| Early Access to Medicines Scientific Opinion - Public Assessment Report | |
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| **Product** | **Nivolumab** |
| **Condition**<br><br><br><br>**Full indication** | **Nivolumab is used to treat a type of advanced lung cancer (characterised by non-squamous non-small cells), which has spread or cannot be removed by surgery following other cancer chemotherapies**<br><br>**Treatment as monotherapy of locally advanced or metastatic non-squamous non-small cell lung cancer (NSCLC) after prior chemotherapy in adult patients whose tumours express programmed death ligand-1 (PD-L1)** |
| **Company** | **Bristol-Myers Squibb Pharmaceutical Limited** |
| **EAMS number** | **15105/0002** |

**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/mobile/news/14327

**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 and squamous non-small cell lung cancer) under the name Opdivo®.

**What is nivolumab used to treat?**
Nivolumab is used to treat adults with advanced lung cancer of a certain type (with non-squamous non-small cells - NSCLC), which has spread or cannot be removed by surgery after having failed treatment with cancer chemotherapy. In addition, the tumour should exhibit a certain level of a protein called programmed death ligand-1 (PD-L1), which is measured in a biopsy by a specialised laboratory.

**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 prevents its binding to PD-L1 on the surface of the tumour cells, hence restoring the capacity of T cells to fight cancer cells. Nivolumab works best in locally advanced or metastatic non-squamous non-small cell lung cancer if the tumour exhibits a certain level of PD-L1, which is measured in a biopsy by a specialised laboratory.

**How has nivolumab been studied?**
The main study of the effects of nivolumab has enrolled 582 patients with advanced or metastatic squamous NSCLC who had previously received standard cancer chemotherapy, after this treatment had not worked or had stopped working. Patients whose tumours had special features (EGFR mutations or ALK translocations) could be enrolled in case of disease progression after the use of appropriate treatment for these tumours. Nivolumab was compared with docetaxel, a commonly used type of chemotherapy.

The measures of effectiveness (how well the medicine worked) were the growth of the tumour, overall survival (how long the patients lived), 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*
If the tumour exhibited PD-L1, its shrinking was observed in 31% of the patients treated with nivolumab compared to 12% of those treated with chemotherapy. Patients treated with nivolumab had also an increase in overall survival: after 12 months, 60% were alive compared to 36.5 % of those treated with docetaxel.

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

The most frequent side effects, affecting at least 10% of the patients, were fatigue (tiredness), nausea (feeling sick), decreased appetite and asthenia (weakness).

**Why has nivolumab been given a positive Early Access to Medicine Scientific opinion?**
Nivolumab has been shown to slow the progression of cancer and increase patient survival in a condition where other treatments currently have poor results. With regard to the medicine's side effects, the most frequent were mild to moderate in severity. Advanced lung cancer is a fatal condition and

currently few therapies are available with low efficacy.

**What are the uncertainties?**
The relationship between the level of PD-L1 on the tumour and the benefits of nivolumab is still under investigation. The company that makes nivolumab has committed to provide further data when they become available.

**Are there on-going clinical studies?**
There are on-going studies in advanced lung cancer where nivolumab is administered early after diagnosis or in combination with chemotherapies or other monoclonal antibodies.

**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 effects 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.

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**