacterial or unspecified pathogen infection)
- Spontaneous bleeding or bruising (possible symptoms of low level of blood platelets)
- Frequent infections, weakness, fever, chills, sore throat or mouth ulcers due to infections (possible symptoms of low level of white blood cells or febrile neutropenia)
- Weakness, spontaneous bleeding or bruising and frequent infections, fever, chills, and sore throat (possible symptoms of low level of red blood cells)
- High fever, chills, muscle pain, joint pain, nausea, vomiting, loss of appetite, fatigue, headache, dizziness, light-headedness, personality changes, confusion, paralysis of part or all of the body, stiff neck, abnormal speech or eye movements, shortness of breath, heavy breathing, rapid breathing, blue discolouration of lips or extremities (possible symptoms of CRS)

- Muscle weakness, muscle spasms, abnormal heart rhythm (possible symptoms of low level of potassium in the blood)
 - Swollen ankles (possible symptom of low level of albumin in the blood)
 - Personality changes, headache, confusion, paralysis of part or all of the body, stiff neck, abnormal speech and eye movements (possible symptoms of encephalopathy)
 - State of severe confusion (delirium)
 - Dizziness, light headedness (possible symptoms of hypotension)
 - Blue discolouration of lips or extremities (hypoxia)
 - Breathlessness (possible symptom of pulmonary oedema)
 - Severely decreased urine output (possible symptom of acute kidney injury)
- Common:** *may affect up to 1 in every 10 people*
- Blood clotting, internal and external bleeding (possible symptoms of disseminated intravascular coagulation)
 - A syndrome of pathologic immune activation characterized by clinical signs and symptoms of extreme inflammation (Histiocytosis haematophagic)
 - Rash (possible symptom of GvHD)
 - Producing less urine than normal and/or muscle spasms, possible symptoms of an increase in potassium, phosphate and uric acid in the blood that can cause kidney problems (possible symptoms of tumour lysis syndrome)
 - Convulsion, fits (seizures)
 - Severe headache, weakness or paralysis of limbs or face, difficulty speaking, sudden loss of consciousness (signs of bleeding or swelling in the brain – possible symptoms of cerebral haemorrhage)
 - Breathlessness, difficulty breathing when lying down, swelling of the feet or legs (possible symptoms of heart failure)
 - Stopped heart beat (cardiac arrest)
 - Swelling and oedema (possible symptoms of capillary leak syndrome in context of CRS)
 - Bleeding in the mouth (mouth haemorrhage)
 - Abdominal swelling (sign of fluid accumulations in the abdomen – possible symptom of ascites)
 - Transient enlargement of organs (possible symptom of abdominal compartment syndrome)
 - High fever, chills, difficulty to breath, yellow skin and eyes, bloody stools, severely decreased urine output (possible symptoms of multiple organ dysfunction syndrome)
 - Swelling of limbs, face or generalized swelling (face or peripheral or generalized oedema)
 - Thirst, low urine output, dark urine, dry flushed skin, irritability (possible symptoms of high level of sugar in blood)
 - Excessive emotional distress (anxiety)
 - Headache
 - Altered state of consciousness
 - Fast heart beat (tachycardia)
 - Headache, dizziness (possible symptoms of hypertension)
 - Cough
 - Nose bleeding
 - Fluid collection on the lungs/chest cavity, which if severe, could make you breathless (pleural effusion)
 - Rapid breathing, shortness of breath (tachypnoea)
 - Vomiting
 - Diarrhoea
 - Nausea
 - Abdominal pain
 - Constipation
 - Rash
 - Pain in muscles, bones or joints (musculoskeletal pain, myalgia, arthralgia)
 - Pain in extremity
 - Back pain
 - Fever
 - Tiredness (fatigue)
 - Chills
 - Abnormal liver blood test result (high level of an enzyme called alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) and/or high levels of bilirubin that gives information about the health of the liver)
 - Abnormal kidney blood test result (high level of creatinine in the blood)
 - Decreased immunoglobulins in your blood that will lead to frequent and persistent infections.
- Other possible side effects**
- Other side effects include the following listed below. If these side effects become severe, please tell your doctor.
- Very common:** *may affect more than 1 in 10 people*
- Loss of appetite
 - Abnormal blood test results (possible symptoms of low level or high of phosphate in the blood, high level of uric acid in the blood, low level of magnesium in the blood)
 - Reduced level of calcium in the blood, sometimes leading to cramps
 - Shortness of breath, laboured breathing, breathlessness (possible symptoms of Fluid overload)

- Defect in blood clotting (International Normalized Ratio increased, prothrombin time prolonged (common), blood fibrinogen decreased (common), coagulopathy, activated partial thromboplastin time prolonged (common))

Common: *may affect up to 1 in every 10 people*

- Dizziness
- Involuntary shaking of the body (tremor)
- Impaired memory or thinking (cognitive disorders)
- Difficulty in speaking or understanding speech (dysphasia)
- Hot flushes
- Itching (pruritus)
- Skin reddening (erythema)
- Excessive sweating (hyperhidrosis)
- Red or purple, flat, pinhead spots under the skin (petechiae)
- Red raised rash (rash maculopapular)
- Rash – flat, small red patches on the skin (rash, macular)
- Cough, difficulty breathing, painful breathing (possible symptoms of interstitial lung disease)
- Bloating (abdominal distension)
- Yellow skin and eyes (possible symptoms of high level of bilirubin in the blood)
- Blood in urine (haematuria)
- Difficulty and pain when passing urine (dysuria)

If you or your child notice any side effects not listed in this leaflet, please inform your doctor.

Some of these side effects (for example defect in blood clotting and decreased immunoglobulins) can only be found when your doctor does tests from time to time to check your progress.

Side effects – diffuse large B-cell lymphoma (DLBCL)

This medicine helps most people with DLBCL, but it may have unwanted side effects in a few people. All medicines can have side effects. Sometimes they are serious, most of the time they are not. You may need medical attention if you get some of the side effects.

Do not be alarmed by the following lists of side effects. You may not experience any of them.

Some side effects could be serious.

If you experience any serious side effects, **tell your doctor immediately.**

Very common: *may affect more than 1 in 10 people*

- Feeling warm, fever, chills or shivering (possible symptoms of an unspecified pathogen, bacterial or fungal infections)
- Spontaneous bleeding or bruising (possible symptoms of low level of blood platelets)
- Frequent infections, weakness, fever, chills, sore throat or mouth ulcers due to infections (possible symptoms of low level of white blood cells or febrile neutropenia or immunodeficiency)
- Weakness, spontaneous bleeding or bruising and frequent infections, fever, chills, and sore throat (possible symptoms of low level of red blood cells)
- High fever, chills, muscle pain, joint pain, nausea, vomiting, loss of appetite, fatigue, headache, dizziness, light-headedness, personality changes, confusion, paralysis of part or all of the body, stiff neck, abnormal speech or eye movements, shortness of breath, heavy breathing, rapid breathing, blue discolouration of lips or extremities (possible symptoms of CRS)

- Personality changes, headache, confusion, paralysis of part or all of the body, stiff neck, abnormal speech and eye movements (possible symptoms of encephalopathy or metabolic encephalopathy)
- Muscle weakness, muscle spasms, abnormal heart rhythm (possible symptoms of low level of potassium in the blood)
- Dizziness, light headedness (possible symptoms of hypotension)
- Swelling of limbs (oedema peripheral)
- Severely decreased urine output (possible symptom of acute kidney injury)

Common: *may affect up to 1 in every 10 people*

- Viral infections
- Blood clotting, internal and external bleeding (possible symptoms of disseminated intravascular coagulation)
- Swollen ankles (possible symptom of low level of albumin in the blood)
- Tiredness, confusion, muscle twitching, convulsions (possible symptoms of low level of sodium in blood)
- A syndrome of pathologic immune activation characterized by clinical signs and symptoms of extreme inflammation (histiocytosis haematophagic)
- Producing less urine than normal and/or muscle spasms, possible symptoms of an increase in potassium, phosphate and uric acid in the blood that can cause kidney problems (possible symptoms of tumour lysis syndrome)
- State of severe confusion (delirium)
- Weakness or paralysis of limbs or face, difficulty speaking (possible symptoms of ischemic cerebral infarction)

- Convulsion, fits (seizures)
- Severe nerve pain (neuralgia)
- Irregular heart beat (possible symptom of atrial fibrillation)
- Breathlessness, difficulty breathing when lying down, swelling of the feet or legs (possible symptoms of heart failure)
- Blue discolouration of lips or extremities (hypoxia)
- Swelling and oedema (possible symptoms of capillary leak syndrome in context of CRS)
- High fever, chills, difficulty to breath, yellow skin and eyes, bloody stools, severely decreased urine output (possible symptoms of multiple organ dysfunction syndrome)

Other possible side effects

Other side effects include the following listed below. If these side effects become severe, please tell your doctor.

Very common: *may affect more than 1 in 10 people*

- Loss of appetite
- Weight loss
- Abnormal blood test results (possible symptoms of low level of phosphate in the blood)
- Abnormal kidney blood test result (high level of creatinine in the blood)
- Fast heart beat (tachycardia)
- Headache
- Dizziness
- Cough
- Shortness of breath, laboured breathing (dyspnoea)
- Diarrhoea
- Nausea
- Constipation
- Joints pain (arthralgia) Pain including pain in extremity
- Fever
- Tiredness (fatigue)

- Chills
- Excessive emotional distress (anxiety)

Common: *may affect up to 1 in every 10 people*

- Abnormal blood test results (possible symptoms of low level of magnesium in the blood, high level of an enzyme called blood alkaline phosphatase, high level of fibrin d-dimer, high level of serum ferritin)
- Reduced level of calcium in the blood, sometimes leading to cramps
- Thirst, low urine output, dark urine, dry flushed skin, irritability (possible symptoms of high level of sugar in blood)
- Abnormal liver blood test result (high level of an enzyme called aspartate aminotransferase (AST) that gives information about the health of the liver)
- Yellow skin and eyes (possible symptoms of high level of bilirubin in the blood)
- Decreased immunoglobulins in your blood that will lead to frequent and persistent infections
- Fluid collection on the lungs/chest cavity, which if severe, could make you breathless (pleural effusion)
- Headache, dizziness (possible symptoms of hypertension)
- Involuntary shaking of the body (tremor)
- Difficulty in speaking or understanding speech (dysphasia)
- Tingling or numbness (paresthesia)
- Bloating (abdominal distension)
- Dry mouth
- Mouth sores (stomatitis)
- Weakness (asthenia)
- Vomiting
- Itching (pruritus)
- Rash

- Skin reddening (erythema)
- Excessive sweating (hyperhidrosis)
- Red or purple, flat, pinhead spots under the skin (petechiae)
- Red raised rash (rash popular)
- Night sweats
- Pain in muscles, or bones (musculoskeletal pain, myalgia)
- Back pain
- Tiredness, chills, sore throat, joint or muscles aching (possible symptoms of influenza-like illness)
- Abdominal pain

If you notice any side effects not listed in this leaflet, please inform your doctor.

Some of these side effects (for example low level of phosphate in the blood and decreased immunoglobulins) can only be found when your doctor does tests from time to time to check your progress.

Product description

What it looks like

Kymriah is supplied as an infusion bag containing a cloudy to clear, colourless to slightly yellow suspension of cells (tisagenlecleucel). Each bag contains 10 mL to 50 mL of the suspension. Kymriah is stored at or below minus 120°C. The product is thawed at bedside when it is ready to be used.

Ingredients

The active substance of Kymriah is called tisagenlecleucel. Each infusion bag of Kymriah contains tisagenlecleucel cell suspension at a batch-dependent concentration of autologous T cells genetically modified to express an anti-CD19 chimeric antigen receptor (CAR-positive viable T cells). 1-3 bags contain a total of $1.2.0 \times 10^6$ -

6.0 x 10⁸ CAR-positive viable t-cells.

Internal document code:
kym131218c based on kym131218i

The cryo-media solution contains:

- Potassium
- Magnesium
- Sodium
- Aluminium
- Acetate
- Chloride
- Dextran 40
- Glucose
- Albumin (HSA)
- Dimethyl sulfoxide (DMSO)
- Dimethyl sulfone
- D-gluconic acid
- Acetytryptophan
- Hydroxymethylfurfural
- Caprylate

This medicine does not contain lactose, sucrose, gluten, tartrazine or any other azo dyes.

Kymriah contains 24.3 to 121.5 mg sodium per dose, equivalent to 1% to 6% of the WHO recommended maximum daily intake of 2 g sodium for an adult.

Kymriah contains potassium, less than 1 mmol (39mg) per dose, ie essentially “potassium free.”

Sponsor

Kymriah is supplied in Australia by:

Novartis Pharmaceuticals Australia
Pty Limited

(ABN 18 004 244 160)

54 Waterloo Road

Macquarie Park NSW 2113

Telephone 1 800 671 203

Website: www.novartis.com.au

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