Medicines & Healthcare products Regulatory Agency

MHRA

Early Access to Medicines Scheme – Treatment protocol – Information for patients

Introduction

The aim of the Early Access to Medicines Scheme (EAMS) is to provide earlier availability of promising new unlicensed medicines (medicines that do not have a marketing authorisation or are used outside their licence) to UK patients that have a high unmet clinical need. The medicines included in the scheme are those that are intended to treat, diagnose or prevent seriously debilitating or life-threatening conditions where there are no adequate treatment options. More information about the scheme can be found here:
http://www.mhra.gov.uk/Howweregulate/Innovation/EarlyaccesstomedicinesschemeEAMS/index.htm

The information below is intended for you, the patient, and is provided by the pharmaceutical company (called scientific opinion holder) that manufactures the EAMS medicine. This medicine, which is used outside its licence, is already authorised in several cancers such as melanoma, lung, kidney, bladder, head and neck cancers. More information about medicines licensing can be found here:
http://www.nhs.uk/conditions/medicines-information

This medicine can be prescribed for individual patients to meet specific needs provided they are given sufficient information about the medicine to make an informed decision. Your physician will be responsible for giving you all the information you need to make this decision and for obtaining informed consent from you prior to treatment. You will be asked to sign a form to confirm that you are providing informed consent to receiving the EAMS treatment. Information on consent can be found here:
https://www.nhs.uk/conditions/Consent-to-treatment

The information below is provided to help you decide with your physician on whether to use the EAMS medicine and helps explain how to use it in accordance with the pharmaceutical company's instructions for safe and proper use. A positive scientific opinion is not a recommendation for use of the medicine and should not be interpreted as such. Under EAMS the risk and legal responsibility for prescribing the medicine remains with the physician, and the opinion and EAMS documentation published by the MHRA are intended only to inform physicians' decision making and not to recommend use. An EAMS scientific opinion does not affect the civil liability of the manufacturer or any physician in relation to the product.

The information below may change during the time you are using the medicine if more data become available. Your physician will highlight to you any changes that you need to be aware of.

Whilst you are using this medicine, data will be collected on the use and safety profile of the medicine, to ensure that the benefits of taking the medicine continue to outweigh any potential risks. Your physician will answer all your questions during and after the treatment and will provide you with contact details that you should use in case of any events or problems.

Each patient enrolled in the scheme will continue to receive the EAMS product until the end of the treatment in line with prescribing and NHS guidance and as long as benefit is seen. In rare cases where the EAMS treatment may not be available anymore, your physician will discuss other options with you.

Information for the patient

NIVOLUMAB 10 mg/mL concentrate for solution for infusion

Read all of this leaflet carefully before you are given this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- It is important that you keep the Alert Card with you during treatment.
- If you have any further questions, ask your doctor or nurse.
- If you get any side effects, talk to your doctor or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What NIVOLUMAB is and what it is used for

NIVOLUMAB is a medicine used to treat: advanced oesophageal cancer (gullet cancer) in adults.

It contains the active substance nivolumab, which is a monoclonal antibody, a type of protein designed to recognise and attach to a specific target substance in the body.

NIVOLUMAB attaches to a target protein called programmed death-1 receptor (PD-1) that can switch off the activity of T cells (a type of white blood cell that forms part of the immune system, the body's natural defences). By attaching to PD-1, nivolumab blocks its action and prevents it from switching off your T cells. This helps increase their activity against the oesophageal cancer cells.

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

You must not be given NIVOLUMAB
- if you are **allergic** to nivolumab or any of the other ingredients of this medicine (listed in section 6 "Contents of the pack and other information"). **Talk to your doctor** if you are not sure.

Warnings and precautions
Talk to your doctor before using NIVOLUMAB as it may cause:
- **Problems with your heart** such as a change in the rhythm or rate of the heartbeat or an abnormal heart rhythm.
- **Problems with your lungs** such as breathing difficulties or cough. These may be signs of inflammation of the lungs (pneumonitis or interstitial lung disease).
- **Diarrhoea** (watery, loose or soft stools) or any symptoms of **inflammation of the intestines** (colitis), such as stomach pain and mucus or blood in stool.
- **Inflammation of the liver (hepatitis).** Signs and symptoms of hepatitis may include abnormal liver function tests, eye or skin yellowing (jaundice), pain on the right side of your stomach area, or tiredness.
- **Inflammation or problems with your kidneys.** Signs and symptoms may include abnormal kidney function tests, or decreased volume of urine.
- **Problems with your hormone producing glands** (including the pituitary, the thyroid, the parathyroid and adrenal glands) that may affect how these glands work. Signs and symptoms that these glands are not working properly may include fatigue (extreme tiredness), weight change or headache, decreased blood levels of calcium and visual disturbances.

- **Diabetes** (symptoms include excessive thirst, the passing of a greatly increased amount of urine, increase in appetite with a loss of weight, feeling tired, drowsy, weak, depressed, irritable and generally unwell) or **diabetic ketoacidosis** (acid in the blood produced from diabetes).
- **Inflammation of the skin** that can lead to severe skin reaction (known as toxic epidermal necrolysis and Stevens-Johnson syndrome). Signs and symptoms of severe skin reaction may include rash, itching, and peeling of the skin (possibly fatal).
- **Inflammation of the muscles** such as myocarditis (inflammation of the heart muscle), myositis (inflammation of the muscles) and rhabdomyolysis (stiffness in muscles and joints, muscle spasm). Signs and symptoms may include muscle pain, stiffness, weakness, chest pain, or severe fatigue.
- **Solid organ transplant rejection.**
- **Haemophagocytic lymphohistiocytosis,** a rare disease in which our immune system makes too many of otherwise normal infection fighting cells called histiocytes and lymphocytes. Symptoms may include enlarged liver and/or spleen, skin rash, lymph node enlargement, breathing problems, easy bruising, kidney abnormalities, and heart problems.

Tell your doctor immediately if you have any of these signs or symptoms or if they get worse. **Do not try to treat your symptoms with other medicines on your own.** Your doctor may
- give you other medicines in order to prevent complications and reduce your symptoms,
- withhold the next dose of NIVOLUMAB,
- or stop your treatment with NIVOLUMAB altogether.

Please note that these signs and symptoms are **sometimes delayed**, and may develop weeks or months after your last dose. Before treatment, your doctor will check your general health. You will also have **blood tests** during your treatment.

Check with your doctor or nurse before you are given NIVOLUMAB if:
- you have an **autoimmune disease** (a condition where the body attacks its own cells);
- you have been told that your **cancer has spread to your brain;**
- you have any history of **inflammation of the lungs**;
- you have been taken **medicines to suppress your immune system.**

Children and adolescents
NIVOLUMAB should not be used in children and adolescents below 18 years of age.

Other medicines and NIVOLUMAB
Before you are given NIVOLUMAB, tell your doctor if you are taking any medicines that suppress your immune system, such as corticosteroids, since these medicines may interfere with the effect of NIVOLUMAB. However, once you are treated with NIVOLUMAB, your doctor may give you corticosteroids to reduce any possible side effects that you may have during your treatment and this will not impact the effect of the medicine.

Tell your doctor if you are taking or have recently taken any other medicines. **Do not take any other medicines** during your treatment without talking to your doctor first.

Contraception, pregnancy and breast-feeding
Tell your doctor if you are pregnant or think you might be, if you are planning to become pregnant, or if you are breast-feeding.

Do not use NIVOLUMAB if you are pregnant unless your doctor specifically tells you to. The effects of NIVOLUMAB in pregnant women are not known, but it is possible that the active substance, nivolumab, could harm an unborn baby.
- You must use **effective contraception** while you are being treated with NIVOLUMAB and for at least 5 months following the last dose of NIVOLUMAB, if you are a woman who could become pregnant.
- If you become pregnant while using NIVOLUMAB **tell your doctor**.

It is not known whether nivolumab gets into breast milk. A risk to the breast-fed infant cannot be excluded. **Ask your doctor** if you can breast-feed during or after treatment with NIVOLUMAB.

Driving, cycling and using machines
NIVOLUMAB may have a minor influence on the ability to drive and use machines; however, use caution when performing these activities until you are sure that nivolumab does not adversely affect you.

NIVOLUMAB contains sodium
Tell your doctor if you are on a low-sodium (low-salt) diet before you are given NIVOLUMAB. This medicine contains 2.5 mg sodium (main component of cooking/table salt) in each mL of concentrate. NIVOLUMAB contains 25 mg sodium per 10 ml vial, which is equivalent to 1.25% of the recommended maximum daily dietary intake of sodium for an adult.

You will also find key messages from this Treatment Protocol in the patient alert card you have been given by your doctor. It is important that you keep this patient alert card and show it to your partner or caregivers.

3. How NIVOLUMAB is given

You will receive treatment with NIVOLUMAB in a hospital or clinic, under the supervision of an experienced doctor.

How much NIVOLUMAB is given
The recommended dose is 240 mg given every 2 weeks
The dose of NIVOLUMAB will be diluted with sodium chloride 9 mg/mL (0.9%) solution for injection or glucose 50 mg/mL (5%) solution for injection before use.

NIVOLUMAB will be given to you as an infusion (a drip) into a vein (intravenously) over a period of 30 minutes, every 2 weeks. Your doctor will continue giving you NIVOLUMAB for as long as you keep benefitting from it or until you no longer tolerate the treatment.

If you miss a dose of NIVOLUMAB
It is very important for you to keep all your appointments to receive NIVOLUMAB. If you miss an appointment, ask your doctor when to schedule your next dose.

If you stop receiving NIVOLUMAB
Stopping your treatment may stop the effect of the medicine. Do not stop treatment with NIVOLUMAB unless you have discussed this with your doctor.

If you have any further questions about your treatment or on the use of this medicine, ask your doctor.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them. The following side effects have been reported with this medicine:

Be aware of important symptoms of inflammation. NIVOLUMAB acts on your immune system and may cause inflammation in parts of your body. Inflammation may cause serious damage to your body and some inflammatory conditions may be life-threatening and need treatment or withdrawal of nivolumab.

The following side effects have been reported **with nivolumab:**

Very common (may affect more than 1 in 10 people)
- Decrease in some white blood cells
- Diarrhoea (watery, loose or soft stools), nausea
- Skin rash sometimes with blisters, itching
- Feeling tired or weak

Common (may affect up to 1 in 10 people)
- Infections of the upper respiratory tract
- Serious lung infection (pneumonia)
- Allergic reaction, reactions related to the infusion of the medicine
- Underactive thyroid gland (which can cause tiredness or weight gain), overactive thyroid gland (which can cause rapid heart rate, sweating and weight loss)
- Decreased appetite
- Inflammation of the nerves (causing numbness, weakness, tingling or burning pain of the arms and legs), headache, dizziness

- High blood pressure (hypertension)
- Inflammation of the lungs (pneumonitis, characterised by coughing and difficulty breathing), shortness of breath (dyspnoea), cough
- Inflammation of the intestines (colitis), mouth ulcers and cold sores (stomatitis), vomiting, stomach pain, constipation, dry mouth
- Skin colour change in patches (vitiligo), dry skin, redness of the skin, unusual hair loss or thinning
- Pain in the muscles, bones (musculoskeletal pain) and joints (arthralgia)
- Fever, oedema (swelling)

Uncommon (may affect up to 1 in 100 people)

- Bronchitis
- Increase in some white blood cells
- Decreased secretion of hormones produced by adrenal glands (glands situated above the kidneys), underactive function (hypopituitarism) or inflammation (hypophysitis) of the pituitary gland situated at the base of the brain, swelling of the thyroid gland, diabetes
- Dehydration, increased acid levels in the blood
- Damage to nerves causing numbness and weakness (polyneuropathy), inflammation of the nerves caused by the body attacking itself, causing numbness, weakness, tingling or burning pain (autoimmune neuropathy)
- Inflammation of the eye (which causes pain and redness), blurred vision, dry eyes
- Fast heart rate, inflammation of the covering of the heart and accumulation of fluid around the heart (pericardial disorders)
- Fluid around the lungs
- Inflammation of the pancreas (pancreatitis), inflammation of the stomach (gastritis)
- Inflammation of the liver (hepatitis)
- Severe condition of the skin that causes red, often itchy spots, similar to the rash of measles, which starts on the limbs and sometimes on the face and the rest of the body (erythema multiforme), skin disease with thickened patches of red skin, often with silvery scales (psoriasis), skin condition of the face where the nose and cheeks are unusually red (rosacea), hives (itchy, bumpy rash)
- Inflammation of the muscles causing pain or stiffness (polymyalgia rheumatica), inflammation of the joints (arthritis)
- Inflammation of the kidney, kidney failure (including abrupt loss of kidney function)
- Pain, chest pain

Rare (may affect up to 1 in 1000 people)

- A disease causing the inflammation or enlargement of a lymph node (Kikuchi lymphadenitis)
- Life-threatening allergic reaction
- Acid in the blood produced from diabetes (diabetic ketoacidosis)
- A temporary inflammation of the nerves that causes pain, weakness, and paralysis in the extremities (Guillain- Barré syndrome), loss of the protective sheath around nerves (demyelination), a condition in which the muscles become weak and tire easily (myasthenic syndrome)
- Inflammation of the brain
- Changes in the rhythm or rate of the heartbeat, abnormal heart rhythm, inflammation of the heart muscle
- Inflammatory disease of blood vessels
- Fluid in the lungs
- Ulcer of the small intestines
- Blockage of bile ducts
- Severe and possibly fatal peeling of the skin (toxic epidermal necrolysis or Stevens-Johnson syndrome)
- Disease in which the immune system attacks the glands that make moisture for the body, such as tears and saliva (Sjogren's syndrome), aching muscles, muscle tenderness or weakness, not caused by exercise (myopathy), inflammation of the muscles (myositis), stiffness in muscles and joints, muscle spasm (rhabdomyolysis)

Other side effects that have been reported (frequency not known) with nivolumab:

- Solid organ transplant rejection
- A group of metabolic complications occurring after cancer treatment characterised by high blood levels of potassium and phosphate, and low blood levels of calcium (tumour lysis syndrome)

- An inflammatory disorder (most likely of autoimmune origin) affecting the eyes, skin and the membranes of the ears, brain and spinal cord (Vogt-Koyanagi-Harada syndrome)
- Inflammation of the covering of the heart and accumulation of fluid around the heart (pericardial disorders)
- Decreased function of the parathyroid gland
- Chronic diseases associated with a build-up of inflammatory cells in various organs and tissues, most commonly the lungs (sarcoidosis)
- Temporary and reversible non-infectious inflammation of the protective membranes surrounding the brain and spinal cord (aseptic meningitis)
- A condition where the immune system makes too many infection-fighting cells called histiocytes and lymphocytes that may cause various symptoms (called haemophagocytic lymphohistiocytosis)

Tell your doctor immediately if you get any of the side effects listed above. Do not try to treat your symptoms with other medicines on your own.

Changes in test results
NIVOLUMAB may cause changes in the results of tests carried out by your doctor. These include:
- Abnormal liver function tests (increased amounts of the liver enzymes aspartate aminotransferase, alanine aminotransferase or alkaline phosphatase in your blood, higher blood levels of the waste product bilirubin)
- Abnormal kidney function tests (increased amounts of creatinine in your blood)
- High (hyperglycaemia) or low (hypoglycaemia) sugar levels in the blood
- A decreased number of red blood cells (which carry oxygen), white blood cells (which are important in fighting infection) or platelets (cells which help the blood to clot)
- An increased level of the enzyme that breaks down fats and of the enzyme that breaks down starch
- Increased or decreased amount of calcium or potassium
- Increased or decreased blood levels of magnesium or sodium
- Decrease in body weight

5. How to store NIVOLUMAB

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 carton and the vial label after EXP. The expiry date refers to the last day of that month.

Store in a refrigerator (2°C to 8°C).
Do not freeze.
Store in the original package in order to protect from light.
The unopened vial can be stored at controlled room temperature up to 25°C with room light for up to 48 hours.

Do not store any unused portion of the infusion solution for reuse. Any unused medicine or waste material should be disposed of in accordance with local requirements

6. Contents of the pack and other information

What NIVOLUMAB contains
- The active substance is nivolumab.
  Each mL of concentrate for solution for infusion contains 10 mg of nivolumab.
  Each vial contains100 mg (in 10 mL) of nivolumab.

- The other ingredients are sodium citrate dihydrate, sodium chloride (see section 2 "NIVOLUMAB contains sodium"), mannitol (E421), pentetic acid, polysorbate 80, sodium hydroxide, hydrochloric acid and water for injections.

What NIVOLUMAB looks like and contents of the pack
NIVOLUMAB concentrate for solution for infusion (sterile concentrate) is a clear to opalescent, colourless to pale yellow liquid that may contain few light particles.

It is available in packs containing 1 vial of 10 mL.

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This protocol was revised in June 2020

Additional information

Informed Consent Form
This document will be explained to the patient thoroughly before their treatment commences. The patient will be requested to sign the form and a copy will be given to them to keep.

Patient Alert Card
This will be given to all patients before starting treatment. It is a wallet-sized card to be carried at all times by the patient to inform Healthcare Professionals that the patient is receiving treatment with nivolumab. It contains important information on the main symptoms of the important adverse reactions and highlights the importance of notifying their treating physician immediately if symptoms occur, persist or worsen and also the importance of not attempting to self-treat any symptoms without consulting with their Healthcare Professional first.

Patient data to be collected
Patient data collected during the scheme are mostly used for safety surveillance and cannot replace a proper clinical trial to support a marketing authorisation. These data are required by the MHRA to help verify that the patient's condition complies with the EAMS indication and help interpret the side effects and other events occurring during and after the EAMS treatment. These data include:

- Unique Patient EAMS Number (England Only)
- Age/year of birth
- Gender
- Race
- Weight
- Fitness status
- Condition which the product is being used for (including tumour type and location)
- Medical history, including:
  - any prior treatments received for oesophageal cancer
  - any prior surgery for oesophageal cancer
- Other details about patient's oesophageal cancer (including sites of metastasis)
- Other ongoing conditions other than oesophageal cancer

- Any medication taken during treatment with nivolumab
- Information on how many doses of nivolumab are received
- All side effects

Additional data will be collected on clinical efficacy and quality of life on a voluntary basis and subject to additional patient consent. These data include:

- Patient disease progression status
- Date of progression for patients who progressed
- How long the patient is free of disease progression
- Patient survival status
- Patient quality of life
- Date and primary cause of death for deceased patients

The reasons for collecting these additional data are to understand the patient needs, the patient characteristics and to understand how the use of nivolumab in a real-world setting may differ from a clinical trial setting. The data may also be used to provide additional evidence for health technology appraisals for this product.

Contact information

Bristol-Myers Squibb Medical Information on 0800 731 1736 or medical.information@bms.com