| Early Access to Medicines Scientific Opinion - Public Assessment Report | |
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| **Product** | **Pembrolizumab (MK-3475)** |
| **Condition**<br><br>**Full indication** | **Pembrolizumab is used to treat advanced melanoma (a type of skin cancer affecting cells called melanocytes), which has spread or cannot be removed by surgery and has progressed after other treatments**<br><br>**Treatment of unresectable or metastatic melanoma with progressive, persistent, or recurrent disease on or following treatment with standard of care agents including ipilimumab, and when indicated a V-raf murine sarcoma viral oncogene homolog B1 (BRAF) inhibitor or mitogen-activated protein kinase (MEK) enzyme inhibitor** |
| **Company** | **Merck Sharp & Dohme Limited** |
| **EAMS number** | **00025/0626** |

**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 and the MHRA can be found here:
https://www.gov.uk/apply-for-the-early-access-to-medicines-scheme-eams

https://www.gov.uk/government/organisations/medicines-and-healthcare-products-regulatory-agency/about

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 pembrolizumab (MK-3475)?**
Pembrolizumab is the active substance of a medicine, which is available as a powder that is made up into a solution for infusion (drip) into a vein.

**What is pembrolizumab (MK-3475) used to treat?**
Pembrolizumab is used to treat adults and children from 12 years of age with advanced melanoma (a type of skin cancer affecting cells called melanocytes), which has spread or cannot be removed by surgery. The positive opinion was given for use in this condition after other melanoma treatments have failed, including ipilimumab and, in case of a tumour with an abnormal "BRAF" gene, a different medicine called a BRAF or MEK inhibitor.

**How is pembrolizumab (MK-3475) used?**
Treatment with pembrolizumab 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.

Pembrolizumab is given as an infusion into a vein over 30 minutes every three weeks. The recommended dose for each infusion is 2 mg per kilogram body weight.

**How does pembrolizumab (MK-3475) work?**
Pembrolizumab 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. Pembrolizumab 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, pembrolizumab restores the capacity of T cells to fight cancer cells.

**How has pembrolizumab (MK-3475) been studied?**
The effects of pembrolizumab have been studied in 411 patients with advanced melanoma who received different doses of treatment at different intervals. One group of 173 patients had previously received ipilimumab, and where appropriate, a BRAF or MEK inhibitor after this treatment had not worked or had stopped working. Another group of 103 patients had not been previously treated with ipilimumab. The two groups received a dose of 2 mg or 10 mg of pembrolizumab per kg bodyweight every three weeks. 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 pembrolizumab (MK-3475) shown during the studies?**

*Benefits*
Amongst the 173 patients who had failed previous therapies, a shrinking of their tumour was observed in 24% and the progression of the disease was halted in 47% for a durable period of time. Approximately 60% of patients survived for at least one year.

*Risks*
Pembrolizumab may be associated with side effects resulting from excessive activity of the immune system. Most will resolve following appropriate treatment or on stopping pembrolizumab. The most frequent side effects, affecting at least 20% of the patients, were fatigue (tiredness), cough, nausea (feeling sick), rash, pruritus (itching), decreased appetite, constipation, joint pain, and diarrhoea.

**Why has pembrolizumab (MK-3475) been given a positive Early Access to Medicine Scientific opinion?**
The MHRA considered that pembrolizumab has been shown to slow the progression of cancer 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 melanoma is a fatal condition and currently few therapies are available with low to moderate efficacy. There is therefore an urgent need for more therapies and the MHRA therefore considered that the benefits of pembrolizumab in this condition are greater than its risks.

**What are the uncertainties?**
The effects of pembrolizumab have not been compared to those of current treatments in the same

study, which is needed to measure its effectiveness more precisely, and the results on survival are still preliminary.

**Are there on-going clinical studies?**
Several studies are ongoing in different groups of patients. One study is comparing pembrolizumab to standard chemotherapy in patients who have progressed after ipilimumab treatment; another study is comparing pembrolizumab to ipilimumab in previously untreated patients.

**What measures are in place to monitor and manage risks?**
A risk management plan has been developed to ensure that pembrolizumab is used as safely as possible. Based on this plan, the company that makes pembrolizumab 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 pembrolizumab 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 who is not familiar with pembrolizumab treatment.

**For other information about pembrolizumab (MK-3475) – see EAMS Treatment Protocol**

MHRA
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