| Early Access to Medicines Scientific Opinion - Public Assessment Report | |
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| **Product** | **Nivolumab** |
| **Condition**<br><br>**Full indication** | **Nivolumab is used to treat a type of advanced stomach cancer, which has spread or recurred following other cancer therapies**<br><br>**Treatment as monotherapy of adult patients with advanced or recurrent gastric or gastroesophageal junction (GEJ) adenocarcinoma after two or more prior systemic therapies** |
| **Company** | **Bristol-Myers Squibb Pharmaceutical Limited** |
| **EAMS number** | **15105/0008** |



**Introduction**
The aim of the Early Access to Medicines Scheme (EAMS) is to provide earlier availability of promising new unlicensed medicines to UK patients that have a high unmet clinical need. The MHRA scientific opinion provides benefit and risk information to doctors who may wish to prescribe the unlicensed 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 the information supplied to the MHRA on the benefits and risks of a promising new 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 licence such a medicine. The General Medical Council's guidance on prescribing unlicensed medicines can be found here: http://www.gmc-uk.org/guidance/ethical_guidance/14316.asp

**What is nivolumab?**
Nivolumab is the active substance of a medicine, which is available as a concentrated solution (liquid) that is diluted for infusion (drip) into a vein. This medicine is already authorised for the treatment of patients with other types of cancer (melanoma, non-small cell lung cancer, renal cell carcinoma, classical Hodgkin lymphoma, squamous cell cancer of the head and neck and urothelial carcinoma) under the name Opdivo®.

**What is nivolumab used to treat?**
Nivolumab is used to treat adults with advanced cancer of the stomach or the junction between the stomach and the gullet (called gastroesophageal junction) of a certain type (adenocarcinoma), which has spread or recurred following at least two other cancer therapies.

**How is nivolumab used?**
Treatment with nivolumab should be started and supervised by a specialist doctor experienced in treating cancer.

The doctor will carry out blood tests to check the patient's liver, kidney and thyroid function before and during treatment.

Nivolumab is given as an infusion into a vein over 60 minutes every two weeks for as long as the patient keeps benefitting from treatment or until it is no longer tolerated. The recommended dose for each infusion is 3 mg per kilogram body weight.

**How does nivolumab work?**
Nivolumab is a monoclonal antibody. A monoclonal antibody is a type of protein that has been designed to recognise and attach to a specific structure (called an antigen) that is found in certain cells in the body. Nivolumab has been designed to attach to and block the activity of a protein called PD-1 that is found on the surface of T cells, a type of white blood cell of the immune system able to detect and fight cancer cells. When the PD-1 pathway is active, it stops T cells from attacking cancer cells. By blocking PD-1, nivolumab restores the capacity of T cells to fight cancer cells.

**How has nivolumab been studied?**
The main study of the effects of nivolumab has enrolled 493 patients with advanced stomach cancer (including gastroesophageal junction cancer) that had progressed or recurred after at least two standard therapy regimens for this type of cancer. Nivolumab was compared with placebo (inactive infusion), as patients usually do not receive anti-cancer therapy when they reach this disease stage.

The main measures of effectiveness (how well the medicine worked) were overall survival (how long the patients lived), the tumour response (growth or shrinkage), and progression-free survival (how long the patients lived without their cancer getting worse).

**What benefits and risks has nivolumab shown during the studies?**

*Benefits*
Patients treated with nivolumab had an increase in overall survival: after 12 months, 26% were alive compared to 11% of those receiving placebo (inactive infusion). A shrinking of the tumour was observed in 11% of the patients treated with nivolumab compared to none in patients receiving placebo. The proportion of patients without progression of disease after 6 months was 20% in those treated with nivolumab compared to 7% in those receiving placebo.

*Risks*
Nivolumab may be associated with side effects resulting from excessive activity of the immune system, including endocrine abnormalities, diarrhoea/colitis, hepatitis, pneumonitis, nephritis, renal dysfunction and skin adverse reactions. Most will resolve following appropriate treatment or on stopping nivolumab.

The most frequent side effects of nivolumab, affecting at least 10% of the patients, are fatigue (tiredness), skin rash, pruritus (itching), diarrhoea and nausea (feeling sick).

**Why has nivolumab been given a positive Early Access to Medicine Scientific opinion?**
Nivolumab has been shown to increase patient survival in a disease stage where no anti-cancer therapy is usually proposed due to toxicity and limited effects. With regard to the medicine's side effects, the most frequent were mild to moderate in severity. Advanced stomach cancer is a fatal condition and currently no anti-cancer therapies are given after several therapy failures.

**What are the uncertainties?**
The trial has been conducted in Asia, where the frequency of this cancer is higher than in Europe, while a limited number of patients have been treated in Europe. The Company that makes nivolumab will

provide additional information when it becomes available.

**Are there on-going clinical studies?**
There are several on-going studies in advanced stomach cancer where nivolumab is administered to previously untreated patients in combination with chemotherapies or earlier after tumour resection as adjuvant therapy.

**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 makes 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 side effects related to the excessive activity of the immune system 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 adverse events experienced by patients receiving nivolumab through the scheme. These safety data will be reviewed and reported to the MHRA on a regular basis by the company. Additional data will be collected on clinical efficacy and quality of life on a voluntary basis and subject to additional patient consent.

Patients in the Early Access to Medicines Scheme will also receive an alert card from their doctor summarising the important risks with the medicine. Patients should carry the card with them in case they need treatment or advice from a healthcare professional that is not familiar with nivolumab treatment.

**Other information about nivolumab – see EAMS Treatment Protocol**