Medicines & Healthcare products Regulatory Agency

MHRA

Early Access to Medicines Scientific Opinion - Public Assessment Report	
Product	**Nivolumab 10 mg/mL concentrate for solution for infusion**
EAMS indication	**Nivolumab is used in combination with chemotherapy to treat adults with cancer (adenocarcinoma) of the oesophagus (gullet) or stomach (including cancer of the junction between the oesophagus and stomach) that has spread beyond the oesophagus or stomach (advanced cancer). Nivolumab is used in patients who have not received other treatments for advanced cancer of the oesophagus or stomach. Patients with oesophagus or stomach cancer that is known to be 'HER2-positive' (the cancer cell surface contains a target protein called 'human epidermal growth factor receptor 2') should not receive nivolumab.**
Company	**Bristol-Myers Squibb Pharma EEIG**
EAMS number	**15105/0015**
EAMS Scientific Opinion date	**13 August 2021**

WITHDRAWN

Introduction
The aim of the Early Access to Medicines Scheme (EAMS) is to provide earlier availability of promising new unlicensed medicines and medicines used outside their licence, to UK patients that have a high unmet clinical need. The MHRA scientific opinion provides benefit and risk information to physicians who may wish to prescribe the EAMS medicine under their own responsibility. More information about the scheme can be found here:
http://www.mhra.gov.uk/Howweregulate/Innovation/EarlyaccesstomedicinesschemeEAMS/index.htm

The scientific opinion is based on assessment of the information supplied to the MHRA on the benefits and risks of the medicine. As such this is a scientific opinion and should not be regarded as a medicine licensed by the MHRA or a future commitment by the MHRA to license such a medicine, nor should it be regarded as an authorisation to sell or supply such a medicine. 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 a 'special' 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 General Medical Council's guidance on prescribing unlicensed medicines can be found here:
https://www.gmc-uk.org/guidance/ethical_guidance/14327.asp

What is nivolumab?
Nivolumab is the active substance of a medicine, which is given by infusion via a drip into a vein. It is supplied as a solution which can be given as it is, or diluted in an infusion bag containing a sodium chloride solution or glucose solution before use.

What is nivolumab used to treat?
Nivolumab is used in combination with chemotherapy to treat adults with cancer (adenocarcinoma) of the oesophagus (gullet) or stomach (including cancer of the junction between the oesophagus and

stomach) that has spread beyond the oesophagus or stomach (advanced cancer). Nivolumab is used in patients who have not received other treatments for advanced cancer of the oesophagus or stomach. Patients with oesophagus or stomach cancer that is known to be 'HER2-positive' (the cancer cell surface contains a target protein called 'human epidermal growth factor receptor 2') should not receive nivolumab.

How is nivolumab used?
Treatment with nivolumab should be started and supervised by a specialist doctor who is experienced in the treatment of cancer. The doctor will carry out blood tests before and during treatment to monitor the patient. Nivolumab will be given in a hospital or clinic.

Nivolumab treatment is combined with chemotherapy treatment. Chemotherapy drugs are anti-cancer drugs that disrupt the way cancer cells grow and divide (cytotoxic). The chemotherapy treatment should include the drug types known as 'fluoropyrimidines' and 'platinum'.

A nivolumab dose of 240 mg every 2 weeks or 360 mg every 3 weeks is given by infusion into a vein over a period of 30 minutes. The dose and timing are chosen to fit in with the timings of the chemotherapy course. The nivolumab infusion is repeated until the cancer gets worse (progresses), or unacceptable side-effects occur. The maximum treatment duration is 24 months.

The dose is not adjusted in older patients (at least 65 years of age), patients with mild or moderate kidney problems and patients with mild liver problems. There is not enough evidence to recommend the use of nivolumab in children and adolescents below the age of 18 years.

Nivolumab can cause certain side effects due to stimulation of the immune system. If these side effects occur, nivolumab treatment may be interrupted or permanently discontinued, depending on the severity of the side effect.

How does nivolumab work?
Nivolumab is a monoclonal antibody (a type of protein) that attaches to a specific target in the body called programmed death-1 receptor (PD-1). PD-1 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 T cells. This helps increase their activity against cancer cells.

How has nivolumab been studied?
A total of 1581 adult patients with advanced cancer (adenocarcinoma) of the oesophagus, stomach or junction between the oesophagus and stomach were enrolled into a study that compared nivolumab and chemotherapy with chemotherapy alone. The patient's study doctor decided which type of chemotherapy to give, either FOLFOX (fluorouracil, leucovorin and oxaliplatin) or CapeOX (capecitabine and oxaliplatin). The study patients had not received other treatments for advanced stomach or oesophagus cancer. The study excluded patients with 'HER2-positive' stomach or oesophagus cancer.

Half of the study patients received nivolumab in addition to chemotherapy and half received chemotherapy alone. Study treatment was decided randomly by a central computer. Study patients were followed-up with regular visits and scans and monitored for side effects. Nivolumab was stopped if side effects were unacceptable, or if the tumour grew. Nivolumab treatment was continued for a maximum of 24 months.

The main measures of efficacy (how well the medicine worked) were progression-free survival (how long the patients lived without their cancer getting worse) and overall survival (how long the patients lived).

What are the benefits and risks of nivolumab?
Benefits

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The study results showed that nivolumab prolongs overall survival. After 12 months, the estimated overall survival rate was 55% in patients receiving nivolumab and chemotherapy, compared to 48% in patients receiving chemotherapy alone. Nivolumab also prolonged progression-free survival. After 12 months, the estimated rate of progression-free survival was 33% in patients receiving nivolumab and chemotherapy, compared to 23% in patients receiving chemotherapy alone.

Risks
When nivolumab is used in combination with chemotherapy, very common side effects (may affect more than 1 in 10 people) are: underactive thyroid gland, overactive thyroid gland, upper respiratory tract infections, decreased appetite, inflammation of the nerves, headache, shortness of breath, inflammation of the intestines, diarrhoea, vomiting, nausea, stomach pain, mouth ulcers, cold sores, skin rash, swelling and pain primarily on the palm of the hand and sole of the foot (palmar-plantar erythrodysaesthaesia syndrome), pain in the joints, pain in the muscles and bones, feeling tired or weak, fever.

Serious side effects are caused by stimulation of the immune system. This can cause inflammation in parts of the body including the lungs, large bowel, liver, kidneys, hormone-producing glands or skin. Immune-related side-effects may need treatment, or withdrawal of nivolumab. Fatal immune-related side effects have occurred. Serious infusion-related reactions can occur.

Why has nivolumab been given a positive Early Access to Medicine Scientific opinion?
Advanced stomach or oesophagus cancer (adenocarcinoma) is a life-threatening condition with a 5-year survival rate of less than 10%. The usual treatment is chemotherapy. There is an unmet need for new treatments to delay disease progression and prolong survival. Based on the study results, nivolumab in combination with chemotherapy has been shown to prolong overall survival, and progression-free survival, when compared to chemotherapy alone. The risks associated with nivolumab can be managed and do not outweigh the benefits.

What are the uncertainties?
Information is missing regarding safety in patients with autoimmune disease and patients who are taking a drug that suppresses the immune system. There is not enough evidence to recommend a dose in patients with severe kidney problems or patients with moderate or severe liver problems. The company that makes nivolumab will provide additional information when it becomes available.

Are there on-going clinical studies?
There is no on-going study of nivolumab in the EAMS indication.

What measures are in place to monitor and manage risks?
A risk management plan has been developed to ensure that nivolumab is used as safely as possible. Based on this plan, the company that make nivolumab must ensure that all healthcare professionals expected to use the medicine, as well as patients, are provided with information on the medicine including the immune-related side effects which may affect different parts of the body including the heart, lungs, liver and stomach and recommendations for minimising these side effects.

Information will be collected about patients before they enter the scheme. Healthcare professionals will be asked by the company to report side effects experienced by patients receiving nivolumab through the scheme, as well as medication errors, overdose and pregnancies. They will receive comprehensive training on adverse events prior to commencement of patient treatment. Safety data will be reviewed and reported to the MHRA on a regular basis by the company.

Patients in the Early Access to Medicines Scheme will receive an alert card from their doctor summarising the serious side effects of the medicines and the details of their treating oncologist. Patients should carry the cards with them at all times in case they need treatment or advice from a healthcare professional who is not familiar with nivolumab treatment.

Other information about nivolumab – see EAMS Treatment Protocol

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