Medicines & Healthcare products Regulatory Agency

MHRA

Early Access to Medicines Scientific Opinion - Public Assessment Report	
Product	**Nivolumab with ipilimumab**
EAMS indication	Treatment of adult patients with inoperable malignant pleural mesothelioma, a type of cancer that affects the lining of the lung.
Company	**Bristol-Myers Squibb Pharmaceuticals Limited**
EAMS number	**15105/0013**
EAMS Scientific Opinion date	**27/01/2021**

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 are nivolumab and ipilimumab?

Nivolumab is the active substance of a medicine which is given as an infusion (a drip) into a vein (intravenously).

Ipilimumab is the active substance of a medicine which is also given as an infusion (a drip) into a vein (intravenously).

What is nivolumab and ipilimumab used to treat?

Nivolumab will be given in combination with ipilimumab for the treatment of malignant pleural mesothelioma, a type of cancer that affects the lining of the lung. It is to be used for patients who have not received any previous therapies and when the disease cannot be removed surgically.

How is nivolumab and ipilimumab used?

Treatment with nivolumab and ipilimumab will be given in a hospital or clinic, under the supervision of a doctor experienced in the treatment of cancer.

When nivolumab is given in combination with ipilimumab for the treatment of malignant pleural mesothelioma, nivolumab is given as an infusion (a drip) into a vein (intravenously) over a period of 30 minutes, every 3 weeks. An infusion of ipilimumab will also be given into a vein over a period of 30 minutes every 6 weeks.

When nivolumab is given in combination with ipilimumab, nivolumab will be given first followed by ipilimumab.

How does nivolumab and ipilimumab work?

Nivolumab is a monoclonal antibody, a type of protein designed to recognise and attach to a specific target protein, in the body attaches 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 lung cancer cells.

Ipilimumab is a protein that helps the body's immune system to attack and destroy cancer cells using immune cells.

How has nivolumab and ipilimumab been studied?
The main study of the effects of nivolumab in combination with ipilimumab enrolled 605 patients with untreated malignant pleural mesothelioma that were inoperable. The combination was compared to standard chemotherapy with the medicine pemetrexed, given in combination with either cisplatin or carboplatin.

The measures of effectiveness (how well the medicine worked) were the complete response to treatment by assessing 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 are the benefits and risks of nivolumab and ipilimumab?

Benefits
Patients that received treatment with nivolumab in combination with ipilimumab had a better overall survival compared to patients that received standard chemotherapy. 41% of the patients were still alive at 2 years compared to 27% of the patients who had received standard chemotherapy.

Risks
The most frequent side-effects affecting at least 10% of patients treated with nivolumab in combination with ipilimumab for malignant pleural mesothelioma in the above study were: rash, fatigue, diarrhoea, pruritus, hypothyroidism (underactive thyroid gland) and nausea. The majority of adverse reactions were mild to moderate in severity.

Treatment with nivolumab is also associated with side effects resulting from excessive activity of the immune system, causing inflammation in various parts of the body. These types of side effects include pneumonitis (inflammation of the lungs), diarrhoea, colitis (inflammation of the intestines), abnormal liver function tests, inflammation of the liver, inflammation of the kidneys and abnormal

kidney function, endocrine abnormalities (problems with hormone producing glands that may affect how these glands work) and skin reactions. The incidence of these types of toxicity is higher when nivolumab is used in combination with ipilimumab. Most of these side effects will resolve following appropriate treatment. However, in some cases, treatment with nivolumab and ipilimumab may need to be permanently stopped.

Why has nivolumab and ipilimumab been given a positive Early Access to Medicine Scientific opinion?

Malignant pleural mesothelioma is an aggressive cancer that affects the lining of the lung. In patients with disease that cannot be surgically removed treatment options are limited and includes standard chemotherapy with the medicines pemetrexed and cisplatin or carboplatin. Treatment with nivolumab in combination with ipilimumab notably prolongs patient survival despite some increase in side effects. These side effects are usually manageable if appropriate measures are in place.

What are the uncertainties?

The results presented are based on an interim analysis of the study results, for the overall survival endpoint.

The improvement in overall survival was seen to be greater in the sub-group of patient whose cancer showed the non-epithelioid histology. Though an improvement was also seen the patients whose cancer was of the epithelioid type the improvement in overall survival was less compared to the non-epithelioid type of cancer.

The difference in outcomes depending on whether the cancer is PD-1 positive or negative, i.e., depending on how much programmed death-1 (PD-1) receptors are present in the cancer, is not clear at present.

The company that makes nivolumab and ipilimumab will provide additional information when it becomes available.

Are there on-going clinical studies?

There is no other on-going study of nivolumab and ipilimumab 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 in combination with ipilimumab is used as safely as possible. Based on this plan, the company that makes nivolumab and ipilimumab must ensure that doctors and other 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 in combination with ipilimumab 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 medicine and the details of their treating oncologist. Patients should carry the card with them at all times in case they need treatment or advice from a healthcare professional who is not familiar with nivolumab and ipilimumab treatment.

Other information about nivolumab and ipilimumab – see EAMS Treatment Protocols.